

SPACE-CABIN ATMOSPHERES

Part III

Physiological Factors of Inert Gases

A literature review by
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Foreword

THIS REPORT is Part III of a study on *Space-Cabin Atmospheres*, conducted under sponsorship of the Directorate, Space Medicine, Office of Manned Space Flight, National Aeronautics and Space Administration. Part I, "Oxygen Toxicity," was published as NASA SP-47, and Part II, "Fire and Blast Hazards," as NASA SP-48. The final report, Part IV, "Engineering Trade-Offs of One- Versus Two-Gas Systems," will complete the series.

This document provides a readily available summary of the open literature in the field. It is intended primarily for biomedical scientists and design engineers.

The manuscript was reviewed and evaluated by leaders in the scientific community as well as by the NASA staff. As is generally true among scientists, there was varied opinion about the author's interpretation of the data compiled. There was nonetheless complete satisfaction with the level and scope of scholarly research that went into the preparation of the document. Thus, for scientist and engineer alike it is anticipated that this study will become a basic building block upon which research and development within the space community may proceed.

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Contents

	PAGE
INTRODUCTION	
Chapter 1: PHYSICAL CHEMISTRY OF INERT GASES	1
<i>ATOMIC STRUCTURE</i>	1
<i>PHYSICAL PROPERTIES OF INERT GASES</i>	1
<i>BIOCHEMICAL PROPERTIES OF INERT GASES</i>	4
Solubility of Inert Gases in Liquids.....	4
Diffusion of Inert Gases in Liquids.....	7
<i>CHEMICAL REACTIONS OF INERT GASES</i>	8
Chapter 2: ROLE OF INERT GASES IN DECOMPRESSION SICKNESS	11
<i>ANALYSIS OF BUBBLE FORMATION IN DECOMPRESSION SICKNESS</i>	11
Physical Factors Controlling Growth of Bubbles in Biological Systems.....	12
Correlation of Bubble and Symptom History.....	17
Pathological Physiology of Decompression Symptoms.....	18
Role of Gas Bubbles in Symptoms at Specific Body Sites.....	22
Factors Controlling Decay of Bubbles in Biological Systems.....	24
Calculation of Gas-Specific Factors Controlling Peak Bubble Size.....	30
<i>EMPIRICAL AND OPERATIONAL DATA ON INERT GASES IN DECOMPRESSION SICKNESS</i>	34
Animal Studies of Decompression From High Pressures.....	34
Human Decompression From High Pressures.....	37
Human Decompression to Altitude From Helium-Oxygen Atmospheres.....	46
<i>DECOMPRESSION SCHEDULES AND DENITROGENATION PROGRAMS IN THE PREVENTION OF DECOMPRESSION SICKNESS</i>	49
Ascent Schedules in Diving.....	49
Computer Programs in Diving.....	51
Denitrogenation Schedules in Decompression to Altitude.....	54
<i>ANALYSIS OF INERT GASES IN "EXPLOSIVE" DECOMPRESSION AND IN THE EBULLISM SYNDROME</i>	72
"Explosive" Decompression.....	72
Gas-Dependent Factors in Lung Expansion During "Explosive" Decompression.....	75
Gas-Dependent Factors in Gas Emboli After Lung Disruption.....	76
Ebullism Syndrome.....	77
<i>SUMMARY OF INERT GAS FACTORS IN DECOMPRESSION</i>	82
Chapter 3: METABOLIC EFFECTS OF INERT GASES	85
<i>INERT GAS NARCOSIS</i>	86
<i>INERT GASES IN CELLULAR METABOLISM</i>	89
<i>CHRONIC EXPOSURE TO INERT GASES</i>	96
Chapter 4: ENGINEERING IMPLICATIONS OF THE USES OF INERT GASES IN SPACE CABINS	101
<i>THERMAL CONTROL</i>	101
<i>VOICE AND SOUND TRANSMISSION</i>	102
<i>LEAK RATES OF GAS</i>	104
Chapter 5: ROLE OF INERT GAS PHYSIOLOGY IN SELECTION OF SPACE-CABIN ATMOSPHERES	115
REFERENCES	119

Introduction

What has been is what shall be
What has gone on is what shall go on
And there is nothing new under the sun.
Men may say of something, "Ah, this is new!"
But it existed long ago before our time.
The men of that old time are now forgotten,
As men to come shall be forgotten,
By those who follow them.

Ecclesiastes 1:9-11

THAT THE CHEMICALLY INERT GASES are far from inert physiologically has been known for over a half century. Caisson engineering, submarine technology, and aviation have, in turn, been plagued with this phenomenon. This study of space-cabin atmospheres will consider the problem.

The physiology of inert gases in space cabins will be approached from an operational point of view. Chapter 1 reviews the physical chemistry of inert gases as it bears on physiological realities. Subsequent chapters treat reviews of the prime role of inert gases in decompression sickness; general physiology of inert gases in biological systems; engineering aspects of inert gases in space cabins; and those considerations directly related to the selection of space-cabin atmospheres optimally suited for specific space missions.

Physical Chemistry of Inert Gases

THE INERT GASES available as diluents of oxygen in space-cabin atmospheres are helium, neon, argon, krypton, xenon, radon, and nitrogen. Radon, a radioactive gas, can be immediately eliminated as a diluent and is not included in the discussion. All except nitrogen are elements of the helium group, or "Group 0," of the periodic table. The atoms of these elements have stable and "satisfied" electronic valence structures. Unlike the atoms of nitrogen or oxygen, the atoms of the helium-group gases do not combine in the gas phase to form stable diatomic molecules. The "aloofness" of these essentially monatomic gases has led to the term "noble gases."

An excellent, exhaustive review of inert gases has been recently presented by Cook et al.¹⁰⁹ Much of the physical data presented in this study is taken from this source. Emphasis is placed on those physical and chemical factors that directly influence the biochemical and physiological activities of these gases.

ATOMIC STRUCTURE

Most of the physical and chemical properties of the noble gases are atomic properties; that is, properties of the individual atoms. The quantum mechanical considerations which ultimately determine these properties are beyond the scope of this review. From spectroscopic data, it had been thought for many years that there were no unpaired electrons in the noble gases, that the outer electron shells were filled, and that only van der Waals forces were available for chemical binding. Recent discovery of many stable compounds of xenon and radon⁵ and unstable compounds of krypton and argon¹²⁰ has led to a drastic change in this concept. It now appears that xenon can undergo covalent bonding with fluorine.⁵ The covalent bonds are

formed with 10 electrons in the valence shell and hybridized sp^3d orbitals to form XeF_2 , with 12 electrons in the valence shell and sp^3d^2 orbitals to form XeF_4 , and with 14 electrons in the valence shell and sp^3d^3 orbitals in XeF_6 . The potential for bonding lies in the five $3d$ unfilled orbitals of argon, the five $4d$ orbitals of krypton, and the five $5d$ orbitals of xenon. Because of the high energy required for hybridizing their orbitals, neon and helium atoms appear to have no ionic or covalent bonding potential. It must be remembered that even the xenon fluoride compounds are very unstable. Exposure to water vapor of the air immediately results in their conversion to oxide. It would be most unlikely that noble gas compounds of this type could exist in the presence of biological fluids.

Nitrogen gas is a diatomic molecule. The arrangement of the 10 valence electrons in the molecule probably resonates between the $:N::N:$ and the $:N::\ddot{N}:$ states of the molecule, resulting in a diamagnetic structure with a heat of dissociation that is probably greater than that of any other diatomic molecule. From thermal data, it has been calculated that at 8000°C the gas is only 40 percent dissociated into atomic nitrogen. It appears that only in the nitrogen fixation process of free soil bacteria or in bacteria-legume nodule systems is nitrogen dissociated into the active-N form at low temperatures by the enzyme nitrogenase.

PHYSICAL PROPERTIES OF INERT GASES

Table 1 is a summary of the physical properties of the inert gases to be considered for use in space-cabin atmospheres. It must be remembered that the actual space cabin will have a mixture of oxygen and inert-gas diluent. Since oxygen mixtures will be used at several different total pressures, the data of table 1 can be used

only indirectly in making engineering calculations. However, the table does present the comparative contributions of the physical characteristics of each gas to the problems at hand.

TABLE 1.—*Physical Properties of Inert Gases*

Property	Gas						Reference
	He	Ne	A	Kr	Xe	N ₂	
Atomic number.....	2	10	18	36	54	7	109
Molecular weight.....	4.00	20.18	39.94	83.80	131.30	28.00	109, 238
Color	Colorless						
Density, gm/liter, at 0° C and 1 atm.....	0.1784	0.9004	1.784	3.708	5.851	1.251	109, 238
Heat capacity (C_p) at 25° C and 1 atm, cal/°C-gm-mole.....	4.97	4.97	4.97	4.97	4.97	6.96	202
Specific heat ratio at 0 to 20° C, C_p/C_v	1.63	1.64	1.67	1.69	1.67	1.404	109, 202
Sound velocity at 0° C and 1 atm, m/sec.....	970	435	319	213	168	337	109, 202
Acoustic impedance at 0° C and 1 atm, dyne-sec/cm ³	17.3	38.5	56.9	42.1	202
Thermal conductivity at 0° C and 1 atm, cal/°C-cm-sec	34.0×10^{-5}	11.04×10^{-5}	3.92×10^{-5}	2.09×10^{-5}	1.21×10^{-5}	5.66×10^{-5}	109, 202
Viscosity at 20° C and 1 atm, micropoise.....	194.1	311.1	221.7	249.6	226.4	175.0	109, 202
Critical properties:							
Density, gm/cm ³	0.069	0.484	0.531	0.908	1.105	0.3110	109, 202
Pressure, atm....	2.26	26.9	48.0	54.3	58.0	33.54	109, 202
Temperature, °C.....	-267.9	-228.7	-122.44	-63.8	16.59	-146.9	109, 202

In the appropriate sections of this work attempts will be made to define data for specific cabin temperatures, pressures, and gas mixtures. No data for the liquid phase of these gases are presented other than the critical properties. Liquid-phase data are given in the engineering tradeoffs of part IV of this series.

Density.—In table 1 it can be seen that the densities of the inert gases increase, as expected, with increase in molecular weight. The densities may be calculated from the normal volumes and atomic weights.

Heat Capacity and Specific Heat Ratio.—The heat capacity of all the monatomic gases is constant, and the C_p/C_v ratios are essentially the same.

Sound Velocity.—The velocity of sound in the inert gases varies considerably with temperature, but only slightly with pressure. In table 1 it is seen that the velocity of sound decreases rapidly as the molecular weight increases. The velocity of sound for any gas or gas mixture can be calculated from the molecular weight, specific heat, and a suitable equation of state for the gases involved.⁵⁹

Acoustic Impedance.—Values for acoustic impedance in table 1 are seen to increase with molecular weight. Acoustic impedance is a function of the density of the gas times the velocity of propagation or, looking at it another way, acoustic impedance is the ratio of the sound pressure to the particle velocity of a gas. These

physical factors are important in determining the voice-communication and noise factors within the space cabin.

Thermal Conductivity.—The thermal conductivity is an inverse function of the molecular weight of the gas. This factor is of great importance to the thermal balance of the crew within a space cabin. Prediction of thermal conductivities of binary mixtures, of monatomic and diatomic gases is possible through complex manipulation of kinetic theory equations.^{108, 408, 307, 77} Figure 1 is an example of such data. The cgs values of table 1 may be converted to the English system ($\text{Btu-ft}^{-1}\text{-hr}^{-1}\text{-}^\circ\text{F}^{-1}$) by multiplying them by 241.9. Thermal conductivity plays a major role in determining air-conditioning requirements in the space cabin covered in chapter 4 and in the engineering trade-off studies in part IV of this series.

Viscosity.—The values for the absolute or dynamic viscosity are given in micropoises. A poise is the tangential force per unit area (dynes/cm^2) required to maintain unit difference in

velocity (1 cm/sec) between two parallel planes separated by 1 cm of fluid. There is some difference between the dynamic viscosities of the noble gases. The viscosity of binary mixtures of monatomic and diatomic gases may be predicted from complex kinetic theory equations.¹⁰⁷ Viscosity factors must be considered in gas-flow calculations for the design of air-conditioning systems.

Critical Properties.—The critical properties of inert gases determine the ease with which the gases may be liquefied. Table 1 shows that the gases of lower molecular weight require greater pressures and lower temperatures for liquefaction. These factors determine the volume and weight penalties for cryogenic storage. Another physical factor determining gas-phase storage of the noble gases is the compressibility of the gas or deviation of the gas from the "ideal" in the equation of state. Figure 2 shows graphically, starting with a given mass of gas at unit pressure, P , occupying unit volume, V , at 21°C (70°F), the values of the product of pressure P and volume V for the same mass at the same temperature and at any pressure up to 2000 psig. The dashed line indicates the ideal gas with molecules occupying no space and being neither attracted nor repelled by one another, $PV = \text{constant}$. The atoms of helium and neon repel each other and are less compressible than "ideal." The atoms of the other gases attract and are more compressible. In determining the total volume of any stored gas

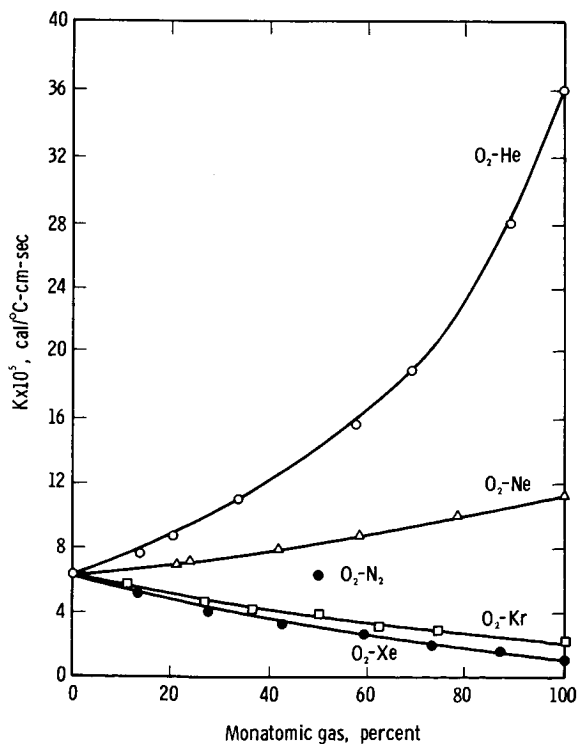


FIGURE 1.—Thermal conductivity of $\text{O}_2\text{-He}$, $\text{O}_2\text{-Ne}$, $\text{O}_2\text{-Kr}$, and $\text{O}_2\text{-Xe}$ mixtures at 30°C . (AFTER SRIVASTAVA AND BARUA.⁴⁰⁸)

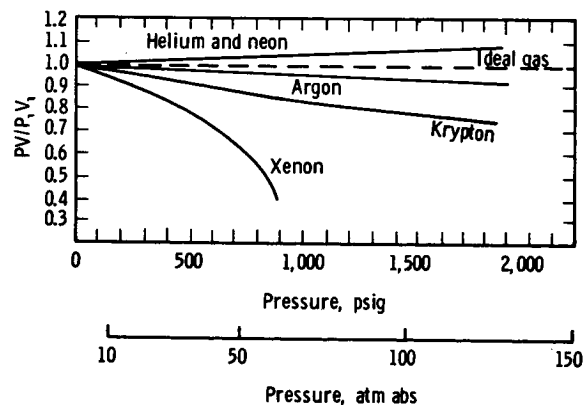


FIGURE 2.—Compressibility of the inert gases at 21°C ($P = \text{pressure}$; $V = \text{volume}$). (AFTER JENKINS AND COOK.²⁴⁵)

available at cabin pressure, these compressibility factors should be taken into account.

BIOCHEMICAL PROPERTIES OF INERT GASES

The physiological and biochemical properties of inert gases are the major considerations of this report. The physicochemical basis for these functions has been summarized in table 2.

Solubility of Inert Gases in Liquids

The Bunsen solubility coefficient (absorption coefficient) of a gas is defined as the ratio of the volume (reduced to STPD) of a gas dissolved at 1 atmosphere to the volume of the solvent. The data of table 2 are restricted to the solubility in biological fluids at 37° to 38° C. Calculation of solubilities at other temperatures can be determined by the equation of Morrison and Johnstone.³²¹ Inert-gas solubilities in many different solvents have been tabulated by Jenkins and

Cook.²⁴⁵ The theory of solubility of the inert gases in liquids can be found in the classic review of Markham and Kobe.³⁰² Because of its importance to the discussion, the solubility of gases is reviewed briefly.

Henry's law states that the partial pressure p of a solute is proportional to the mole fraction N of the solute in the solvent:

$$(p_{\text{solute}} = KN_{\text{solute}})$$

This relationship holds for gaseous solutes as well as solids. Up to a pressure of 1 atmosphere this relationship holds within 1 to 3 percent for most gases. The solubility of each individual gas in a mixture is, according to Dalton's law, independent of the presence of others. The theory of solution of inert gases in liquids is not fully developed, although the following basic facts can be brought to bear on the subject:

TABLE 2. — *Biochemical Properties of Inert Gases*
[Numbers in parentheses were calculated by Graham's law from nitrogen data]

Property	Gas						Reference
	He	Ne	A	Kr	Xe	N ₂	
Bunsen solubility coefficient in water at 38° C...	0.0086	0.0097	0.026	0.045	0.085	0.013	276, 242, 163, 273.
Bunsen solubility coefficient in olive oil at 38° C.....	0.015	0.019	0.14	0.43	1.7	0.061	276, 242, 241.
Bunsen solubility coefficient in human fat at 37° C.....		0.020		0.41	1.6	0.062	241, 474.
Oil-water solubility ratio.....	1.7	2.1	5.3	9.6	20.0	5.1
Relative diffusion through gelatin at 23° C.....	1.0	(0.42)	0.30	0.21	0.13	0.36	249.
Diffusion constants through liquids at 37° C, cm ² /sec × 10 ⁻⁶ :							
Olive oil.....	(18.6)	(8.34)	(5.92)	(4.10)	(3.27)	7.04	132
Lard.....	(9.28)	(4.15)	(2.94)	(2.08)	(1.62)	3.50	132
Serum.....	(57.6)	(25.7)	(18.2)	(12.6)	(10.1)	21.7	191
	^a 44.4						
Agar gel.....	(71.3)	(32.0)	(22.7)	(15.8)	(12.6)	27.0	155
Water.....	(79.2)	(34.8)	(25.2)	(17.5)	(13.9)	30.1	191, 155
	63.2						

^a Calculated from data of ref. 191.

(1) The order of increasing solubility of inert gases in liquid remains the same in different liquids.

(2) The increase in volume caused by the solution of a mole of gas in a solvent is nearly equal to the corresponding value of b in the van der Waals equation.

(3) The solubility of a gas in water is usually decreased by an increase in temperature. This relationship does not hold true for all solvents. The solvent specificity in this relationship is discussed subsequently.

(4) The solubility of gases in water is usually decreased by the addition of solutes, especially electrolytes. This "salting out" of gases varies considerably for each electrolyte, but the relative decrease in solubility is generally the same for different gases.

The solubility of the unreactive gases is thought to be caused by an attractive force between the solute molecules and the solvent molecules through the dipole-induced dipole forces of van der Waals. Electrically charged dipoles in the electrically neutral molecules of the solvent can induce charges of opposite sign in the neutral gas solute molecules. For instance, water molecules have considerable dipole moments in their electrically neutral molecules and can induce an opposite charge even in a helium atom. This initiates a force of attraction between the two induced dipoles, causing helium to be dissolved in the water. In some circumstances to be discussed, inert gas hydrates and clathrates may be formed in some inert gas-solvent systems. The "salting out" effect may be explained by the fact that water dipoles will tend to combine with the salt ions rather than induce dipoles in the inert gas.

Table 2 contains the Bunsen solubility coefficients at 37° to 38° C for the inert gases in water, olive oil, and human fat. The increase in van der Waals constants²³³ with molecular weight predicts an increasing solubility of the gases in water and lipids with molecular weight of the gases. The lipid solubilities are all greater than the corresponding water solubilities. The presence of polar groups reduces the solubility of nonpolar gas in an organic liquid, since two electrically polar molecules will have greater mutual attraction than two that are not polar.

In a solution of nonpolar molecules (inert gas) in a polar solvent (water), this greater mutual attraction may be thought of as expelling the nonpolar molecules. The higher the molecular weight of the gas, the greater the oil-water solubility ratio. This phenomenon is probably related to the relatively greater ease of dipole induction in the gases of higher molecular weight by the lipid molecules. As will be discussed in the appropriate sections, the oil-water solubility ratio plays an important role in the physiology of the inert gases. It is of interest that the solubilities of the inert gases in olive oil are essentially the same as those in human fat. Since the olive oil systems have been studied more thoroughly than the human fat systems, this is a fortunate circumstance.

Molecular factors in lipid solubility were studied by Nussbaum,³³¹ who reported that the solubilities of the highly soluble radon in fatty acids and synthetic triglycerides increase with the increasing number of carbon atoms per mole of fatty acid up to 7 carbons. A slight decline in solubility occurs as the number of carbon atoms increases above 8.

The prediction of temperature coefficients of inert gas solubility in organic solvents is an interesting problem. The generally accepted idea that the solubility of gases in liquids decreases with rise in temperature is due to the fact that most measurements have been made with water as the solvent. Lannung,²⁷³ however, has shown that, in general, the log of the solubility of gases varies directly with the absolute temperature for many organic solvents, but varies inversely with the absolute temperature for water.

Some polar organic molecules will probably behave intermediately between water and the nonpolar solvents. The temperature coefficients of solubility in vegetable and animal lipids are quite small but vary in size and direction from gas to gas and from lipid to lipid.^{276, 474, 155, 472} In general, the solubility of helium, neon, and argon in lipids follows that of the nonpolar organic solvents by increasing with increasing temperature, while that of krypton and xenon tends to decrease with increasing temperature.

The decrease in gas solubility in an aqueous system as temperature is raised is due to the

modification of water structure as gas atoms dissolve. The change probably produces a lesser crystallinity of the structure that water builds in the form of a microscopic "iceberg" around the gas atoms.¹⁸⁰ As the temperature rises, the "icebergs" melt and the amount of gas trapped in the water is decreased. The clathrate-hydrate theory of Pauling³³⁷ would offer a similar explanation for the deviation from the expected relationship. Figure 3 represents the changes of water solubility of biologically significant gases with temperature.

Another pertinent relationship is the equivalence of Bunsen coefficients of the inert gases in whole blood and in water. This finding was analyzed in great detail by Van Slyke et al.,⁴³⁴ who partitioned the solubility of nitrogen in the blood components as seen in table 3.

TABLE 3.—*Solubility of Nitrogen in the Blood Components*

[AFTER VAN SLYKE ET AL.⁴³⁴]

Component	Bunsen coefficient of nitrogen
Normal blood.....	0.0130
Normal plasma.....	.0117
Red cells.....	.0146
Water.....	.0127

Table 3 shows that normal whole blood dissolves only 1 to 2 percent more nitrogen than does water. Plasma dissolves 8 percent less and red cells, 12 percent more nitrogen than water. The relationship between solubility of nitrogen in whole blood and hemoglobin content is:

$$\alpha = 0.0117 + 0.00064 \text{ (volume percent oxygen capacity)}$$

Of the 8 percent by which the solubility of nitrogen in plasma is depressed below its solubility in water, one-half is attributed to the "salting out" effect discussed previously and one-half to the displacement of water molecules by proteins. Plasma lipids only partly counter this effect. Hemoglobin, on the other hand, takes up 1.3 times as much nitrogen as water, making

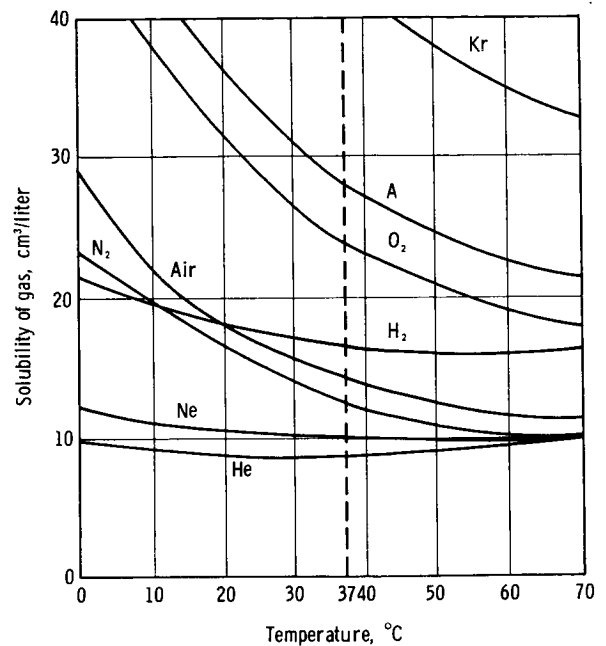


FIGURE 3.—*Solubility of gases in water at different temperatures.* (AFTER TIETZE.⁴²²)

nitrogen 1.12 times as soluble in red cells as in water and 1.23 times as soluble as in plasma. Henry's law appears to hold for all components of the whole blood. The degree of oxygenation of the red cells is not a factor in the nitrogen solubility. As would be expected from these considerations, the Bunsen solubility of helium in blood (0.0088) is almost the same as that in water (0.0086).

Plasma and cell lipids affect the solubility of the whole blood by only 1 or 2 percent. This finding has recently been confirmed by Greene.²⁰⁵ The mean value for whole blood lipid is only 0.0059 g/ml of blood, or only 0.58 percent of the total blood volume by weight. On the other hand, total blood water is 77.33 percent of the total blood volume by weight. Blood lipid, therefore, can dissolve only $(0.066 \times 0.0058) = 0.0004$ ml N₂/ml whole blood, while blood water can dissolve $(0.0127 \times 0.7733) = 0.0098$ ml N₂/ml whole blood. Therefore, in spite of the high lipid-water solubility ratio, blood water exerts 25 times greater influence than blood lipid in dissolving nitrogen. Even after massive lipid meals, total plasma lipids increase by less than a factor of 2.²⁹⁷ Postprandial lipids would, therefore, not be expected to have much effect on the

nitrogen-carrying capacity of the blood. This conclusion has been borne out in U.S. Air Corps experience during World War II.⁸⁵

Diffusion of Inert Gases in Liquids

The diffusivity of inert gases through liquid solvents is another biochemical parameter of importance in this study. Unfortunately, the determination of diffusion coefficients is fraught with difficulties and uncertainties. The most complete study of the inert-gas diffusion has been reported by Jones.²⁴⁹ His values for relative diffusion coefficients (helium = 1.0) through a gelatin-water gel are recorded in table 2 for all gases except neon. The value for neon was calculated from Graham's law, which states that the diffusivities of inert gases are inversely proportional to the square root of the densities or the molecular weights. Unfortunately, the experimental method and absolute values were not discussed in his report. There are very little data on the diffusion constants through other physiologically significant liquids. The data in table 2 for olive oil, lard, serum, and water were obtained from three sources,^{132, 155, 191} with appropriate extrapolation to 37° C conditions. Unfortunately, much of the data in the older literature were obtained by methods that have been shown to be, for one reason or another, open to experimental error. Lard appears to be less permeable to nitrogen by a factor of 2 than is olive oil. Serum appears to be 0.70 as permeable as water and three times more permeable than oils to this gas. The lipid and water determinations, however, were performed by different techniques and the validity of the comparison is open to question. It is of interest that, empirically, helium appears to be a little more than two times more diffusible through water than is nitrogen, but three times more diffusible through gelatin. The interactions between the specific gases and the protein gel may be responsible for this difference, but, once again, variations in experimental techniques may also be a cause of the discrepancy. That an agar gel should have a negligibly small effect on the diffusion coefficient of readily diffusible substances has been deduced by Liesgang²⁸⁵ and demonstrated by Eggleton et al.¹⁵⁵ The same

should hold for protein gels, though the interaction of inert gas with proteins may somewhat alter these calculations.^{382, 383}

The diffusibility of helium through serum was calculated from the findings of Gertz and Loeschcke¹⁹¹ that each inert gas appears to be 1.3 times more diffusible through water than through serum. According to Graham's law, the ratio of diffusibility through lipid to that through aqueous solvents should be constant for each inert gas. This concept should allow calculation of the many deficiencies for diffusion of the inert gases present in table 2. In general, there is an inverse relationship between the diffusion constant of a solute in a solvent system and the viscosity of the system, a relation for which Einstein has provided a theoretical basis.¹⁵⁶ The exceptions to this hypothesis found by Davidson et al.¹³² in their study of diffusion in different lipids may result only from anomalies such as the presence of crystalline solid esters within the lard system. Peterson³³⁹ has pointed out that in dealing with lipid systems, diffusion theory that holds for aqueous systems does not appear to be fully applicable. He feels that there may well be lipid surface-energy barriers and convective anomalies which have caused his preliminary empirical findings to deviate from theory. Although extrapolation of diffusibility of nitrogen in different solvents to that of other inert gases is not fully warranted from the data available, it is felt that for the purposes of this paper such an approach will be adequate. In table 2, the values in parentheses were calculated from the nitrogen data using Graham's law. It can be seen that the empirical values for helium are somewhat lower than the values calculated from the nitrogen data.

The diffusion of inert gases through organic membranes is an interesting area for which there are little empirical data. Theoretical analyses of diffusion constants and solubility constants from fundamental properties of gases and barriers have met with limited success although certain general patterns have been determined.^{46, 430, 431} Breakdown of theory probably arises from the fact that solution of gases in membranes does not follow Henry's law for dilute solutions. The rate of permeation increases more rapidly with pressure than predicted by the equation.

The empirical data of Brubaker and Kammermeyer⁷⁸ are of interest in this regard.

Prediction of the temperature coefficient of diffusivity in any given gas-solvent system is most difficult.⁴¹⁹ In general, this value is determined by the activation energy of diffusion which has to be supplied to the solvent to separate the solvent molecules a sufficient distance to permit the gas molecule to be displaced or to make for itself a new hole. This energy is a function of the kinetic energy of both the gas and the solvent. As expected, the larger the gas molecule, the greater is the activation energy, since larger openings will be required between solvent molecules for passage of the gas. The stronger the intermolecular binding energy of the solvent (heat of evaporation), the greater is the activation energy. Thus, presence of polar groups or methyl groups in the solvent could increase the activation energy of diffusion and generally decrease the rate of diffusion and permeability of an inert gas through the solvent.

CHEMICAL REACTIONS OF INERT GASES

In the section on atomic structure, it was indicated that stable fluoride compounds of xenon and radon have been prepared, and unstable krypton oxide has been demonstrated by spectroscopy. It was also pointed out that these compounds are unstable in aqueous systems. Helium and neon should be unable to form compounds by the *d*-orbital mechanism. Argon has the potential but the compounds are probably too unstable to be isolated by present techniques. Diatomic molecules of inert gases exist only in high-pressure systems, as do short-lived metal-inert gas molecules and inert gas ions in electric discharge systems.¹¹⁰

Ionic or covalent bonds between inert gases and biological fluids probably do not exist under physiological conditions. There is a far greater possibility, however, of inert gases forming clathrate or hydrate compounds in biological systems or reacting with protein materials through van der Waals bonds. "Clathrate" is the name given to a class of compounds in which the small atoms or molecules of one substance, called guests, are held by van der Waals forces in crystalline cages formed by the molecules of a second substance, called the host. There ap-

pear to be no strong chemical bonds, but there is definite stoichiometry. Clathrates can be designated by a maximum composition formula, $nH \cdot mG$, where n = number of host molecules H per unit cage; and m is the maximum number of guest molecules G that can be held in a single cage.

Villard⁴³⁵ and de Forcrand¹⁷⁶ were the first to prepare hydrates (water clathrates) of argon, xenon, and krypton. These crystals have $n = 46$ and $m = 8$, or a maximum of less than 6 host atoms per guest molecule. No hydrates of helium or neon have been formed even under high pressure. The properties of the hydrates are seen in table 4.

TABLE 4.—*Properties of Inert-Gas Hydrates*
[AFTER COOK¹¹⁰]

Property	Hydrate of —			
	Argon	Krypton	Xenon	Radon
Decompression temperature at 1 atm pressure, °C.....	-42.8	-27.8	-3.4
Dissociation pressure at 0° C, atm.....	105	14.5	1.5	1
Heat of formation (1g 5.75 H ₂ O ^a), kcal/mole.....		13.9	16.7

^a Ig is any inert-gas atom.

It is seen that the stability of the hydrate increases as the atomic number of the guests increases. Since the heat of formation of ice from liquid is 8.3 kcal/mole, the krypton hydrate has a binding energy of gas to hydrate of $13.9 - 8.3 = 5.6$ kcal/mole, and xenon hydrate has $16.7 - 8.3 = 8.4$ kcal/mole. These binding energies are in the van der Waals range and approximate the heats of adsorption of inert gases onto charcoal. The actual structure of the hydrate has been presented in the elegant studies of von Stackelberg and coworkers,^{322, 409} Barrer and Stuart,²³ and van der Waals and Platteeuw.⁴³⁸ The two types of host lattice built from a continuous framework of water molecules in tetrahedral coordination have been defined and examined thermodynamically. The treatment, however, is quite beyond the scope of this study.

Other inert-gas clathrates have been synthesized.¹¹⁰ The β -hydroquinone clathrate is formed by recrystallization of α -hydroquinone from methanol in the presence of guest atoms which stabilize the β -cage form and may form a model for aromatic clathrates in biological systems. Argon, krypton, and xenon clathrates have been formed. Helium atoms are thought to be too small and too difficult to polarize for van der Waals bonding in this clathrate. The neon atom is borderline; its clathrate could be formed at a pressure of gas in excess of 160 atmospheres. Phenol clathrates of argon, krypton, and xenon exist as do clathrates of other cage-forming hosts.^{23, 322}

The exact role of gas hydrate or other hydrogen-bonded clathrate structures in biological

systems is still open to question. The role of these structures in anesthesia and other physiological phenomena is discussed in chapter 3. The potential for hydrate and organic clathrate structures of all types is present in the biological system.^{131, 165, 181, 265, 325, 326} However, the very high dissociation pressures of even the most stable inert gas-clathrate structures cast some doubt on their role in the physiological or pharmacological process. One would have to postulate that proteins and other structures within the cells can stabilize the water structure to allow inert gas hydrates at pressures lower than required for pure water systems⁶⁰ or that direct adsorption of gases onto proteins and other cellular components may play a direct role in biological activity.^{58, 382, 383, 384, 167, 168}

Role of Inert Gases in Decompression Sickness

The little Bubbles generated upon the absence of the Air in the Blood, juyces, and soft parts of the Body, may be their Vast number, and their conspiring distention, variously streighten in some places, and stretch in others, the Vessels, especially the smaller ones, that convey the Blood and Nourishment; and so by choaking up some passages. and vitiating the figure of others, disturbe or hinder the due circulation of the Blood!

Robert Boyle, 1670

AMONG THE RISKS of space operations the hazard of decompression looms large. Decompression of space cabins by meteoroid penetrations, internal explosions, or military projectiles is an ever-present danger. Decompression of space suits by meteoroids, tears caused by vehicular and planetary structures, and failure of suit joints and tubing is also an ever-present possibility. It would thus appear that the decompression problem has a direct and important bearing on the selection of space-cabin atmospheres.

It has been known for decades that the 100 percent oxygen environment is the safest from which to decompress. Since 100 percent oxygen does present many other problems in space cabins,^{186, 369, 370} however, this optimum may have to be compromised by the addition of inert gases to the cabin atmosphere. This chapter is, therefore, devoted to an analysis of the relative effects of the different inert gases during a decompression event. The first section of this chapter presents a theoretical analysis of the gas-dependent bubble factors in "nonexplosive" decompression sickness to altitudes below 60 000 feet. The next section is a review of empirical and operational data on inert-gas effects in altitude and diving decompression sickness. The third section reviews the theory of ascent schedules in diving and presents attempts to control decompression sickness through use of computer programs. These programs are re-

lated to the denitrogenation problem in altitude decompression. The fourth section covers the gas-dependent factors in "explosive" decompression and the ebullism syndrome. Finally, a review of all of the above data is presented in an attempt to establish inert-gas preference for minimizing decompression sickness in space cabins.

ANALYSIS OF BUBBLE FORMATION IN DECOMPRESSION SICKNESS

The discussion that follows is a review and an extension of an analysis of the general problem presented several years ago by Roth.³⁶⁸ A theoretical analysis of gas-bubble formation in the body will be followed by a review of the empirical data that define the boundaries of the generalized model. This review is far from exhaustive—only those aspects of the vast literature on decompression sickness that have a very specific relation to the space-cabin problem are covered.

Our basic understanding of decompression sickness has been retarded by lack of a definitive theoretical framework. In recent years advances in cavitation theory, bubble physics, and multiphase flow theory have not been systematically applied to parallel phenomena in the decompression syndrome. Since the specific role of inert gases in this syndrome can best be understood in the framework of these physical theories, a brief review is presented. An attempt

is made to involve only aspects of those theories which have specific relationship to the problem at hand. Bibliographic notations of the broader aspects of the problems are presented for the interested reader.

Physical Factors Controlling Growth of Bubbles in Biological Systems

It is reasonably well established that the source of pain, discomfort, and disability in decompression sickness arises from the appearance of gas bubbles within supersaturated body fluids after the decompression event.^{186, 189} The likelihood of symptoms depends on the number of bubbles, their size, and their position. The greater the supersaturation ratio, the greater the number of bubbles.³⁴² The basic quantitative link between bubble size and the physiological events has been summarized by Nims.³²⁹ In brief, a gas bubble growing in tissue must displace and deform adjacent structures or obstruct fluid flow and tissue nutrition to trigger off pain responses or compromise function in these structures. The equilibrium forces acting on the bubble within the tissue may be given by the expression

$$P_B = H + (2\lambda/r) + D \quad (1)$$

where

- P_B sum of the partial pressures of the gases, dynes/cm²
- H hydrostatic pressure of the fluid surrounding the bubble and independent of the size of the bubble, dynes/cm²
- λ gas-water interface tension, dynes/cm²
- r radius of bubble, cm
- D deformation pressure of bubble, a function of bubble volume, dynes/cm²

The value of $2\lambda/r$ represents the pressure exerted by the surface tension on the bubble. The hydrostatic pressure H is the sum of the ambient pressure P_A on the body and the tissue turgor pressure P_T or blood pressure, and is independent of bubble size. The deformation pressure D is dependent on bubble volume. When the bubble is of such size that D exceeds the value required for pain threshold or its ischemic and metabolic equivalent, symptoms are noted.

This relationship may be further expanded by partition of the total barometric pressure to include the partial pressure of all gases in the bubble (σP):

$$P_B = \sigma P = p_{N_2} + p_{CO_2} + p_{O_2} + p_{H_2O} + p_X \quad (2)$$

where X represents any other inert gas, or gases, in the bubble. The expanded form of the static equilibrium equation may be expressed thus:

$$P_b = \sigma P = p_{N_2} + p_{CO_2} + p_{O_2} + p_{H_2O} + p_X \\ = (P_A + P_T) + (2\lambda/r) + D \quad (3)$$

From this relationship it can be seen that the bubble radius can be modified by change in several factors. For a static bubble

$$r = (2\lambda/\sigma P) - H$$

If the bubble encounters an environment where $P_B < \sigma P$, the following hold true

$$\sigma P > H + (2\lambda/r); \quad \sigma P - H > (2\lambda/r); \\ r > (2\lambda/\sigma P) - H$$

and the bubble expands. Alternatively, if $P_B > \sigma P$, $r < (2\lambda/\sigma P) - H$, and the bubble shrinks. If a bubble passes into a condition where $H > \sigma P$, the bubble will shrink, or if it passes into a region where $H < \sigma P - (2\lambda/r)$, it will expand. Thus changes in the gaseous pressures or hydrostatic pressures determine changes in bubble radius. It must be remembered that during a decompression-recompression cycle, any of these changes may occur to either an intravascular or extravascular bubble.

The focal events responsible for the initial production of the bubbles, while of immense theoretical interest, do not relate specifically to the problem at hand. As discussed by Harvey,²¹⁴ Dean,¹³⁵ Pease and Blinks,³³⁸ and more recently by Webster⁴⁴⁷ and Liebermann,²⁸⁴ bubbles may arise in solution from preformed micronuclei or *de novo* from cavitation events. Microbubbles of $< 10^{-3}$ to 10^{-5} centimeter radius are unstable at 1 atmosphere pressure (absolute) because of the high $2\lambda/r$ factor and will tend to disappear spontaneously. However, aspherical bubbles

sequestered in acutely angled, cone-shaped cavities of container walls or in tiny hydrophobic niches within biological molecular structures can remain of stable size and persist. As mentioned above, changes in the environment can cause expansion or shrinkage of the bubble. As Harvey pointed out, in the absence of preformed nuclei, Brownian motion of liquids about the apex of conical cavities in wall structures can theoretically initiate micronuclei within the molecular dimensions of the apex where the apical volume is not large compared with the volume of the individual molecules. This would probably hold true in the niches produced by the tertiary structure of macromolecules within biological systems.

A final method of micronucleus stabilization has been proposed by Fox and Herzfeld,¹⁷⁸ who suggest that bubbles may be surrounded by a rigid permeable skin composed of organic materials present in the liquid. Such skin could act either as an elastic shell in sustaining a pressure differential across the wall or as a diffusion barrier. The results of measurements of the dissolution rate of small air bubbles in water suggests that the coefficient of diffusion of air through the "skin" is about one-eighth that of air through pure water.²⁹⁸ This mechanism could be of importance in biological systems. However, the experiments of McElroy and Whiteley²⁹⁵ cast doubt on the presence of preformed micronuclei in cats.

In spite of these very plausible stabilization mechanisms, it appears that formation of cavities by muscle and joint movement or in vortices of turbulent zones of blood flow is a more probable source of bubble nuclei. The dynamics of the cavitation process has been of chronic concern to hydrodynamicists and designers of underwater propellers and hydrofoil systems. Excellent reviews of this subject are available^{351, 133, 349} for those interested in the initial events of bubble formation. The work of Stonemetz on cavitation in pipe bends is especially pertinent.⁴¹⁴ For the purposes of this study, it is sufficient to say that in decompression sickness, the early period of bubble growth is controlled by the large local decreases in hydrostatic pressure forming the original cavity within the liquid. The first event that occurs is probably

the formation of a water-vapor cavity, or vaporous cavitation.

For a very short time a pure vapor bubble is present. As the radius expands, growth of the bubble is driven by the decreasing surface tension force, $2\lambda/r$. An excellent theoretical analysis of this vapor phase growth has been presented by Plesset.^{349, 350} In the presence of supersaturated gaseous components dissolved in the liquid, the bubble will continue to grow by inward diffusion of gas. In the absence of supersaturation of the gaseous components dissolved in the liquid, the vapor cavity will eventually collapse with mass diffusion of gas out of the bubble, the dissolution being driven by the steadily decreasing radius in the surface tension factor $2\lambda/r$. In the presence of gaseous supersaturation, as is found in a decompression event, the bubble will continue to grow, being fed by the gases in the surrounding liquid.

In decompression sickness, the supersaturation factor is brought about by reduction in ambient pressure P_A with a resultant decrease in the free hydrostatic pressure H . The equilibrium defined by equation (3) would therefore be upset, and diffusion of gas from the liquid to the vaporous cavity would result. The bubble radius would continue to increase. The simultaneous increase of tissue deformation pressure D would finally control the ultimate bubble size. In "loose" tissue, the volume-elastic properties would allow great bubble size with no pain. In "tight" tissue, the maximum bubble size would be reached rather quickly, and the internal bubble pressure would increase at constant volume.

The role of inert-gas factors during the growth phase of a bubble can be understood only after a thorough analysis of growth dynamics. Gas molecules will move into the initial water vapor cavity at an initial rate proportional to the total amount of gas available at the liquid vapor interface. This rate will be related to the solubilities of the gases. At first, solubility should control the rate of gas buildup, but with the passage of time, the bubble gas compositions should change to proportions of gas representing relative tensions. The Bunsen coefficients for nitrogen, oxygen, and carbon dioxide at 37° C are $N_2=0.013$, $O_2=0.024$, and $CO_2=0.561$. Since the molec-

ular sizes and diffusion coefficients of these gases are similar, one would expect that the early bubbles formed at altitude would contain mostly carbon dioxide. The *in vitro* studies of Harvey,²¹⁴ Dean,¹³⁵ and Metschul³¹² tend to confirm this general point as do the physiological studies of Blinks et al.⁶⁶ The solubility of none of the inert gases in table 2 approaches that of carbon dioxide, and so the same rule should hold when another inert gas is substituted for nitrogen in the ambient atmosphere.

As the bubble continues to grow, both the amount of the gas in the surrounding liquid and the diffusion constant of the gas determine the rate of bubble growth. Analytic studies of bubble growth rate have been performed for many years. The early derivations by Mache²⁹⁶ and Bateman and Lang²⁷ have been followed by the equations of Harvey²¹⁴ and Nims.³²⁹ A very rigorous analysis of bubble growth factors has been presented by Epstein and Plesset,¹⁵⁹ and an elegant mathematical review of the generalized bubble growth problem was presented by Keller.²⁵¹ For the purposes of the present discussion, however, the formalism of the last two references is simplified by a more direct derivation from the equation of state for ideal gases. This approach was suggested by Nims.³³⁰

For a mixture of gases, the ideal gas law states that

$$PV = RT \sum_g n_g \quad (4)$$

where

- P pressure
- V volume
- n_g number of moles of a specific gas in the bubble
- R gas constant
- T absolute temperature
- g each specific gas

The pressure-volume history of a bubble can be expressed by the total derivative of this equation with respect to time:

$$P \frac{dV}{dt} + V \frac{dP}{dt} = RT \sum_g \frac{dn_g}{dt} \quad (5)$$

The rate of change of the number of moles of

gas in the bubble can be approximated by Fick's law of diffusion written in the form

$$\frac{dn_g}{dt} = AD_g \frac{\Delta C_g}{\Delta x}$$

where

- A the surface area of the bubble
- D_g the Fick diffusion coefficient
- $\frac{\Delta C_g}{\Delta x}$ the concentration gradient of the gas from the tissue to the bubble along the diffusion of path length x

Since Henry's law states that

$$C_g = \alpha_g P_g$$

where

- α_g solubility of gas
- P_g pressure of gas

the concentration gradient $\Delta C_g/\Delta x$ can be converted to a factor involving the pressure gradient between tissue and bubble

$$\alpha_g \frac{\Delta P_g}{\Delta x}$$

and equation (5) can be expanded to

$$P \frac{dV}{dt} + V \frac{dP}{dt} = ART \sum_g \alpha_g D_g \frac{\Delta P_g}{\Delta x} \quad (6)$$

Solving this equation under boundary conditions existing at various sites within the body yields a very complex mathematical relation that requires some simplification. Bubbles expanding in the blood stream would be producing little or no deformation pressure (D) (see eq. (1)) in the surrounding tissues and would be increasing in volume with essentially no change in pressure. This pressure according to equation (3) would be represented by the sum of the external atmospheric pressure, the blood pressure, and the pressure exerted by surface tension factor ($2\lambda/r$). Symptoms of ischemic pain or physiological malfunction would arise when the volume of the bubble is increased to the point where the blood vessel was occluded. If only one gas were the major offender, the expanding

volume could be described in terms of this one gas g by the equation

$$\frac{dV_g}{dt} = \frac{ART\alpha_g D_g \Delta P_g}{P\Delta x} \quad (7)$$

This is essentially the equation used by Bateman and Lang.²⁷ This can be seen by taking the diffusion area A as that of a theoretical bubble ($4\pi r^2$); D_g is taken as their diffusion coefficient (δ); ΔP_g is $P_1 - P_2$; P is the bubble pressure ($P > 2\lambda/r$); and $1/273$ is the diffusion path length, plus all the other constants of equation (6). This results in the Bateman-Lang equation²⁷

$$\frac{dV}{dt} = \frac{4\pi r(\alpha_g \delta_g)(P_1 - P_2)}{273P} \quad (8)$$

As discussed subsequently, symptoms of decompression sickness may arise extravascularly in "tight" tissue where the tissue deformation pressure D affects the bubble growth and rapidly converts bubble dynamics to those of constant volumes and changing pressures. Equation (6) can, therefore, be written as

$$\frac{dP_g}{dt} = \frac{ART\alpha_g D_g (\Delta P_g)}{V\Delta x} \quad (9)$$

In evaluating the role of the specific inert gases in the constant volume or constant pressure bubble, one must extract those constant factors that are specifically dependent on the inert gas or gases in question. It would appear that only the $\alpha_g D_g$ factor is gas dependent. Therefore, the gas with a minimum product of solubility and diffusion coefficients in the fluid immediately surrounding the bubble would, upon decompression, produce a minimum rate of pressure or volume rise. This product, in another context, has been called the permeation coefficient (D').¹³⁹ The units of D' are in $\text{cm}^2/\text{sec}/\text{atm}$ and are physically indicative of the volume of gas (ml STPD) diffusing per unit of time (sec) across unit area (cm^2) and unit diffusion shell thickness with a difference in partial pressure of gas of 1 atmosphere in the direction of gas flow. It can be seen that $D' = \alpha D$, since $\alpha = \text{ml STPD of gas dissolved per milliliter of liquid at a partial pressure of 1 atmosphere and } D = \text{cm}^2/\text{sec}$.

The more sophisticated equations of Epstein and Plesset¹⁵⁹ and Keller²⁵¹ do not alter the basic $\alpha_g D_g$ permeation coefficient, nor do they introduce any other gas-specific considerations. The gas density factor in the Epstein-Plesset¹⁵⁹ equation is canceled by the mass per volume used as the gas concentration factor. These equations merely increase the accuracy of the analysis by accounting for the motion of the bubble boundary during expansion under constant pressure conditions. Only the increasing surface area between phases is accounted for. The effect of the expansion motion on the diffusion process itself is neglected as it was in the development presented above. The translatory motion of the free bubble arising from buoyancy factors is accounted for in the Epstein-Plesset analysis. Such factors may well influence bubble growth intravascularly and could be gas specific, since they would alter the diffusion layer around the bubble. They would tend to decrease the role of the diffusion factor by providing a mechanical mixing factor. In as complicated a fluid flow system as the vascular tree, rigorous quantitative analysis of the total mixing factor would be too difficult. In any event, there appears to be an "effective diffusion shell" about a bubble even in a well-mixed liquid. An interesting calculation from the data of Wyman et al.⁴⁷⁰ indicates that the thickness of the "effective diffusion shell" about a bubble in water is 3.3×10^{-3} cm. This does not mean that there is a sharply defined water shell supporting a uniform diffusion gradient around the bubble, but it suggests that the mixing of water is practically complete up to a distance from the air-water interface of the same order of magnitude as the calculated thickness of the shell. The lipid and protein film about bubbles *in vivo* may alter this shell thickness by an undetermined factor.²⁹⁸

It appears appropriate at this point to present a quantitative example of what might be the actual bubble growth rate within the aqueous phase of the body of an air bubble at constant pressure using the Epstein-Plesset analysis.¹⁵⁹ Figure 4 represents the calculated time-size history of a bubble forming in a water solution supersaturated with air. The ordinate is in the dimensionless form $\epsilon = r/r_0$ or the ratio of final radius to initial radius. The abscissa is also a dimen-

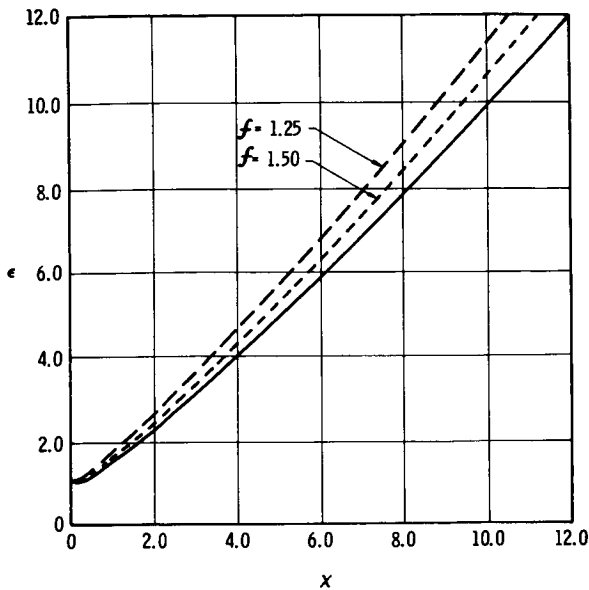


FIGURE 4.—Radius-time relation for growing bubbles neglecting surface tension. (AFTER EPSTEIN AND PLESSET.¹⁵⁹)

sionless variable (χ) which is proportional to the square root of time ($t^{1/2}$). The curves neglect the relatively small surface tension factor.

The solid curve represents a simplified quasi-static solution of the problem, and gives the bubble growth form for any supersaturated solution. The dashed curves are a more accurate analysis dependent on a concentration/gas density ratio of 0.02. They are specific for supersaturation ratios f or ratios of the dissolved gas concentration to that of a saturated solution. Table 5 represents the actual time (t) to give a growth of air bubbles in water at 22° C from an original radius r_0 to $10r_0$. Since the original

radius determines the time to reach $10r_0$, results for two radii ($r_0 = 10^{-3}$ cm and $r_0 = 10^{-2}$ cm) have been presented. The data have been calculated for supersaturation ratios f of 1.25 to 5.0. The role of surface tension and other second-order bubble factors are demonstrated by the values t , t_a , and t_s . In calculating column t , surface tension is neglected, but second-order factors which tend to increase rate of growth are added. Column t_a also neglects surface tension and represents quasi-static approximation shown as the solid curve of figure 4. Column t_s is the quasi-static approximation including surface tension. It is seen that the surface tension and second-order dynamic factors do not greatly influence the time required for tenfold growth.

As would be expected, a smaller bubble takes less time to increase tenfold in radius, since its radius is increasing at a relatively greater rate than is that of the larger bubble. Surface tension plays a smaller role in the larger bubble. In altitude decompressions, the supersaturation ratios should lie in the 2 to 5 range, probably closer to 2. From table 5 it is seen that with a decompression ratio of 2, a constant pressure bubble of air of radius 10^{-3} cm would take about 110 to 130 seconds to increase tenfold in size, while a bubble of radius 10^{-2} cm would take about 12 400 seconds to do the same.

Times are calculated for 22° C instead of 37° C. However, it is to be expected that the rate of growth of a bubble in water would be relatively independent of temperature. As mentioned above, the diffusion coefficients of inert gases in water decrease with temperature. That the two effects almost cancel each other has been

TABLE 5.—Times of Growth of Air Bubbles in Water From r_0 to $10r_0$ at 22° C
[AFTER EPSTEIN AND PLESSET¹⁵⁹]

f	$r_0 = 10^{-3}$ cm			$r_0 = 10^{-2}$ cm	
	t , sec	t_a , sec	t_s , sec	t_a , sec	t_s , sec
1.25	466	496	567	496×10^2	501×10^2
1.50	228	248	266	248	249
1.75	149	165	174	165	166
2.00	110	124	129	124	124
5.00	24.6	30.9	31.7	30.9	31.0

shown by Wyman et al.⁴⁷⁰ Since the equation of state for ideal gases and its derivatives (eqs. (8) and (9)), related to absolute temperature, the rate of bubble growth or pressure increase would be expected to be proportional to the absolute temperature. There would, therefore, be little difference between these theoretical growth values at 22° C and those at 37° C. There would be even less variation from point to point in the body. The role of protein and lipid films about a bubble forming *in vivo* is as yet undetermined, but it would most certainly affect the growth rate of the smaller bubbles by reducing both surface tension and diffusion.²⁹⁸

Correlation of Bubble and Symptom History

In the living organism, there is a physiological event that modifies the actual growth rate of the bubble and controls the peak size and rate of decay. This modifying factor is the circulation of only slightly supersaturated blood through the tissue or intravascular site where the bubble is formed. After a decompression event the blood stream very quickly gives up its inert gas overload to the lungs.^{177, 74} The inert gas in this fluid becomes rapidly equilibrated with the ambient gas pressure, and, on the average, remains only slightly supersaturated.

The slight supersaturation results from the constant uptake of extra gas in the highly supersaturated tissues. As soon as a bubble is formed, the slightly supersaturated blood will compete with the bubble for gas from the highly supersaturated tissue. Before this competitive effect can be analyzed, it would be well to review two factors. The first is the actual relevance of the peak bubble size to the overall problem. The second is the actual site of bubble formation within the body and the gas-specific factors that control bubble decay.

As for the first factor, Nims³²⁹ attempted to correlate the history of a bubble with the pressure history of decompression sickness in a large population exposed to altitude in a pressure chamber. The formula Nims used for bubble growth did not overtly include "solubility" as a factor.^{329, p. 200} Nims, however, has related to the author that the "apparent diffusion constant" k_2 of this formula was meant to include all of the factors of the term

$$\frac{RT\alpha_g D_g}{V\Delta x}$$

in equation (9) and so, in reality, does have a solubility factor. Nims developed the equation relating the rate of symptom development to the increase and decay of pressure in a bubble of constant volume as

$$\begin{aligned} \frac{d(N_s/N)}{dt} &= C(D - D^*) = C(p_{N_2} - p_{N_2}^*) \\ &= C \left[\frac{k_2 \ 0p_t}{k_2 - k_1} e^{-k_1 t} - e^{-k_2 t} \right. \\ &\quad \left. + \ 0p_{N_2} e^{-k_2 t} - p_{N_2}^* \right] \quad (10) \end{aligned}$$

where

N_s	number of subjects experiencing symptoms in time interval t out of a total population, N
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, assuming factors of interfacial tension, hydrostatic pressure, and minor gas tensions are constant
$p_{N_2}^*$	partial pressure of nitrogen in tissues when deformation pressure reaches threshold, or when $D = D^*$
t	time
k_2	apparent diffusion constant between bubble and tissues
k_1	apparent diffusion constant between tissues and alveolar air
$0p_t$	partial pressure of nitrogen in tissue fluids prior to decompression.

The actual history of decompression symptoms in a population exposed to altitude also suggests a growth and decay factor. It is common experience that immediately after ascent, the rate of production of symptoms is very low. The rate then increases, reaching a peak in 20 to 60 min-

utes, depending on altitude, and then declines to almost zero. It has been shown that some individuals can sit out the symptoms and be free of symptoms after a given period at altitude. The latent period, the rate of onset, and peak are functions of altitude. The data of Anthony et al.⁹ and Henry^{222, 223} illustrate this rate of onset of symptoms. In the data of Anthony et al. plotted in figure 5 the peak of 20 to 40 minutes is shown to be rather well marked. Lawrence and Hamilton²⁷⁷ have demonstrated that the rate of onset of new symptoms in a large population follows the formula:

$$\frac{d(N_s/N)}{dt} = A_1 e^{-k_1 t} - A_2 e^{-k_2 t} \quad (11)$$

where

- N_s number of subjects experiencing symptoms
 N number of subjects exposed to altitude
 t time
 A_1, A_2 constants relating to maximum potential intensity of symptoms
 k_1 velocity constant of "growth factor"
 k_2 velocity constant of "decay factor"

The equation of Nims³²⁹ relating to a bubble can be reduced to the equation of Lawrence and Hamilton²⁷⁷ by addition of the small constant $Cp_{N_2}^*$ and the inclusion of the factor $C[k_2 \rho t / (k_2 - k_1)]$ in the constant A_1 and in the inclusion of

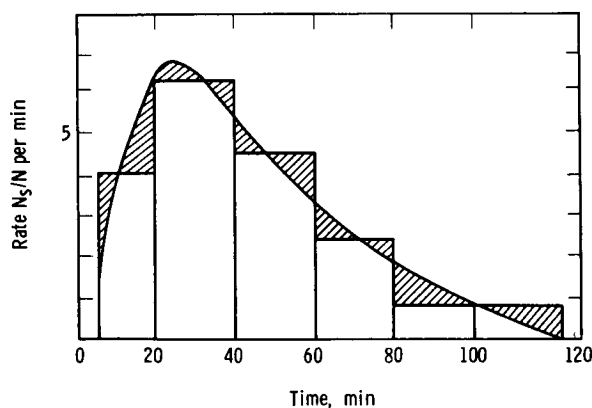


FIGURE 5.—Rate of appearance of decompression sickness in a given group at altitude as a function of exposure time. (AFTER ROTH,³⁶⁸) (DATA AFTER ANTHONY ET AL.⁹ GRAPH AFTER NIMS.³²⁹)

($A_1 - Cp_{N_2}^*$) in the constant A_2 . This suggests that analysis of the growth and decay factors of idealized bubbles within an organism should be an index of the symptom pattern of that organism after decompression. It also suggests that for the present analysis, attention should be paid to the gas-specific factors in the organism which controls the decay process.

Unfortunately, these factors have been probably the most controversial aspects of the decompression syndrome. They are intimately connected with the specific symptomatology of this syndrome which has been well covered in great statistical and descriptive detail by many reviews.^{2, 61, 62, 169, 203, 258, 453} An exhaustive review is beyond the scope of this report. A brief review of the salient features will, however, help to clarify some of the issues to follow.

Pathological Physiology of Decompression Symptoms

Expansion of gas pockets in the teeth, sinuses, and gastrointestinal tract may be experienced at altitudes of 2000 feet. These are called the "trapped gas syndromes." Prolonged exposure to altitudes above 22 000 feet and occasionally to altitudes as low as 18 000 feet¹⁸⁵ may result in the appearance of bends, chokes, circulatory collapse, skin changes, and neurological disorders. These are manifestations of bubble formation from dissolved gases.

BENDS

The most common symptom, pain in the locomotor system, is referred to as "bends." This pain usually begins in the periarticular tissue and extends distally along the bone shaft. Pain tends to occur in joints that are being flexed.⁴⁶⁹ It is deep and poorly localized with periods of waxing and waning. Relief is obtained by relaxation of the part or application of external pressure to the overlying tissues. After sufficient time at altitude, crepitation is often noted along many tendon sheaths in which gas bubbles can actually be seen roentgenographically.⁸⁶ Bubbles are found by X-ray with certainty in the synovial space of the joints, in bursae, and in tendon sheaths and with less certainty in the fascial planes and connective tissue spaces in muscles and in tissue spaces around blood vessels. Symptoms may be present in the absence of X-ray bubbles and,

conversely, X-ray bubbles may be present in the absence of symptoms. As demonstrated in animals, some of the thin, radiolucent lines and diffuse areas described as extravascular bubbles by X-ray may actually be long, cylindrical intravascular bubbles.⁹⁵ Presence of bubbles in capillaries and veins leading from exercising muscles^{66, 95, 213} also suggests that intravascular bubbles at tendon insertions may also be a cause of pain in bends.⁸⁶ Therefore, it can be said that both intravascular and extravascular bubbles may play a role in the most common symptom of decompression sickness.

CHOKES

The next most common symptom complex is chokes. Chokes refers to a syndrome of chest pain, cough, and respiratory distress. Longer altitude exposure is usually required to produce chokes than that required for bends. Chokes begins with a substernal burning pain during deep inspiration which is relieved by shallow breathing. It gradually becomes more severe and constant. Paroxysms of coughing become more frequent and are followed by cyanosis, anxiety, syncope, and shock. Interestingly, auscultation, roentgenograms, and electrocardiograms show no very specific abnormalities. Strangely, the pharynx and larynx may show a fiery red mucosa which persists for several hours after descent. Chokes symptoms may persist several hours after descent and may be precipitated during this period by tobacco smoke or deep inhalation. Pulmonary congestion with rales may also appear after the flight.

Chokes is thought to be part of a reflex phenomenon resulting from irritation of the pulmonary tissues when gas emboli from the periphery cause obstruction of pulmonary arterioles and capillaries. There has been no direct demonstration of bubbles in the pulmonary vascular bed of humans during chokes symptoms, although enlargement of the right side of the heart has been demonstrated.⁸⁶ Increased pulmonary capillary resistance could have been due to blockage by the bubbles themselves or to reflex pulmonary vasoconstriction caused by irritation by the bubbles. Bubbles have been found in the right side of the heart and pulmonary vessels in caisson workers who succumbed to decompression sick-

ness. The clinical syndrome resulting from intravenous injection of air in humans is extremely variable, but often resembles chokes. Hetherington and Miller have simulated the choke syndrome by injection of intravenous nitrogen in cats,²³⁰ and Leverett et al. in dogs.²⁸² In guinea pigs, the gas bubbles in the bloodstream did not reach the capillary bed. The smallest vessels occluded were 40 μ in diameter.⁹⁵ It is doubtful that oxygen toxicity, which can give symptoms similar to chokes, is responsible for the chokes syndrome.^{174, 369} The role of fat emboli reaching the lung from disrupted adipose tissue as a cause of chokes is controversial^{101, 216, 459} and is discussed subsequently. In spite of the uncertainties remaining, air emboli in the pulmonary vasculature appear to be the most probable precipitating factor in the chokes syndrome.

SKIN MANIFESTATIONS

Skin manifestations at altitude are in themselves mild and may be divided into four types:

(1) A subjective cold sensation may be noted during ascent which may or may not be attributable to decompression per se.

(2) Tiny intracutaneous blebs may occur and cause intermittent prickling, itching, or burning. These may be gases trapped in glands of the skin.

(3) Subcutaneous emphysema, a rare finding, may appear in the forearms or thighs. It is accompanied by moderate pain and tenderness, causes crepitation, and can be seen roentgenographically.

(4) Skin lesions begin as a small area of pale cyanotic mottling. They spread peripherally with an irregular edge. The pale center becomes erythematous and warm. Mild to moderate pain and tenderness are noted, but no crepitation. During descent the lesion becomes diffusely red and hot, disappearing in 3 to 5 minutes after descent. Four to six hours after descent, the involved area again becomes tender. The discomfort is maximal at 24 to 36 hours after the flight, at which time other signs of inflammation are occasionally seen. These lesions appear most frequently in subjects susceptible to the chokes and are usually found on the chest and shoulders. Subcutaneous edema may persist for several days.

Except for the cold sensation, skin lesions usually occur only after prolonged altitude exposure and are associated with or precede more serious manifestations of decompression sickness. About 10 percent of those cases going on to neurocirculatory collapse present previous skin changes.

Emboli to the skin appear to be the most probable mechanism. Dilatation of superficial venules and capillaries adjacent to areas of severe vasoconstriction is responsible for the cyanotic mottled appearance. Capillary hemorrhage is seen occasionally, although it occurs more frequently after exposure to high pressures. While subcutaneous fat may be a primary source of the gas, it would appear more probable that the emboli to the cutaneous vessels come down the arterial tree from arteriovenous shunts in the pulmonary circulation or through patent foramen ovale.¹⁸⁹ In necropsied human lungs, glass spheres of 10 to 250 μ can actually be passed from the pulmonary artery to the pulmonary vein.⁴²³

NEUROCIRCULATORY MANIFESTATIONS

Neurocirculatory manifestations of dysbarism have been classified in several ways.^{2, 3, 61, 185} The following discussion taken from Ferris and Engel¹⁶⁹ is oriented more toward specific mechanisms. Cardiovascular reactions include four types:

(1) *Vasodepressor syncope*. This is the most common type of syncopal reaction. A fall in blood pressure occurs, followed by the usual symptoms of hypotension. The hypotension is relieved by assuming a recumbent position. In some cases of collapse related to altitude exposure, frank cardiac disturbances are seen: one coronary occlusion, one paroxysmal auricular fibrillation, and one case of shortening of the PR interval with a bundle branch block have been observed.³³

(2) *Nonvasodepressor syncope*. The blood pressure does not decrease, and lightheadedness is noted. This fluctuates in intensity over a considerable period of time before requiring descent. Actual loss of consciousness is rare. The condition is almost always associated with chokes and is usually correlated with paroxysms of coughing and cyanosis.

(3) *Hyperventilation*. Usually, hypocapnic symptoms are numbness, tingling, lightheadedness, reduction in consciousness, and tetany.

(4) *Postflight syncopal reactions*. Most cases are end results of vasodepressor syncope which began at altitude and subsided within 30 minutes. In rare cases, severe and progressive peripheral vascular collapse develops in 1 to 5 hours after the flight. This reaction may or may not have been preceded by other syncopal complaints. Signs and symptoms of shock with or without focal neurological findings are seen. Delirium and coma are more common when neurological findings are present. All fatalities following altitude exposure are preceded by delayed shock. Such shock usually develops in subjects who have experienced severe decompression sickness (especially severe chokes), but may be preceded by few or no symptoms.

Three types of neurologic manifestations may be seen:^{174, 305, 306}

(1) Convulsions occur due to cerebral anoxemia accompanying hypotensive episodes.

(2) Weakness of an extremity simulating a neurologic lesion can be seen with pain accompanying bends.

(3) Focal neurologic signs usually accompany only cases in which other manifestations of decompression sickness are widespread. Homonymous scintillating scotomata with central sparing are the most common finding.⁴⁵² Other possible findings include hemiparesis, monoparesis, focal or general convulsions, various aphasias, sensory disturbances, and sensorial clouding. A throbbing headache frequently develops on the side contralateral to the neurologic lesions after such lesions disappear. The headache may become quite intense and may be associated with nausea, vomiting, prostration, photophobia, and increased pain from movement. It usually lasts from 1 to 12 hours. Headache has been noted occasionally without antecedent neurologic symptoms. The incidence of spontaneous migraine is higher in individuals who are susceptible to headaches and scotomata. Similar electroencephalographic and neurologic findings have been seen in spontaneous migraine and headache-scotomata syndrome of altitude.^{174, 305, 306} The electroencephalogram is normal in patients at altitude who show no symptoms or

only headache. Irregular slow waves are seen at foci corresponding to neurologic findings and persist until the findings disappear.

The neurocirculatory collapse syndrome appears to be primarily caused by air emboli scattered throughout the body via the arterial tree. Certainly the massive loss of blood plasma to the extravascular compartment often seen in the collapse syndrome is most probably triggered by bubbles in both the pulmonary and systemic arterial circulation obstructing capillary flow throughout the body.^{79, 105, 122} Spreading of bubbles from the arterial side appears to explain much of the symptomatology,³⁰⁵ although vasospasm secondary to extravascular bubbles cannot be ruled out in all cases. Indeed, a most striking aspect of the syndrome is that symptoms very often arise after descent to higher pressures. A logical explanation of this phenomenon would be the following: The persistence of bubbles after recompression is well known.^{142, 214} Gas bubbles lodging in the arterial side of the pulmonary or peripheral circulation may originally be large enough to land proximal to sites of collateral circulation.²⁶⁴ The tissues distal to the blood do not experience ischemia until the bubbles have become so reduced in size that they pass beyond the collateral circulation point. In the lung, a decrease in bubble size may also allow subsequent passage through arteriovenous anastomoses and out to the systemic circulation to produce delayed symptoms. Even the recurrence of scintillating scotoma of the same specific pattern in multiple exposures to altitude, formerly

used as an argument against the bubble origin, may be explained by turbulent sites at the branching of the cerebral vascular tree.^{44, 123, 214, 264, 379, 410, 411, 414} Bubbles preferentially generated at these sites in the cavitation centers of the vortices would tend to lodge in the same area of the occipital cortex after each altitude exposure, producing vasospasm³⁵⁴ or frank infarcts. Vasospasm secondary to extravascular bubbles appears to be a poor hypothesis in this case.

The specific role of fat and bone marrow emboli in neurocirculatory collapse is still not clear. The findings of Haymaker and Johnston,²¹⁶ Rait,³⁵⁷ Wittmer,⁴⁵⁹ Clay,¹⁰¹ and Fischer¹⁷¹ suggest that fat and bone marrow emboli do play a role in the human syndrome. The relative roles of air and fat emboli in the pathogenesis of the syndrome in humans are still open to question.³⁶⁶ Patent foramina ovale certainly would increase the potential for fat embolism. The dearth of adequate underwater dissection in past post mortem examination skews the human pathological data in favor of fat emboli as the prime factor in neurocirculatory collapse.¹⁰⁴

Recent animal studies of Henn and Wünsche²²¹ shed some light on the controversy between air and fat emboli. These investigators found that the time of ascent to altitude was critical in determining the type of emboli. Table 6 represents the specific organ embolization for rats, rabbits, and guinea pigs at different ascent rates. In ascents with durations of 20 seconds to 3 minutes at rates of 6000 m/min (20 000 ft/min) to altitudes of 18 kilometers (58 000 ft),

TABLE 6. — *Gas and Fat Embolism in Animals*
[AFTER HENN AND WÜNSCHE²²¹]

Exp. no.	Species	Time of ascent to 18 km	Gas bubbles	Fat embolism			
				Lungs	Brain	Kidney	Heart
A ₁	Rat.....	20 sec.....	++	—	—	—	—
A ₂	Rat.....	1 min.....	++	—	—	—	—
A ₃	Rat.....	2½ min.....	++	—	—	—	—
A ₄	Rat.....	3 min.....	+	—	—	+	—
A ₅	Rat.....	5 min.....	+	—	—	+	—
A ₆	Rat.....	7 min.....	(+)	—	—	+	—
A ₇	Rat.....	> 7 min.....	(+)	—	—	—	—
R.....	Rabbit.....	20 sec.....	++	(+)	—	—	—
GP.....	Guinea pig..	20 sec.....	++	(+)	—	—	—

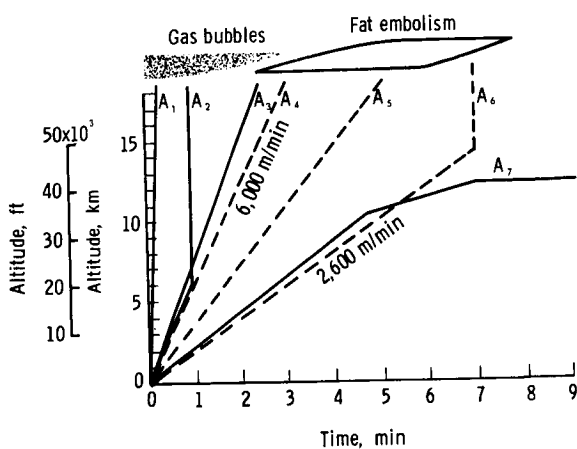


FIGURE 6.—Effect of ascent rate on the formation of gas and fat emboli in rats. (AFTER HENN AND WÜNSCHE.²²¹)

gas bubbles were found in large vessels. In ascents of longer duration, few bubbles were found.

Fat was found in the rats only in the kidneys of animals decompressing over a period of 3 to 7 minutes (2600 to 6000 m/min or 8500 to 20 000 ft/min). In rabbits and guinea pigs, some fat emboli were seen in the lungs of rapidly decompressed animals. If the ascent time was greater than 7 minutes (< 2600 m/min), no fat emboli occurred. Figure 6 shows these results graphically. The authors felt that in the absence of hypoxia and gas embolization, which can cause rapid death, enough time is available for autochthonous gas bubbles to form with secondary disruption of fatty tissue. The exact altitude and rate thresholds remain to be determined. A review of the literature on human fat emboli and two cases of their own suggested to these investigators that the threshold for fat emboli in humans is between 8 and 12 km/min (26 400 to 37 000 ft/min). Rates of 1000 to 1500 m/min (3000 to 4800 ft/min) have produced fat emboli in humans. Further investigation of these phenomena is certainly warranted.

Role of Gas Bubbles in Symptoms at Specific Body Sites

In the review of symptoms, mention was made of the potential mechanism involved in each symptom group. It appears appropriate at this point to analyze the specific bubble phenomena

which may cause symptoms at different body sites.

One of the major problems in this analysis is the difference in bubble formation after return from high pressure as opposed to exposure at altitude. Animal experiments indicate that in the case of diving decompression the role of air bubbles is much more definite than in the altitude form of the syndrome.^{95, 189, 440, 198, 199} Bubbles are seen intravascularly in the arteries and veins as well as in the capillaries. Bubbles are seen intracellularly in lipid organs such as adipose tissue, adrenal gland, and liver. This is not true in altitude decompression. Relatively few bubbles are seen in large arteries in animals undergoing altitude decompression.¹⁸⁹ Bubbles have been seen in the capillaries of fat, in the arterioles of the adrenal capsule, and in "intra-neural vessels of the rabbit." Venous bubbles have been seen in a decreasing order of frequency in muscle, fat, adrenal, lung, and marrow in many animals. None have been seen in the veins of the brain.

The basic physical difference between the two decompression conditions is well explained by the analysis of Piccard,³⁴² who reviewed the relationship between the internal pressure of a tiny gas bubble and the surface tension factor. (See eq. (1).) To prevent the spontaneous collapse of a bubble at the critical radius, an adequate internal pressure must be present. Piccard calculated that if water is saturated with air at 5 atmospheres absolute and the pressure is reduced to 1 atmosphere, no gas bubble will grow unless its radius is 0.36μ . If water is saturated to 1 atmosphere absolute and the pressure is decreased to $1/5$ atmosphere, no bubble can form unless the radius is 1.82μ or greater. The smaller radius represents 28×10^6 gas molecules. From the solubility coefficient, it can be calculated that this gas has to be taken from $12.8 \mu^3$ of water. The altitude bubble requires 690×10^6 molecules of gas, and has to be taken from $1620 \mu^3$ of water. The chances of a bubble forming in the high-pressure case is, therefore, many orders of magnitude greater than in the altitude case.

Other factors have been invoked to explain the difference in the symptom complex of diving as compared to altitude decompression.^{258, 34} One

is the duration of supersaturation of slowly perfused fatty tissues. During the typical short-duration operational dive, the nitrogen content of the nonfatty tissues and the brain will be high. The nitrogen content of the fatty tissue will be relatively low. It has been hypothesized that, upon return to sea level, the nonfatty tissues and brain may even desaturate into the fatty tissue as well as to the air. In this way, the fatty tissue may actually act as a buffer against bubble formation. There are, however, no specific data to support this hypothesis. Busby has actually shown that the pulmonary blood at sea level is cleared of 99 percent of the nitrogen in one passage through the lungs.⁸⁷ However, on return from depth, a larger volume of dissolved gas has to be cleared. It is uncertain how close the 1-percent residue is to the maximum threshold of nitrogen clearance. Altitude decompressions should more closely parallel the more rare, long-duration dive where fatty tissues actually become a site of bubble formation and a source of gas for other bubbles which do their damage elsewhere.

Another major difference between diving and altitude decompression appears to be in the nervous system. Delayed neurocirculatory collapse is thought to be more rare in diving.²⁰⁷ However, in the infrequent situation where a diver is suddenly forced after a prolonged dive to rise to the surface with no decompression stops, a more fulminating form of the full-blown neurocirculatory collapse syndrome is seen.

A more striking difference between diving and altitude exposure is the relative rarity of paraplegic symptoms of spinal cord involvement in the latter. Even though first reports of severe nervous system disorder in altitude decompression involved the spinal cord,⁶⁷ this site is rarely compromised at altitude. Only four other cases have been reported.²⁰⁷ There have been many explanations of the differences.^{95, 207, 258} The white fatty areas of the cord appear to be most involved. Presence of extravascular bubbles in these areas is still open to question.^{216, 258} Poor vascularization of the white as opposed to the grey areas is also in evidence. One would expect that extravascular or autochthonous bubbles should be present in the fatty, poorly vascular area, and that the high nitrogen burden possible in diving decompression should favor this loca-

tion. However, the shower of nitrogen emboli from the periphery, landing in the end arteries of the white matter in the cord, could also be invoked. Unfortunately, this difference between altitude and diving decompression, so often used in the analysis of mechanism, has, in reality, only confused the issue. It would be desirable to achieve a better understanding of the differences in the microscopic pathology arising from vascular embolization as opposed to autochthonous bubble formation in the cord.

The absence of bone lesions in altitude decompression is also striking. The relative rarity of this finding in naval diving suggests that the longer duration of exposure of the caisson worker and the poor decompression discipline associated with this occupation are major factors.²⁰⁷ Poorly controlled, high-pressure exposure for long durations with gas saturation of the fatty marrow may be a key to the mechanism.

Finally, a difference is noted in the case of relief of symptoms upon recompression. Behnke,³⁶ who has had the most combined experience with both diving and altitude decompression, claims that altitude decompression symptoms are more easily relieved by recompression. He attributes this finding to the relatively greater water and carbon dioxide content of bubbles at altitude as well as to the smaller total number of bubbles seen intravascularly and extravascularly.

What specific roles do gas bubbles play in altitude decompression of humans? It appears that in altitude decompression, bubbles most frequently appear in the extravascular spaces in and around joints and muscle insertions. These sites are most likely of aqueous nature. Bubbles in fatty tissue and extravascular structures associated with joints may contribute to some of the problems of bends. Most of the other manifestations of the decompression syndrome appear to involve lipid or intravascular sites of bubble origin and growth.³⁹⁷

That bubbles actually form autochthonously in the adipose tissue if not within the fat cells themselves has been suggested by post mortem studies of humans.²¹⁶ It must be emphasized, however, that only in exposure to high pressures have these types of extravascular bubbles been seen within the fat cells themselves. Extravascular gas bubbles have actually never been found in ani-

mals after decompression to altitude.^{95,213} Another important point is the absence of evidence to indicate that extravascular bubbles occur in the lipid-rich brain.⁹⁵ The high level of blood perfusion in this structure may well be responsible.²⁴⁶ Only in diving has there been found in humans questionable evidence of autochthonous bubbles in the poorly perfused spinal cord. It is clear that extravascular bubbles within fatty tissues, do not, per se, cause local symptoms in decompression sickness of altitude.

It appears that by disrupting adipose tissue, extravascular bubbles do send fatty emboli to the periphery. These may, in humans, be involved in the neurocirculatory collapse syndrome. Adipose tissue also appears to be a source of gas for bubbles being formed intravascularly in the venous drainage from this tissue. Fat is the only tissue in which gas bubbles have been found within the capillary bed during altitude exposure. It is at first surprising that in some animal studies there appears to be no correlation between the overall fat content of animals exposed to altitude and the time of appearance of intravascular gas bubbles, the severity of symptoms, or the time of survival.^{95,295} It must be kept in mind, however, that the tissue perfusion in small experimental mammals is much more efficient than in man.⁹⁵ This may well account for the general resistance of the rodents and similar creatures to decompression sickness.^{34,37}

A point often overlooked is the fact that exercising muscles are an excellent source of nitrogen for intravascular bubbles.^{95,295,340,451} It would appear that cavitation phenomena as well as the high level of carbon dioxide are probably responsible for the role of this tissue in producing symptoms.⁶⁶ The bubbles appear to be intravascular, obtaining the gas from the aqueous phase of the muscle tissue. These bubbles can pass to the systemic circulation and cause symptoms far removed from their site of origin.

Factors Controlling Decay of Bubbles in Biological Systems

Let us now return to the basic problem at hand. How does the site of bubble origin determine the factors controlling growth rate, peak size, and decay rate of bubbles? What gas-specific factors are involved?

The key to these questions, as mentioned above, is the perfusion of slightly supersaturated blood around the site of bubble formation. The competition between the bubbles and blood for the gas in the supersaturated solution immediately surrounding the bubble is the crux of the problem. However, there are three sub-problems:

- (1) What factors control the rate of gas transfer from the tissue to the blood?
- (2) What factors control the rate of gas transfer from the bubble to the tissue?
- (3) What factors control the rate of gas transfer from the extracellular pockets to the blood-stream?

Let us examine each of these subproblems.

TRANSFER OF GAS FROM TISSUE TO BLOOD

Using the theory of von Schrötter,³⁹⁵ Smith and Morales,^{319,404} point out in an excellent theoretical analysis of the problem that the role of desaturation of inert gases in tissues by gas exchange at the lungs is determined by five physiological factors: the oil-blood solubility ratio of the gases, the volume of blood in the tissue at any time, the volume of tissue containing the gas, the permeability of the tissues to the gas, and the rate of tissue blood flow. They attempted to weigh the importance of each of these factors. They arrived at the following in decreasing order of importance: tissue permeability, 68 percent; oil-water solubility ratio, 20 percent; rate of blood flow, 7 percent; and blood and tissue volumes, 5 percent. The equations of Morales and Smith were expanded by a series of theoretical analyses which culminated in a paper³¹⁸ indicating that the relative roles of permeability and perfusion were much less certain than in the first reports. The greatest defect appeared to be the absence of adequate data on the permeability of gases through plasma membranes and the simultaneous measurements of blood-flow and surface-volume ratios of specific tissues.

The study of Kety²⁵⁹ reviewed many other attempts at theoretical definition of inert-gas exchange in the tissue-blood-lung system and arrived at the same uncertainty regarding the relative roles of perfusion and diffusion. The theoretical analyses of Riggs and Goldstein³⁶² also cover the lung-blood-tissue kinetics as does

the study of Shore.⁴⁰¹ While these studies present excellent frameworks for analyzing compartment kinetics, they also do not clarify the issue of the relative roles of perfusion and diffusion in limiting tissue gas exchange.

The most cogent empirical data to this point are presented by the studies of Jones,²⁴⁹ who indicated that the diffusion of nitrogen from the tissues to the blood is too fast to have any limiting effect on the rate of the overall exchange process. This point is of great enough importance to the present study to justify a more detailed expansion of his results. Jones found that the total amount of nitrogen exhaled or absorbed by the body up to time t , or in differential form, the time rate of these processes, can be represented by the following equations:

$$Q_{N_2} = A_1(1 - e^{-k_1 t}) + A_2(1 - e^{-k_2 t}) + \dots + A_n(1 - e^{-k_n t}) \quad (12)$$

$$dQ_{N_2}/dt = k_1 A_1 e^{-k_1 t} + k_2 A_2 e^{-k_2 t} + \dots + k_n A_n e^{-k_n t} \quad (13)$$

where Q_{N_2} is the volume of nitrogen, and A and k are constants. In one very fully studied case, the constants of this equation were found to be

$$A_1 = 111 \text{ cm}^3 \quad A_2 = 193 \quad A_3 = 428$$

$$A_4 = 95 \quad A_5 = 600$$

$$k_1 = 0.462 \quad k_2 = 0.087 \quad k_3 = 0.0235$$

$$k_4 = 0.008 \quad k_5 = 0.0025$$

This composite, exponential decay process is attributed to the existence in the body of some five systems of varying tissue-blood perfusion relationship:

The first is the blood itself, plus the very vascular organs, such as the kidney in which the ratio of the blood flow per minute to the volume of the organ is high.

The second and third probably comprise, in the main, the large muscle mass of the body.

The fourth is the poorly circulated tissues that possibly contain some fat.

The fifth is the tissue that contains considerable fat.

In each case, it is expressed that the exchange process is only conditioned by the volume of the system and the blood circulation through it and is not limited to any appreciable extent by diffusion of nitrogen within the tissues or by permeability factors. On such a basis it is shown that if

$$A_1 = V_{A_1} \alpha_{A_1} p_0 \quad (14)$$

where

A_1 volume of dissolved nitrogen in the system A at zero time

V_{A_1} volume of the system A_1

α_{A_1} average solubility coefficient of nitrogen in A

p_0 partial pressure of nitrogen in A_1 at zero time

then

$$k_1 = \frac{F_{A_1} \alpha_{\text{blood}}}{V_{A_1} \alpha_{A_1}} \quad (15)$$

where

F_{A_1} blood flow through A per minute

α_{blood} solubility coefficient of nitrogen in blood

and similarly for A_2, k_2 , etc.

That diffusion of nitrogen from the tissues to the blood is too fast to have any limiting effect on the rate of the overall exchange process is strongly indicated by Jones' experiments on the rates of elimination of the different noble gases from the body, all of which also conformed to equations (12) and (13). Thus, in studies ranging from helium (atomic weight 4) to xenon (atomic weight 130), no difference could be found between the value of the k constants, although the diffusion constants of these gases in water vary inversely as the square root of the atomic weight. Table 2 of this paper indicates the relative diffusion constants through gelatin which compare the actual diffusion constants. The only exception to the uniformity in the k constants is seen in the k_5 constant for xenon, which is considerably less than k_5 for nitrogen. Jones points out that this may well be due to the lower value of the $\alpha_{\text{blood}}/\alpha_5$ factor for xenon because of the presence of the high proportion of fat in the A_5 system. In table

2 it can be seen that the oil-water solubility ratio for nitrogen is one-fourth that for xenon. These experiments are indeed convincing even if the number of subjects is limited. However, direct and conclusive proof that the empirical constants k of Jones are, in fact, simply tissue perfusion rates is still lacking.

In support of the Jones hypothesis is the excellent theoretical study of Roughton.³⁷¹ This investigator reviewed and elaborated on the capillary diffusion equations of Krogh,²⁶⁹ who assumed that each blood capillary of radius b has about it a coaxial cylinder of tissue of diameter equal to the average distance $2a$ between open capillaries in the tissue. Since about 4 percent of the blood volume in man is in the capillaries and since the total blood volume in man is about 8 percent of the body weight, each capillary can be regarded as serving, on the average, a cylinder of radius equal to $1/[(0.04)(0.08)]^{1/2}$, or 17.7 times the radius of the capillary. Assuming the average capillary has a radius b of 4.0×10^{-4} cm, then the value for the diffusion radius, a , about each capillary = 7.1×10^{-3} cm. Figure 7 represents the relation calculated from Roughton's pure diffusion equation between the log of the coaxial ratio $\theta = b/a$ and the log of the half time for the rate of elimination of dissolved nitrogen from the space between the two coaxial cylinders into the blood flowing through the central capillary cylinder. He assumed that the rate of elimination of nitrogen is entirely conditioned by diffusion and that the mean value for diffusion coefficient of nitrogen through animal tissues is 1×10^{-5} . (See table 2 for empirical range.) It is seen from figure 7 that for a $\theta = 17.7$, the half time for elimination is 4 seconds. The half times $\ln 2/k_A$ for the five compartments of Jones are $A_1 = 90$ seconds; $A_2 = 480$ seconds; $A_3 = 1760$ seconds; $A_4 = 5170$ seconds; and $A_5 = 18\,200$ seconds. It, therefore, appears that the half time of 4 seconds calculated from the assumption that diffusion is the main limiting factor is less than 5 percent of the observed half time of even the fastest system A_1 and is certainly less than 1 percent of the half times of the average system. Roughton further analyzed the case for the most highly perfused heart system (see table 12) as opposed to the most poorly circulated tissue in Jones' experiments²⁴⁹ and once again concluded that diffusion

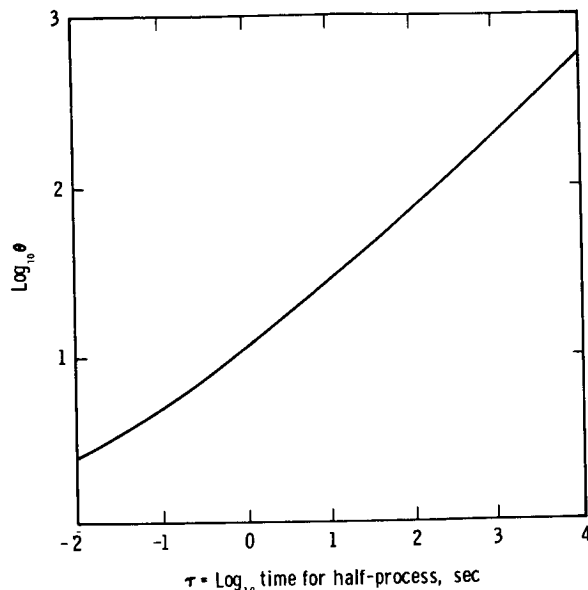


FIGURE 7.—Relation between θ and τ for diffusion of dissolved nitrogen from space between two coaxial cylinders of radii a and b , for $b = 4 \times 10^{-4}$ cm, $\theta = a/b$, $\tau =$ half process time. (AFTER ROUGHTON.³⁷¹)

is almost definitely not the rate-limiting process in the exchange of tissue, blood, and inert gas.

Even though direct and conclusive proof is absent, it would appear that there is good justification in assuming that perfusion and not diffusion is generally the rate-limiting factor in the diffusion of gas from tissues into the bloodstream and that the process is strongly determined by the factors of equation (15). Hempelman²¹⁹ has stressed that some diffusion limitation must still be considered for specific tissues which may play a critical role in bends.

TRANSFER OF GAS FROM BUBBLE TO TISSUE

From the analysis of Epstein and Plesset¹⁵⁹ and the empirical data and analysis of Wyman et al.⁴⁷⁰ it appears that the decay of a bubble in saturated or unsaturated solutions of the gases will follow the same general equations as those describing bubble growth in supersaturated solutions. As would be expected for bubbles containing several gases, the relative percentage of each gas in the bubble changes with time depending once again on the solubility and diffusion coefficients of the gases. From the empirical

data of Wyman et al. on the decay of an air bubble in water arose the calculation discussed above that the "effective diffusion shell" about the bubble is 3.3×10^{-3} cm.

Empirical curves describing the decay in size of an air bubble in air-saturated water or blood has been presented by Pattle.³³⁶ Figure 8 represents a typical time course of a bubble 50μ (5×10^{-3} cm) in diameter in a drop hanging from a microscopic slide. The surface tension factor $2\lambda/r$ is rather large in such a small bubble and is responsible for the rapid terminal collapse rate.

A more generalized picture of bubble decay can be seen from the calculations of Epstein and Plesset.¹⁵⁹ Figure 9 represents the radius-time relation for dissolving bubbles with and without surface tension. The ordinate ϵ is the ratio of final bubble radius to the initial radius r/r_0 and the abscissa χ is a dimensionless parameter proportional to the square root of time, $t^{1/2}$. The solid curve represents the quasi-static solution for a gas bubble in an undersaturated solution with surface tension neglected. The dashed curves include surface tension for an air-water interface and depend in form on the supersaturation ratio f or the ratio of initial dissolved air concentration to the concentration at saturation. All curves are drawn for an initial radius r_0 of 10^{-3} cm.

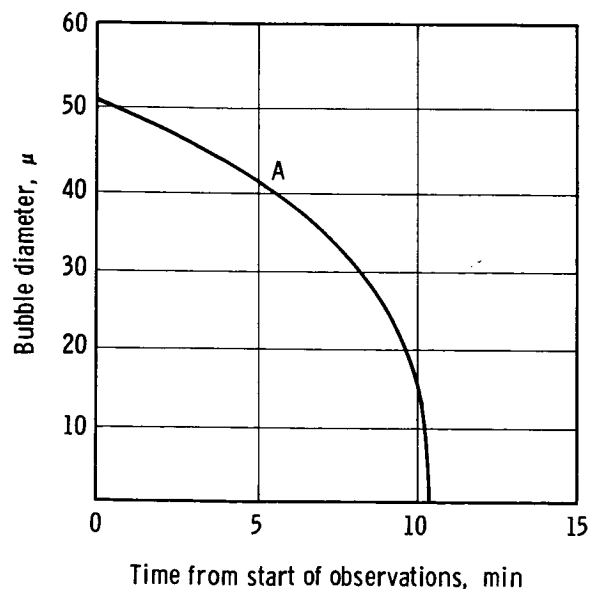


FIGURE 8.—Time course of contraction of bubbles in air-saturated oxalated whole guinea pig blood. (AFTER PATTLE.³³⁶)

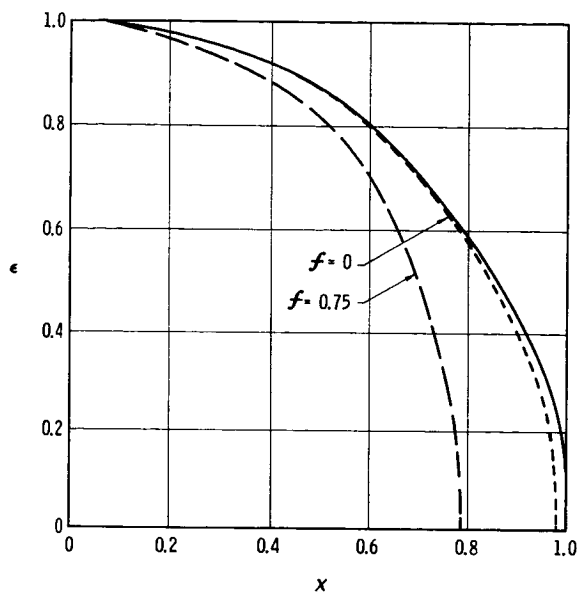


FIGURE 9.—Radius-time relation for dissolving bubbles. (AFTER EPSTEIN AND PLESSET.¹⁵⁹)

The role of surface tension is more obvious when it is remembered that the abscissa represents $t^{1/2}$.

Table 7 represents some of the actual times (seconds) for complete solution of air bubbles of different initial radius r_0 in water solutions of different ratios of unsaturation f . Times are given for the complete solution neglecting surface tension t , a quasi-static approximation also neglecting surface tension t_a , and the same quasi-static approximation including surface tension t_s . It should be noted that the surface tension effect (t_a versus t_s) is more pronounced in the smaller bubbles. The values of t and t_a are proportional to the r_0^2 , since, in the absence of surface tension, surface area determines the rate of dissolution of the bubble. When saturated, all three bubbles would persist indefinitely were there no surface tension. In altitude decompression, one would expect an unsaturation ratio of from 0.25 to 0.50. The value of 0.50 would be the more common. From the table it is seen that in the presence of surface tension t_s , a bubble with an initial radius of 10^{-3} cm should last only 1.96 seconds; a bubble with an initial radius of 10^{-2} cm should last 2.41 seconds; and a bubble with an initial radius of 10^{-1} cm should last 24 900 seconds, or about 5 hours. It is also of interest to note that the 600-second empirical lifetime of a

TABLE 7.—Time for Complete Solution of Air Bubbles in Water

[AFTER EPSTEIN AND PLESSET¹⁵⁹]

<i>f</i>	$r_0 = 10^{-3}$ cm			$r_0 = 10^{-2}$ cm		$r_0 = 10^{-1}$ cm	
	t , sec	t_a , sec	t_s , sec	t_a , sec	t_s , sec	t_a , sec	t_s , sec
0.....	1.05	1.25	1.17	1.25×10^2	1.24×10^2	1.25×10^4	1.25×10^4
0.25.....	1.44	1.67	1.46	1.67	1.64	1.67	1.66
0.50.....	2.21	2.50	1.96	2.50	2.41	2.50	2.49
0.75.....	4.58	5.00	2.99	5.00	4.60	5.00	4.95
1.00.....	~	~	~	~	58.8	~	580.0

bubble of radius 5×10^{-3} cm under saturated conditions $f=1$ as seen in figure 8 would have been predicted by the theoretical calculations of Epstein and Plesset.

Another interesting bubble-decay study was performed by Downey et al.¹⁴² These investigators decompressed a container of serum to 43 000 feet and studied the changes in bubble size. Unfortunately, no attempt was made at direct quantification of actual bubble size.⁴⁶⁶ By comparing the photographs of a bubble with a No. 50 thread (0.127 mm) used as a trap in the experiment, one can calculate that during the 15 minutes the bubble remained at 43 000 feet it increased from 1 mm to 1.6 mm in radius, or fourfold in volume. Upon recompression to sea level, the bubble did decrease in size by 50 percent, but it persisted. Worley⁴⁶⁶ reports that bubbles in the same container reached different peak sizes. This probably results from variation in the size and stability of preformed gas nuclei.²¹⁴ The larger ones, such as the one in the photograph, tended to persist on return to sea level; the smaller ones collapsed. It must be remembered that unlike the serum *in vivo* which is always desaturating at altitude, the serum in the container probably remains supersaturated. The long persistence of the bubble on return to sea level is not surprising in view of the theoretical calculations seen for the ($f=1$) case of table 7 for a bubble of 2- to 3-mm radius produced by decompression in these studies. Bubbles in synovial fluid and blood act consistently the same as those in serum.⁴⁶⁶ The size and persistence of bubbles in urine varied from batch to batch probably as a function of the level of crystalloid matter in the fluid.²¹⁴ Experiments such as these could

go far in establishing the role of the lipid and protein "skin factors"²⁹⁸ of bubble dynamics *in vivo*.

TRANSFER OF GAS FROM EXTRACELLULAR POCKET TO BLOOD

Subcutaneous pockets of gas have been produced by direct air injection.^{343, 433} The factors controlling the collapse rate of these large pockets (20 ml) of gas are more complicated and less certain than the tissue-to-blood or bubble-to-blood transfer. The varying tissue content of the pocket wall is a major factor in the variable conclusions regarding the relative role of perfusion and diffusion. An analytical model of this problem is presented in figure 10. In this model, an inert gas with partial pressure p_g diffuses with a rate \dot{V} through the heavily hatched diffusion barrier which has a resistance to diffusion $1/D$, into the blood flowing with perfusion rate \dot{Q} . The gas solubility coefficient in blood is α . The pressure of gas in the blood changes from P_1 to P_2 . The diagram and equation in figure 10(a) are for simple perfusion limitation; figure 10(b), for combined perfusion and diffusion limitation; and, figure 10(c), for simple diffusion limitation by the tissues between gas pockets and the blood.

The actual collapse rates of gas pockets were determined with the mixture of 80 percent inert gas, 20 percent oxygen. The ratios of absorption rate of the inert-gas components compared with those of nitrogen were: nitrogen, 1.00; helium, 1.2; hydrogen, 1.7; and argon, 1.9. Prediction of empirical collapse rates by comparing physical properties of different inert gases in the pockets was best accomplished by the model and equations representing a mixed perfusion-diffusion limitation. In the case of nitrogen and

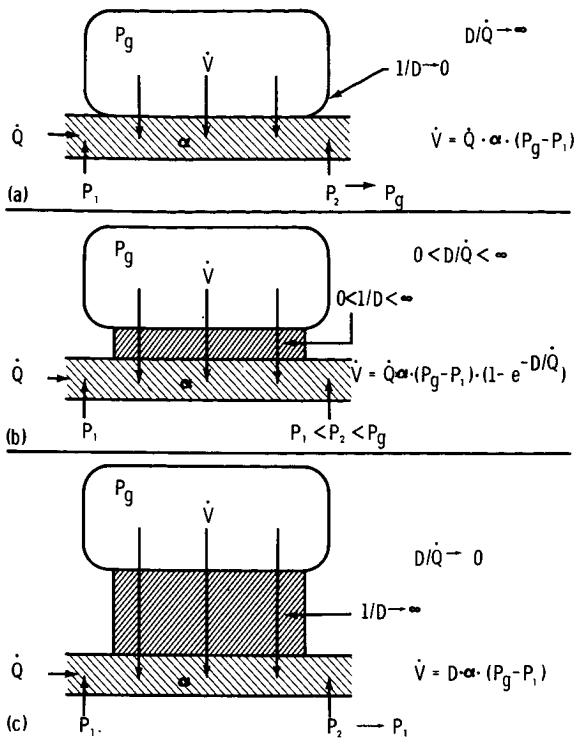


FIGURE 10.—Analytical model for inert gas absorption from gas pockets. (AFTER PIIPER ET AL.³⁴³)

argon, diffusion limitation predominates. In the case of helium and hydrogen, perfusion and diffusion were of comparable magnitude. It should be remembered that the solubility of the gas in the diffusion barrier itself had been omitted from the model. In an area where the gas pocket wall is predominately lipid, the lipid-water solubility ratio would play a considerable role in the absorption process of this model system. The inert gases of larger molecular weight would be

more strongly affected by this consideration (tables 1 and 2).

It must be remembered that these gas pockets are probably of larger volume than those seen with X-ray⁸⁶ in bends. Larger amounts of gas are seen in the articular cavity and in bursae, but seem to be associated with little pain. An injection of 50 cc or more of air may actually be injected into the knee joint, for example, with an associated feeling of tension, but not of pain.¹⁰⁷ In the gas pockets in "tight" tissues where pain correlates well with bubble size, the volume appears to be less than 20 cc. Exact volume determinations from two-dimensional films are difficult.

The effective diffusion thickness of these gas pockets has been very roughly estimated from perfusion and diffusion data. Besides inadequate knowledge of the absolute values of diffusion coefficients and perfusion parameters, there is a deficiency in the knowledge of the percent of surface area of a pocket that is effectively exchanging gas. Piiper et al.³⁴³ estimate the effective thickness of their pockets at 130 μ if the whole surface area is considered. If the whole area is not considered the probable range is 10 to 100 μ depending on the percent of total area available for diffusion. In the 25-ml pockets that Van Liew⁴³³ studied in the rat, the average effective diffusion thickness was calculated to be from 180 to 480 μ , depending on the selection of diffusion coefficient of oxygen in connective tissue or serum. This author compared the permeability coefficients and calculated effective membrane thickness of alveolar membrane, bubble in water, and subcutaneous gas pocket of the rat. The results are seen in table 8. The permeability coefficient is defined by Davson and Danielli¹³⁴

TABLE 8.—Comparison of Permeability Coefficients and Membrane Thickness of 3 Interfaces at 37° C [AFTER VAN LIEW⁴³³]

Interface	Permeability coefficients, ml $\times 10^{-4}$ /min-cm ² -atm		Effective thickness of membrane, μ	Reference
	O ₂	N ₂		
Alveolar membrane.....	300 to 900	1 to 11	177
Bubble in water.....	150	{ 57 at 20° C 64 at 21° C	33 31	470 191
Subcutaneous gas pocket, rat...	6.6	3.3	180 to 480	433

as the amount of substance diffusing through a membrane per unit tissue area and unit concentration or pressure difference. This table indicates that the oxygen permeability coefficient of a typical gas pocket in rats is $1/50$ to $1/150$ that of the lung, and $1/25$ that of a bubble in water. The nitrogen permeability coefficient is about $1/20$ that of a bubble in water. The calculated membrane thickness or diffusion shell thickness in the case of the bubble is also recorded.

Since the relatively thick connective tissue gas pocket is only partly diffusion limited, diffusion would be expected to play much less of a limiting role in the thinner, undisturbed tissue-blood barriers. A recent study of relative roles of perfusion and diffusion in control of the passage of gas across a cutaneous barrier further indicates the complexity of the problem.²⁶³

Calculation of Gas-Specific Factors Controlling Peak Bubble Size

From the above discussion it is apparent that bubbles forming at each body site will have gas-specific growth and decay factors which should determine peak size for the specific bubble in question. It also appears that peak bubble size at a specific body site as well as the number of bubbles is related to symptoms at that site. The case of bubbles remaining at the site of origin as well as those transported to distant sites must be considered. It may also be possible to quantitate in some way the degree of hazard presented by an inert gas during the decompression episode in space. From the previous discussion it is suggested that the following classes of bubble need be considered: (1) bubble forming autochthonously in adipose tissue; (2) bubble forming intravascularly within adipose tissue and remaining *in situ*; (3) bubble forming intravascularly in adipose tissue or muscle and lodging in a blood vessel at any remote site; and (4) bubble forming extravascularly as a gas pocket in connective tissue about a joint.

CASE 1. BUBBLE FORMING AUTOCHTHONOUSLY IN ADIPOSE TISSUE

A bubble of this type is a factor in generation of the most serious neurocirculatory collapse syndrome. Fat emboli arising from disrupted adipose tissue are the specific danger. There

appears to be no evidence of autochthonous bubbles in the brain and the spinal cord at altitude, although the histological criteria for this interpretation are not clear.²¹⁶

The growth of the bubble from gas dissolved in the fat tissue is determined by the permeation coefficient ($\alpha_{\text{fat}}D_{\text{fat}}$). The depletion of nitrogen from the tissue conflicting with this process is determined by the constants k_4 and k_5 of Jones which probably represent relative tissue perfusion rates and solubility factors for adipose tissue seen in equation (15).

$$k = \frac{F_{\text{adipose}}}{V_{\text{adipose}}} \times \frac{\alpha_{\text{blood}}}{\alpha_{\text{fat}}}$$

That gas with the lowest constant (k) or the highest value of $\alpha_{\text{fat}}/\alpha_{\text{blood}}$ will show the lowest rate of transfer from tissue to blood. The peak bubble size for an autochthonous bubble in adipose tissue will, therefore, be a function of the product of

$$(\alpha_{\text{fat}}D_{\text{fat}}) \times (\alpha_{\text{fat}}/\alpha_{\text{blood}}) = \frac{\alpha_{\text{fat}}^2 D_{\text{fat}}}{\alpha_{\text{blood}}}$$

How do the different inert gases compare with respect to this bubble factor? Table 9, case 1, represents the bubble peak factor for autochthonous bubbles in adipose tissue and the relative bubble peak factor normalized to nitrogen = 1. The values for α_{fat} , D_{fat} , and α_{blood} are obtained from table 2. The value of $\alpha_{\text{human fat}}$ is essentially equal to $\alpha_{\text{olive oil}}$ and, so, the $\alpha_{\text{olive oil}}$ values were used for helium and argon where there are no values available for $\alpha_{\text{human fat}}$. The values of D_{fat} are extrapolated from nitrogen data on D_{lard} by Graham's law in table 2. As was discussed in chapter 1, the value of α_{blood} is essentially that of α_{water} and, so, the α_{water} values of table 2 were used. A sample calculation for helium would, therefore, be

$$BF = \frac{0.015 \times 0.015 \times 9.28}{0.0086} = 0.23$$

It is entirely fortuitous that the bubble factor for nitrogen turns out to be 1.0. The row entitled "relative bubble factor (nitrogen = 1)" indicates that the peak autochthonous bubble

TABLE 9.—*Inert Gas Bubble Factors in Decompression Sickness*
 [These factors hold for any given supersaturation ratio]

Bubble site and factors	Gas					
	He	Ne	A	Kr	Xe	N ₂
<i>Case 1</i>						
Adipose tissue (autochthonous):						
Bubble factor ($\frac{\alpha_{fat}^2 D_{fat}}{\alpha_{blood}}$).....	0.24	0.17	2.2	7.8	49.0	1.0
Relative bubble factor (N ₂ = 1).....	.24	.17	2.2	7.8	49.0	1.0
<i>Case 2</i>						
Adipose tissue (intravascular <i>in situ</i>):						
Phase 1—early bubble:						
Bubble factor ($\alpha_{blood} D_{blood}$).....	.50	.25	.47	.57	.86	.28
Relative bubble factor (N ₂ = 1).....	1.8	.88	1.7	2.0	3.0	1.0
Phase 2—terminal bubble:						
Bubble factor ($\alpha_{fat} D_{fat}$).....	.14	.08	.41	.85	2.50	.22
Relative bubble factor (N ₂ = 1).....	.64	.34	1.9	3.9	12.0	1.0
<i>Case 3</i>						
Bubbles originating intravascularly in adipose or muscle tissue and lodging in the pulmonary or systemic vasculature: bubble factor (relative rank).....	2	1	3	4	5	2
<i>Case 4</i>						
Gas pockets in connective tissue: bubble factor (relative rank).....	2	1	3	4	5	2

size in adipose tissue of a bubble with helium would be 0.24 times the peak size of a bubble of nitrogen. Comparison of the relative values suggests that for any local supersaturation ratio, neon is the safest gas, with helium a close second, and nitrogen third. The other gases increase in hazard with increasing molecular weight. It would thus appear that neon and helium are more than four times safer than nitrogen if autochthonous bubbles in adipose tissue are at issue. It must be kept in mind that there will be a low but variable level of carbon dioxide and oxygen in these bubbles. This would dilute the effect of the inert gas in the overall bubble factor.

CASE 2. BUBBLES FORMING INTRAVASCULARLY IN ADIPOSE TISSUE AND REMAINING IN SITU

Case 2 bubbles are dangerous because of their potential for also disrupting adipose tissue and producing fat emboli. The relative roles of the intravascular as compared with the autochthonous bubbles in disrupting adipose tissue is still a moot question. One can assume, however, that a bubble trapped in a capillary of the adipose tissue may grow and eventually disrupt the

tissue. Let us now analyze the gas-dependent factors involved.

Gas leaving the adipose tissue and entering the bloodstream passes through many diffusion barriers. These are the intracellular lipid, the adipose cell membrane, and the capillary membrane. On the whole, these barriers are of lipid and lipoprotein materials. The rate of passage of an inert gas across this barrier would be most closely dependent on the permeation coefficient $\alpha_{fat} D_{fat}$. The gas then would have to cross the diffusion barrier presented by the blood surrounding the bubble. The bloodstream from the arterial side of the capillary is perfusing the bubble with fluid less supersaturated than the adipose tissue. This moving fluid is, therefore, diluting the inert gas dissolved in the blood around the bubble. When the bubble is small and the adipose tissue is supersaturated, the great flow of blood and the thick blood barrier would probably make the "effective capillary-to-bubble diffusion path" the limiting factor in early bubble growth. This permeation coefficient would be $\alpha_{blood} D_{blood}$. Since α_{blood} is essentially equal to α_{water} and D_{blood} is essentially equal to

D_{serum} , the permeation factor α_{water} and D_{serum} is used to establish the early rate of bubble growth. As the bubble increases in size and begins to obstruct capillary flow, the effective diffusion barrier in blood decreases and the tissue barriers become more effective. The bubble finally obstructs the capillary flow and increases in internal pressure until it disrupts the capillary wall. The increase in bubble pressure becomes then a function of the permeation coefficient of the gas through an "effective diffusion shell" composed of the lipid in the adipose tissue, the adipose cell membrane, and the capillary membrane. The $\alpha_{\text{fat}}D_{\text{fat}}$ coefficient then would serve as the limiting factor in the terminal phase of the bubble. The values are obtained from table 2 where D_{lard} is used for D_{fat} .

Let us look at the bubble factors presented by the permeation coefficients of early and late phase bubbles. Table 9, case 2, represents the calculations for the two phases of the life history of such a bubble. The relative bubble factors (nitrogen=1) are of prime interest. In the early phase, and for any given supersaturation ratio, neon again appears to be the most favorable gas, nitrogen is second, and helium and argon third and are of equal danger. In the early phase, a bubble of neon would reach a size about 0.9 times the size of a nitrogen bubble; helium and argon bubbles would be about 1.8 times larger than the nitrogen bubble. In the terminal phase of the bubble, neon is again the best gas, with helium second, nitrogen third, and the other gases increasing in danger. A neon bubble would reach a terminal pressure of only 0.3 times that of nitrogen. A helium bubble would reach a peak 0.6 times the pressure of a nitrogen bubble for the same local supersaturation ratio.

The question still remaining is a difficult one. At what stage of the bubble growth does the phase 1 condition become phase 2, and what are the relative durations of each phase? Because of the complex factors in establishing the role of blood mixing in determination of the "effective diffusion barrier," the answer to this question is not available. The crossover point between phase 1 and phase 2 is, therefore, uncertain. Regardless of the crossover point, neon appears to be the least hazardous gas, with

helium and nitrogen a close second for the same supersaturation ratio.

CASE 3. BUBBLE FORMING INTRAVASCULARLY IN ADIPOSE TISSUE OR MUSCLE AND LODGING IN A BLOOD VESSEL AT A REMOTE SITE

The formation of an intravascular bubble in muscle or adipose tissue would be controlled by the same general factors as those described in case 2. The early phase of the bubble would be determined by the $\alpha_{\text{blood}}D_{\text{blood}}$ factor. Because the muscle tissue is more highly perfused than the fat, it would be expected that the early phase would last longer in this tissue. Some time before the bubble passes out the venous channels, there may be a point at which the tissue permeation coefficient becomes limiting. For the same reasons presented in case 2, the crossover point is difficult to determine. The longer a bubble remains *in situ*, the greater will be the role of the tissue permeation coefficient. In the capillaries of adipose tissue, the tissue permeation coefficient will be the same as that calculated for the terminal phase of a bubble *in situ*. In the case of muscle tissue, the permeation coefficient is more difficult to determine. The issue is confused by the presence of sarcoplasm in the initial part of the barrier. The permeation coefficient of nitrogen in muscle appears to be only about one-third that in water.¹³⁹ What part of the total diffusion barrier is muscle tissue and what part is lipoprotein membrane is not known. Since the permeation coefficient of muscle is partly determined by the presence of lipid reticulum in the sarcoplasm, it would appear that the total permeation barrier for muscle tissue would lie between the values of phase 1 and phase 2 of case 2 in table 9, but much closer to phase 2. Neon is, no doubt, the least hazardous, with helium and nitrogen close seconds. No further quantification is possible from the data available.

Since they are being continually perfused with venous blood which is supersaturated with inert gas, the bubbles from adipose tissue or muscle lodging in the pulmonary capillaries will probably continue for a while to increase in size and continue to determine the pattern of chokes symptoms. In the capillaries the $\alpha_{\text{blood}}D_{\text{blood}}$ factor will control the bubble growth rate. This is the same factor as case 2, phase 1.

As soon as the body stores are depleted to the point where the venous blood is unsaturated with respect to the pulmonary bubble, the bubble will decrease in size at a rate again determined by the $\alpha_{\text{blood}}D_{\text{blood}}$ factor. The bubbles lodging in the arterial side of the systemic vasculature will always be perfused by relatively unsaturated blood and will decrease in size in accordance with the $\alpha_{\text{blood}}D_{\text{blood}}$ factor for the gas. However, the perfusion rate of the site around the lodged bubble will probably be the actual rate-controlling factor in bubble decay in both the pulmonary and systemic vasculature. At bifurcation points where adequate flow may be passing into the unblocked branch to allow diffusion to limit bubble decay, this may not hold true.

From the above discussion it would appear that prediction of an overall bubble factor hazard index for intravascular bubbles lodging in remote sites is much less certain than case 1 or 2. The bubble size representing a crossover point from an effective serum diffusion barrier to tissue diffusion barrier is not clear. The relative importance of each phase of bubble growth is not clear. In the case of bubbles lodging in pulmonary capillaries, the ratio of effective bubble growth at the site of origin to that in the pulmonary capillary is not clear. With all of these uncertainties it can only be stated that for bubbles originating in muscle or fat and lodging in the pulmonary or systemic circulation, the degree of hazard will lie somewhere between that calculated for phase 1 and phase 2 in case 2 of table 9. For bubbles originating in fat, the factor will be weighted more heavily in favor of phase 2. For bubbles lodging in the pulmonary circulation, the factor may be weighted in favor of phase 1. Again, the presence of carbon dioxide and oxygen in the bubble will dilute the inert gas effect. This may be an appreciable factor in active muscle where carbon dioxide levels are relatively high. In any case, analysis of these bounding conditions suggests that neon is probably the safest gas; helium and nitrogen are close seconds; and argon is most likely third for any given supersaturation ratio in this type of bubble.

CASE 4. BUBBLES FORMING EXTRAVASCULARLY AS A GAS POCKET IN CONNECTIVE TISSUE

This case is probably of the most frequent occurrence in decompression sickness although

it is the least hazardous from a medical point of view. Let us once again review the growth and decay factors controlling peak bubble size in connective tissue pockets. The growth factor, as in previous cases, is the permeation coefficient of the gas in connective tissue $\alpha_{\text{ct}}D_{\text{ct}}$. The decay factor for the connective tissue gas pocket, as was discussed above, includes both a diffusion and perfusion limitation. In the case of nitrogen and argon, diffusion predominates. In the case of helium and hydrogen, perfusion equals diffusion limitation. In the case of nitrogen and argon, the gas-dependent decay factor would, therefore, be a compromise between the perfusion-limited $\alpha_{\text{ct}}/\alpha_{\text{blood}}$ factors of equation (15), and the diffusion-limited $\alpha_{\text{ct}}D_{\text{ct}}$ permeation coefficient, with the latter predominating. For nitrogen and argon, however, the $\alpha_{\text{ct}}/\alpha_{\text{blood}}$ is probably close to unity^{139, table 10} and so there would be little or no gas dependency in the perfusion factor. In the case of helium and, no doubt, neon, the $\alpha_{\text{ct}}/\alpha_{\text{blood}}$ would be even closer to unity than in the nitrogen-argon case; therefore in spite of the relatively larger perfusion role, there would again be little or no gas-dependent discrimination in the perfusion sector of the decay dynamics. It, therefore, seems that only the diffusion process would involve gas-dependent factors in gas pocket decay within connective tissue.

From the above analysis, it would appear that only the $\alpha_{\text{ct}}D_{\text{ct}}$ factor would significantly determine peak bubble size. Unfortunately, there are almost no data to calculate the permeation coefficients for the different inert gases in connective tissue. The variability in structure of this tissue from site to site about a joint further confuses the issue. The calculation of connective tissue permeation coefficient for nitrogen of 0.53×10^{-5} cm²/min/atm is about one-third that of serum (1.5×10^{-5}), and slightly less than that of muscle tissue, (0.84×10^{-5}).¹³⁹ These ratios would not, of course, hold for all the inert gases. Presence of nonaqueous collagenous materials and lipids is no doubt responsible for reduction of this permeation coefficient below that of serum. It would appear that the $\alpha_{\text{ct}}D_{\text{ct}}$ lies somewhere between the $\alpha_{\text{blood}}D_{\text{blood}}$ and $\alpha_{\text{fat}}D_{\text{fat}}$ factors used in case 2 of table 9. Because of the variability in connective tissue of the collagen-

lipid ratio, the exact position of the permeation coefficient between the two permeation boundaries is most difficult to determine. Fascia and tendons would probably fall very much closer to the $\alpha_{\text{blood}}D_{\text{blood}}$ factor than to the $\alpha_{\text{fat}}D_{\text{fat}}$. Areolar tissues about the joint may have a somewhat larger fatty component, but would still lie closer to the $\alpha_{\text{blood}}D_{\text{blood}}$ in permeation coefficient. Analysis of the bounding conditions suggests that neon is probably the least hazardous gas, with helium and nitrogen a close second, and argon in third place. The other gases would be much more hazardous from the point of view of the peak bubble factor in connective tissue pockets. The relative rankings are recorded in table 9 and are limited to conditions of equal supersaturation ratios at the bubble site.

The relative bubble factor of case 1 is the most clear cut of the indices. A choice must be made between the relative bubble factors of early or late bubble phases in case 2, or an arbitrary compromise must be established between the two factors. In cases 3 and 4 there are no clear-cut indices other than the relative rankings noted in table 9.

Do these theoretical considerations allow the establishment of an overall decompression sickness hazard index for different inert gases? It is obvious from the previous discussion that each of the four bubble types has its own specific hazard index related to peak bubble size for any local supersaturation ratio. To present an overall index, the inert-gas factors controlling the local supersaturation ratio at the site of bubble formation would have to be determined. The local supersaturation ratio determines two factors: the number of bubbles forming and the rate of growth of each bubble. The supersaturation ratio is, in turn, a function of the initial amount of gas dissolved in specific body tissues and the desaturation rate of these tissues. As discussed in the next two sections, the gas desaturation curves are the key factor in establishing allowable decompression time in diving tables.⁴²⁷ These tables are based on the fact that if a given degree of supersaturation of a critical tissue is reached, symptoms will arise. By adjusting decompression rates so that these critical supersaturation ratios are not surpassed, the development of symptoms can be avoided.

The ultimate pattern of bubble formation is, therefore, a function of the total amount of gas available in any tissue site, the degree of supersaturation at the surface of the bubble, as well as the bubble-growth factors determined. In the acute type of decompression events expected in space cabins, consideration of the tissue-desaturation rates may be as important as the bubble-growth factors. Assuming that gas-dependent factors can be established for critical supersaturation ratios at any critical site, how can the absolute bubble number and size be related to an overall hazard index? Two other facts are required. They are the empirical frequency of symptoms arising from each of the four bubble types and the danger to mission or life represented by these symptoms.

EMPIRICAL AND OPERATIONAL DATA ON INERT GASES IN DECOMPRESSION SICKNESS

Now that the theoretical aspects of inert gas factors in decompression sickness have been reviewed, it seems appropriate to compare predictions with empirical and operational facts. Unfortunately, most of the data have been generated in the field of diving where inert gases other than nitrogen have been used, primarily to avoid the problem of nitrogen narcosis or "rapture of the deep." The theoretical differences between diving and altitude decompression have been covered in the previous section. The practical differences will become obvious before long. Animal studies will be considered first.

Animal Studies of Decompression From High Pressures

In 1926, Sayers and Yant³⁷⁷ exposed guinea pigs to 10 atmospheres of helium-oxygen and nitrogen-oxygen mixtures in an attempt to compare the relative effects of these mixtures in decompression sickness. After exposures at depth from 1 to 5 hours, the shortest decompression time for helium-oxygen was 4 minutes; that for nitrogen-oxygen was 26 minutes. No bubbles were seen in tissue or veins of animals decompressed from helium-oxygen after 15 minutes of decompression. The same was true for animals decompressed from nitrogen-oxygen over a period of 45 minutes. No bubbles were seen in

fatty tissue of the helium-oxygen group, but they were observed in all but one of the nitrogen-oxygen group. This suggests that the overall threefold or fourfold decrease in decompression time was no doubt a result of the factor of solubility coefficients.

Gersh et al.¹⁹⁰ have compared the effects of mixtures containing 20 percent oxygen and 80 percent of either nitrogen, helium, or argon with 100 percent oxygen on microscopic tissue changes in decompressed guinea pigs. After compression in small chambers for 60 minutes at 30 to 150 psi, the animals were decompressed within 4 seconds. In fatty tissue, extravascular bubbles occur, in order of decreasing frequency, after exposures to argon-oxygen, nitrogen-oxygen, 100 percent oxygen, and helium-oxygen mixtures. Intracellular bubbles occurred after breathing argon-oxygen, nitrogen-oxygen, and helium-oxygen mixtures, but not after breathing pure oxygen. The minimum pressures required for bubbles with each gas were: argon-oxygen, 60 psi; nitrogen-oxygen, 75 psi; and helium-oxygen, 90 psi. Intravascular bubbles were present with all gas mixtures. In the adrenal cortex, bubbles occurred with the same frequency as in fat, except that only rarely were bubbles seen after the subject had breathed 100 percent oxygen. The same is true in the liver and myelin sheaths where 100 percent oxygen produces no bubbles. After decompression in any of the gas mixtures, gas bubbles are not found in muscle fibers or in tissue spaces of skeletal muscle. These findings are in contrast to the altitude decompression results reported by Gersh and Catchpole^{95, 189} and reviewed in a previous section. The total number of gas molecules available for bubbles in the higher pressure condition is no doubt responsible for the difference seen in these small animals which have relatively high resistance to decompression sickness.³⁴² The order of bubbles seen in fat after different inert-gas mixtures would have been predicted from the analysis of case 1 in table 9.

Pressure-dependent survival limits of the guinea pigs for the different inert gases were also studied. The upper pressure limits compatible with survival were 75 psi in oxygen (oxygen toxicity was a factor in setting this limit); 75 psi in helium-oxygen; 45 psi in nitrogen-

oxygen; and 30 psi in argon-oxygen. This is the order of survival limits predicted by the bubble factors in case 1 and phase 2 of case 2 in table 9. The role of fat must be greater than that of aqueous media in determining the survival of guinea pigs after decompression from high pressures.³⁴ However, the relative dangers of nitrogen and helium appear to follow phase 2 of case 2 more closely than case 1 in table 9. Unfortunately, little else regarding the specific bubble mechanisms responsible for death can be inferred from these lethality ratios.

Confirmation of the role of fatty tissue in decompression from high pressure has been presented recently in experiments on obese rodents.³⁴¹ Genetically obese animals have been used to increase the symptom rate in those small, easily handled species such as mice which are ordinarily resistant to decompression sickness.^{10, 37} Mice are capable of extremely rapid decompression from pressures of 97 percent nitrogen. Attempts to determine the limiting tissue for decompression indicate the slowest tissues in the nonobese mouse may have a half time for nitrogen elimination of about 2 minutes.¹⁷⁵ In human diving experience there is much less correlation between adiposity and frequency of decompression symptoms.⁴⁵⁵ This is in distinct contrast to experience in altitude decompression where the correlation is far better.^{89, 196, 203, 335} It may well be that the relatively short periods at depth in operational diving prevent significant gas saturation of the fatty tissue and reduce the effect of adiposity.³⁷

There have been few studies of animals decompressed after prolonged stay at depth. Goats have been used to study decompression sickness after prolonged exposure to high pressures of helium and nitrogen.⁴⁶⁵ These animals have been used extensively by the British Royal Navy because of the similarity to humans in time of onset and type of symptoms.^{72, 417, 152} They tend to suffer attacks of the bends which are very similar in their site and outward signs to those suffered by man. The similarity may be seen in table 10 where the depth-time relationship of the two species for nonstop times is compared. For times up to 6 hours at depth, resemblance is very close. For times over 6 hours, the two sets of figures diverge.²¹⁸ Hempleman suggests

TABLE 10.—*Comparison of Threshold Sensitivity of Goats and Men—Air Diving*
[AFTER HEMPLEMAN²¹⁸]

Depth		Time, min	
Meters	ft	Man	Goat
61	200	13.30	10.00
52	170	17.30	15.00
46	150	18.30	19.00
30	100	37.30	38.00
13 to 15	45 to 50	360	360

that it is possible to transfer directly results in goats to those in man only for dives up to 6 hours in duration. Workman,⁴⁶² however, points out that even for short exposures there are serious differences between goat and man. He feels that at 100 feet, the safe exposure time for man on air is closer to 25 to 30 minutes; and at 50 feet, closer to 100 to 106 minutes. Goat data from longer dives, which simulate more closely the tissue saturation factors in space cabins, must be used with much reservation. Hempleman²¹⁸ has indicated that for a single animal, resistance to bends in short-duration dives may have no relation to resistance in long-duration dives. These points must be kept in mind in extrapolating data from animal to man; from long-duration dives to short-duration dives; and, especially, from diving decompression to altitude decompression. Hempleman²¹⁸ has briefly reported that in saturation dives with argon-oxygen, nitrogen-oxygen, and helium-oxygen mixtures in goats, the degree of hazard decreases in the above order. No quantitative data were presented.

In the recent study of Workman et al.⁴⁶⁵ goats were exposed for 72 hours at a depth of 200 feet of water to a mixture of 97 percent helium and 3 percent oxygen and were decompressed over a period of 72 hours using a conservative, two-stop decompression. No evidence of decompression sickness was noted. In another experiment, the carbon dioxide concentration rose to 4.5 percent (sea level effective) during the first 48 hours and fell to 2.1 percent (sea level effective) over the last 24 hours. Within 10 minutes after initiation of the same decompression schedule, bends pains in the left front and rear limbs were

evident. Recompression to 200 feet for 3 hours allowed safe return to the surface. The experiment was then repeated with adequate carbon dioxide control during the 72-hour exposure at depth, but with a much more strenuous decompression schedule. The animals were raised from 200 feet to 84 feet (7 atm to 3.5 atm; a 2:1 ratio) in 17 minutes and observed for 10 minutes. Pressure was then reduced to 70 feet in 3 minutes and the animals observed for 5 minutes. The chamber pressure was further reduced by increments of 10 feet for observation stops of 5 minutes until a depth of 40 feet was reached (3.16:1 ratio from the bottom). After 24 hours at this pressure, the animals were brought to the surface in 20 minutes (2.21:1 ratio from 40 ft).

No symptoms were noted at any of the stops. From previous experience with even shorter nitrogen dives, these ratios would have resulted in severe supersaturation of the slowly perfused tissue with resulting symptoms. These preliminary experiments point to the relative safety of decompression after saturation exposures to helium as compared with previous experience with nitrogen. They also indicate that excessive carbon dioxide buildup in a cabin atmosphere can predispose to bends symptoms in an otherwise safe helium decompression schedule. Unfortunately, there are too few data to quantitate the relative hazards of nitrogen and helium. This comparison must be made on the more adequate, yet insufficient, data on humans.

A limited number of decompression runs have been conducted with mice breathing a neon-oxygen mixture at 200 psig.³⁸⁸ Animals were decompressed in less than 3 hours after bottom times of up to 16 hours without major adverse effects. This is all the information available. Studies are also in progress at the Royal Naval Physiological Laboratories comparing the bends dose₅₀ of helium, neon, and nitrogen in rats.⁵²

Preliminary experiments on the exposure of rats to 7 atmospheres of mixed inert gases (10 percent oxygen, 45 percent helium, and 45 percent nitrogen) suggest that the mixed inert gases produce a higher incidence of bends in rats than does a 20-percent oxygen in helium mixture.²⁷² This would be expected from the greater sum of partial pressures of the inert-gas components in the triple mixed system than in the helium mix-

ture. The specific contribution of the nitrogen to the difference in bends incidence has not as yet been determined.

Human Decompression From High Pressures

The early history of helium use in diving mixtures is fascinating yet often forgotten in reviews of the subject. In 1919, a series of letters from Elihu Thomson to W. R. Watson of the General Electric Laboratories suggested that helium be used in caisson and diving work. This was suggested to avoid the limit on diving set by the supposed unavailability of oxygen at great depths. The idea was based on "the principle of the superior rapidity of diffusion of the low density gas."⁴²¹

Several years later, J. H. Hildebrand, the eminent physical chemist, suggested to Sayers and Yant that the coefficient of solubility of helium had recently been determined to be less than that of nitrogen and that it might be of use in combating caisson disease. Sayers and Yant^{377, 378} followed this up with experiments in guinea pigs (described in the previous section) and suggested that helium be tried in human diving. However, a patent for the idea went to Cooke in 1923,¹¹⁶ based on the solubility and diffusion characteristics of the gas.

In 1937, End¹⁵⁷ reported on the use of helium in human diving. Some divers were decompressed safely in times as low as 1/23 of that predicted by the air tables being used at that time. These tables, however, were known to be very conservative even for air dives.

In 1938, Behnke and Yarbrough⁴¹ reported their experiences with helium in diving operations. The gas was used primarily to avoid the narcotic effects of nitrogen at depths as great as 300 feet. These investigators suggested that the lower oil-water solubility ratio of helium should decrease decompression sickness as well as nitrogen narcosis. They noted in these studies that there was a distinct absence of grave symptoms of decompression sickness in a large number of divers who experienced the bends. No cases of unconsciousness or paralysis were reported. Itching and skin rashes occurred without sequelae. This was quite unlike the situation in air diving where these symptoms were often followed by neurocirculatory col-

lapse. Unlike the pains that tended to persist in equivalent air dives, pains occurring in one-third of the cases were promptly relieved by recompression. Behnke postulated that in diving operations employing helium the important or controlling tissues during decompression are those which are rapidly saturated and unsaturated, whereas with nitrogen, the slow or fatty tissues are controlling.

In 1939, Behnke and Yarbrough⁴² reported on the use of argon in deep sea diving. Argon had a much greater narcotic effect than did nitrogen. Unfortunately, the incidence or patterns of decompression sickness were not reported.

Behnke and Willmon⁴⁰ continued the study of helium with a comparison of saturation-desaturation curves for nitrogen and helium. The helium capacity of the body was found to be 8.0 ± 1.3 cc/kg of body weight when the tissues are in equilibrium, with a helium alveolar pressure corrected to 760 mm Hg or 1 atmosphere. This value is about 40 percent of the total nitrogen absorbed under these conditions. They also found that 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 curve of figure 11 drawn by Behnke.³¹

As was suggested in the analysis of goat data, the time at depth is an important factor in predicting decompression hazard. The total amount of gas dissolved in the body at depth is determined by the saturation-time relationship implied

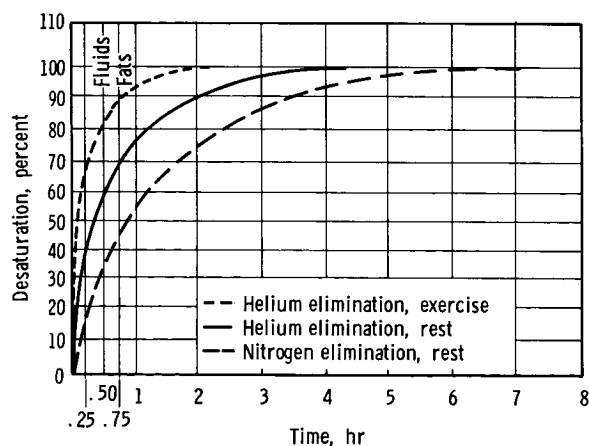


FIGURE 11.—Desaturation rate for man comparing nitrogen to helium. (AFTER BEHNKE.³¹)

by the desaturation curves of figure 11. Therefore, in considering the relative hazard of helium and nitrogen in decompression from depth, the duration at depth must be compared. Behnke³⁶ in analyzing this specific question, suggested that about 75 percent of the total body nitrogen is eliminated from the bodies of lean men in about 2 hours. After exposure at the usual diving depths, this rapidly exchanging nitrogen is eliminated without causing symptoms. It is the small amount of gas dissolved in fatty tissue that requires many hours for elimination. Behnke demonstrated with the data of table 11 that for a subject breathing air at a depth of 90 feet, 100 minutes of exposure dictate a period of 57 min-

TABLE 11. — Comparison of Total Decompression Time Following Exposure in Compressed Air and Exposure in a Helium-Oxygen Atmosphere [AFTER BEHNKE³⁶]

Depth, ft	Exposure, min	Decompression, min, in —	
		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	126
200	65	217	154
200	90	164

utes for decompression to avoid all symptoms. At the same depth, 9 hours of exposure required about 12 hours for decompression. If helium-oxygen mixtures are used instead of air, no more than 79 minutes of decompression time is required after all durations of exposure at 90 feet. Oxygen breathing was used throughout the decompression period on the helium-oxygen dives.⁴⁶² Behnke attributes these findings only to the rapid rate at which the body saturates and desaturates with helium. However, use of 100 percent oxygen must have also played a role. Since these points are rather critical in evaluation of diving experience for extrapolation to the space situation, it behooves us to attempt

a more specific understanding of the available data.

If lipid substances are indeed responsible for the prolongation of nitrogen absorption or elimination, helium, which possesses a lower solubility coefficient in slowly perfusing fatty tissue, should be eliminated in a shorter period of time. How does the organ-to-organ elimination of the two gases compare? Table 12 represents the fraction of nitrogen removed per minute from each organ in humans as determined from the tissue-specific volumes, gas volumes, and blood flow.²⁴⁶ The reference sources for these values may be found in the original paper. The relative low rate of nitrogen removal from the fatty tissues is quite clear. Recent organ-to-organ studies in dogs show that 80 to 90 percent of the total nitrogen is stored in slow compartments perfused by 10 to 15 percent of the cardiac output and has a time constant of 150 to 250 minutes.¹⁶⁴

No comparable organ-by-organ values have been calculated for helium. However, total body helium-elimination curves are available and can be compared with nitrogen curves for a direct comparison of half times of elimination. Many curves of total body nitrogen elimination have been published from which can be deduced the washout of several body compartments (exchange components).^{16, 31, 68, 246, 294} Figure 12 represents the nitrogen elimination curve of Jones.²⁴⁶ Discussion of this curve and equation (13) was presented in the first section of this chapter in the evaluation of tissue perfusion as a limiting factor of inert gas elimination. Jones and others have interpreted the four lines as representing the change with time of the rate of elimination of gas from each of four tissue compartments. The constants A of equation (13) represent the amount of nitrogen (at saturation) associated with each component and can be calculated by use of equation (14). The product Ak represents the amount of blood perfusing that tissue component for each stated time interval. The product Ak is often called the R constant. (See fig. 13.) The values of k are calculated as the reciprocal of the time required to effect a change in rate to $1/e$. This constant can be used to determine the component half times:

$$t_{1/2} = \frac{\log_e 2}{k}$$

TABLE 12. — *Distribution of Cardiac Output and Tissue Denitrogenation*
[AFTER JONES ²⁴⁶]

Tissue	Volume tissue, cc	Nitrogen volume, cc	Blood volume, liters/minute	Fraction of nitrogen removed per minute	
Lungs.....	1200	12.0	5.8	4.8	
Thyroid.....	30	0.2	0.30 ^a to 0.10	10 to 3.0	
Kidney.....	270	2.7	< 1.33	5.0	
Heart.....	300	3.0	0.15 ^a	0.5 ^a	
Adrenals, 7 cc.....	78	0.8	0.08 ^a	1.0 ^a	
Testes, 50 cc.....					
Prostate, 23 cc.....					
Salivary glands.....					
Brain.....	1400	14.0	0.02	0.5	
Marrow (hematopoietic).....	1400	30.0 ^b	0.76	0.5 ^c	
			0.30	0.15	
Hepatic portal:					
Liver.....	1560	17.0 ^b	1.5	Hepatic 0.27 ^a	
Spleen.....	150	1.5			
Pancreas.....	85	0.9			
Intestines.....	1350	13.5			Intestines 0.7 ^a
Stomach.....					
Colon.....					
			(Average 0.5)		
Intestinal contents.....	1500 ^a	100.0 ^a		0.008	
Muscle, 40 liters ^a	45 000 to 55 000	450 to 550	Probable minimum:		
Connective tissue, 5 liters ^a			1.0 to 0.40	0.025 to 0.01	
Skin, 5 liters ^a			0.1 to 0.05	0.02 to 0.005?	
			0.35 ^a to 0.25	0.07 to 0.01	
Fat, 12 liters ^a	15 000 to 5000	600 to 250	0.2 to 0.15	0.005 to 0.003	
Whole body.....	70 000	900 ^d			
70-kilogram man (1.85 m ²).....			Probable minimum: 5.89 to 5.09	Expected: 5.8 ^e	

^a Approximated.

^b Includes organ lipids.

^c 0.35—modal perfusion rates; 1.5—of cerebral tissues.

^d Not including intestinal gas.

^e Calculated from average value of direct Fick measurements of resting cardiac output.

The half times calculated for the body exchange components for nitrogen in one carefully studied case were presented in the first section of this chapter. The more general values for half times and the relative amounts of nitrogen at saturation associated with each (the constants *A*) are seen in figure 12: component (1), 1.5 min, 111 cc (8 percent); (2) 8.0 min, 193 cc (14 percent); (3) 29.5 min, 428 cc (29 percent); (4) 147.5 min, about 700 cc (49 percent).

Comparable curves have also been presented for helium ^{31, 35, 147, 246}. The early data of Behnke ³¹ were presented in figure 11. It was from these data, obtained at the Naval Experimental Diving Unit (EDU), Washington, D.C., that the first and most widely accepted helium elimination curve was constructed. Helium-oxygen saturation periods of only 3½ hours were used. The difficult estimate of helium elimination during the first 6 minutes was finally

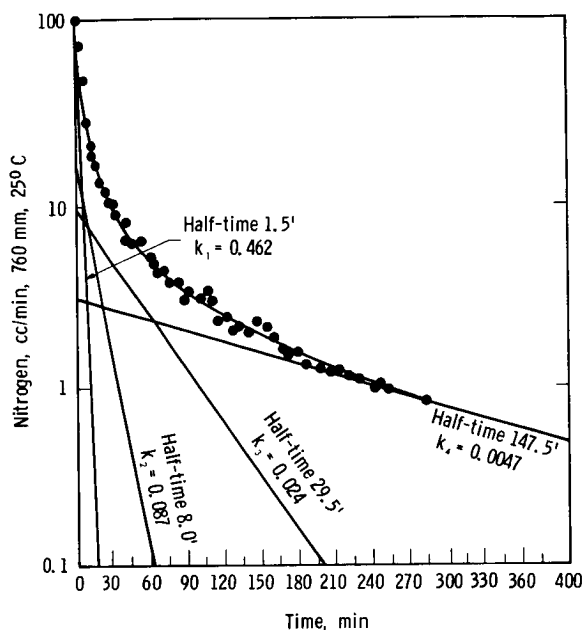


FIGURE 12.—Rate of nitrogen elimination. (AFTER JONES.²⁴⁶)

performed by extrapolation and is probably a source of error. It was found that the fit of the data could be obtained by employing an exponential equation with only three terms:

$$R_t = 0.085e^{-0.3t} + 0.0095e^{-0.02t} + 0.0015e^{-0.006t} \quad (16)$$

The time constants k (0.3, 0.02, and 0.006) were converted to half times and interpreted as indicating that about 28 percent of the helium is associated with a component which half saturates in 2.3 minutes. Forty-eight percent of the helium is in a component that half saturates in 35 minutes, and about 25 percent of the helium is in a component that half saturates in about 115 minutes.

As discussed previously in this chapter, Jones²⁴⁹ compared the elimination curves for all the inert gases. After several hours of saturation exposure, Jones obtained for helium the following time constants k (0.50, 0.094, 0.022 and 0.01). The equivalent half times were 1.4 minutes, 7.4 minutes, 31.5 minutes, and possibly 70 minutes.

In 1958, Duffner and Snider¹⁴⁷ published results of helium desaturation data collected

at the Naval Medical Research Institute (NMRI) during the period 1947 to 1948. These data, collected after 12 hours of helium saturation, fit the curve (fig. 13) for the equation

$$R_t = 0.25e^{-0.5t} + 0.045e^{-0.135t} + 0.0022e^{-0.025t} + 0.0006e^{-0.0073t} \quad (17)$$

The k constants (0.5, 0.135, 0.025, and 0.0073), converted to tissue half times, indicated that about 50 percent of the body helium is contained in a body component that half saturates in about 1.4 minutes, 33 percent in a component that half saturates in 5 minutes, and the remaining 17 percent in a component that half saturates in about 115 minutes.

The results of these three studies are compared in table 13. It can be seen that the NMRI data¹⁴⁷ are more nearly in agreement with those of Jones²⁴⁹ than with those of the EDU.⁴⁰ Actually, the NMRI curve (fig. 13) bears a close resemblance to the EDU curve of Behnke presented in figure 11 for elimination of helium with exercise. The EDU data were calculated in a more systematic way than those of the NMRI. The NMRI data were obtained after longer saturation periods (12 h). The data from both sources suffer from the uncertainties regarding the rate of helium elimination during the first 6 minutes, but the EDU data are probably more valid.

The differences in half times of desaturation of nitrogen and helium are quite distinct. As mentioned above, these have been used as a major criterion in establishing the differences between the air and helium diving tables. They serve at the present time to clarify the effect of duration at depth on the relative hazard of the two gases. Smith and Morales⁴⁰⁴ interpreted the EDU helium and nitrogen data as indicating that helium is released from one body component, mainly aqueous, while nitrogen is released from two, aqueous and fatty. This interpretation was based on the supposition that the number of exponential expressions describing the desaturation equals one more than the number of gas solvents in the body. The more recent data presented above would suggest that there are probably more slow components than were at

TABLE 13.—Comparison of Various Data on Helium Elimination
[AFTER DUFFNER AND SNIDER ¹⁴⁷]

	NMRI data ¹⁴⁷	EDU data ⁴⁰	JONES ²⁴⁹
R_0'	0.25	0.085
R_0''045	.0095
R_0'''0022	.0015
R_0''''0006
A_0'5	.283
A_0''33	.475
A_0'''088	.25
A_0''''082
K_150	.30	0.50
$T_{1/2}(1)$ ^a	1.387	2.31	1.387
K_2135	.02	.094
$T_{1/2}(2)$ ^a	5.13	34.6	7.37
K_3025	.006	.022
$T_{1/2}(3)$ ^a	27.7	115.5	31.5
K_4007301(?)
$T_{1/2}(4)$ ^a	95	(?)

^a $T_{1/2}$ = half time.

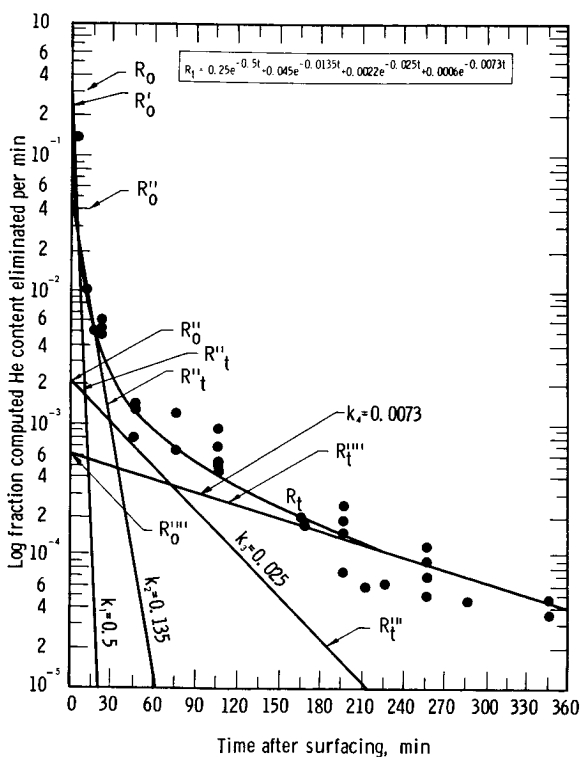


FIGURE 13.—Rate of helium elimination following 12-hour exposure to 1.72 to 2.05 atmospheres (absolute) helium in oxygen. (AFTER DUFFNER AND SNIDER.¹⁴⁷)

first suspected, and that the earliest component probably contains gas from the most highly perfused tissue of the body as well as from the lungs and blood. As seen in table 2, the low oil-water solubility ratio of helium (1.7:1) as compared with nitrogen (5.1:1) probably dictates that for helium dives of short duration, mostly the aqueous phases are saturated. Since phase 1 of the case 2 bubble in table 9 predicts helium to be more hazardous in bubbles forming primarily from aqueous media, the greater danger of helium in short-duration dives (table 11) becomes more reasonable. With these gas kinetics in mind, let us return to the saturation exposures at depth.

The data of table 11 most pertinent to the comparison of the two gases in space decompression would be the near-saturation dive of 540 minutes. In this case, an air dive required 683 minutes, while a helium-oxygen dive required only 79 minutes for return to the surface without symptoms. This eightfold difference is greater than the fourfold hazard difference predicted by the most differentiating bubble type, case 1 of table 9. Behnke also reported briefly that in exposures for 12 hours at a depth of 90 feet, air divers required 12 hours, while helium-oxygen divers required only 2½ hours to surface without

symptoms.²⁷¹ Here the relative time ratio was 4.8:1. It must be remembered that only the helium divers used oxygen decompression.⁴⁶² It is also pertinent that the number of subjects for exposures of these durations were limited and person-to-person variability may be great in helium diving (see below).¹⁴⁷ The original experimental protocols were not available for review, but it has been suggested that some of the cited data are not corroborated by the EDU diving logs.⁴⁶²

More important, however, is the fact that these times required for decompression are not a simple measure of the relative degree of danger expected after an acute decompression event. They are strongly dependent on the total amount of gas in each body component and the half time of each component as well as on the local factors which determine the peak size of a bubble at any given body site. Some disagreement would, therefore, be expected between the relative time required for safe decompression and the predictions from bubble peak index for saturated conditions. At the end of 9 or 12 hours at depth, there should be enough residual nitrogen in the slower storage compartments of the body (figs. 11 and 12) to be a possible significant factor.

The current Navy Diving Tables⁴²⁷ may be used for a first-order estimate of the degree of hazard expected for the two gases in long duration dives. In extracting the appropriate data from these tables, it must be remembered that there are variable periods at depths above 50 feet where pure oxygen is breathed on the way to the surface. There are time corrections which can be invoked for emergency ascents where no oxygen stops are used. It is from such corrected times that the comparative table times were determined. In dives of 240 minutes to 90-foot depth, the total decompression time required for air is 395 minutes; for helium, only 89 minutes. For dives of 240 minutes at 250 feet, the decompression time required for air is 1107 minutes and for helium, 294 minutes. These times may reflect the factor of safety predicted by table 9. However, it must be remembered that a direct test of the bubble-hazard index is not justified by these data. In the first place, the adequacy of the emergency schedules has not been determined.⁴⁶² In the second

place, the size and rate of desaturation of each of the gas storage components of the body becomes a factor in the slow, programmed decompressions of this type.

In the third place, although 4 hours at depth may be adequate for saturating most storage components with helium, it may not be adequate for desaturating the body components of nitrogen. This difference, suggested by a review of figures 11, 12, and 13 and the associated text, does not appear to be as clear on repetitive diving where the 240-minute $t_{1/2}$ tissue of helium must be controlled.⁴⁶² These factors may explain why there was only a fourfold difference between nitrogen and helium in the emergency tables as compared with the eightfold difference after the 540-minute dive in table 11.

A more clear-cut comparison of the relative hazard of the two gases is available from the study of Duffner and Snider.¹⁴⁷ The same men were exposed for 12 hours on air and then on helium-oxygen to increasing depths until they succumbed to decompression sickness during ascents of 25 ft/min. Table 14 represents the results of maximum depth determinations. In each case, greater depths could be tolerated after breathing the helium-oxygen mixture than after breathing air. What is striking, however, is the great variation in tolerance from person to person in helium dives. It is quite possible that not all extremes were encountered in this small population. No data are available on a significant factor, the general adiposity of each subject. However, the uniformity of maximum

TABLE 14.—*Maximum Depth of 12-Hour Exposures Tolerated Without Symptoms of Decompression Sickness, While Breathing Air as Compared to Helium (Ascent (Decompression) Was at a Rate of 25 ft/min)*

[AFTER DUFFNER AND SNIDER¹⁴⁷]

Subject	Age, yr.	Depth breathing air, ft	Depth breathing helium-oxygen, ft	Greater depth breathing He than air, ft
A.....	28	33	36	3
B.....	34	36	40	4
C.....	28	34	40	6
D.....	25	34	44	10
E.....	21	36	50	14

depth while breathing air shifts the focus away from adiposity. One would expect air dives to be more sensitive to adiposity than helium dives. Whatever factors are involved, the variability from person to person should be kept in mind during evaluation of helium atmospheres in space cabins.

From the above discussion it is evident that unequivocal quantitative data regarding frequency of symptoms after equivalent air and helium dives are lacking. The variables peculiar to diving operations obscure much of the data. It would, however, appear worthwhile to analyze the general spectrum of symptoms seen after dives with the two gases.

The absence of grave symptoms of decompression sickness following bends with helium diving has already been noted.⁴¹ Behnke has recently reconfirmed this impression given by his earlier report.³⁷ He further added that of 600 decompressions he monitored during salvage operations on the submarine *Squalus*, he remembers only one case with circulatory collapse and one with neurological defects. This is far lower than would be expected in operational diving while breathing air. Behnke also expressed the feeling that when bubble phenomena do occur, they are seen with helium much more rapidly than with air. The symptoms are also much more short lived than is usually the case with air. Behnke is sure that intravascular bubbles do occur after helium even though symptoms of the bubbles are rare. He often felt the crepitus of bubbles in the veins of the skin and saw lymphedema, but these signs did not advance to more serious sequelae.

In contrast to these reports, Workman⁴⁶² indicated that it is his impression that there is little difference between the symptom complexes of air and helium. In a review of recent data at the EDU, there appeared to be no difference in incidence of bends (0.83 percent) between air and helium-oxygen diving. It must be remembered that these data are equivocal for two reasons: Helium-oxygen dives are at greater depth; and there is a considerable oxygen stop with these deep dives which would tend to reduce the symptoms. The overall equality in incidence of bends would speak in favor of the relative safety of helium. Other variables that

Workman covered in comparing helium-oxygen and air bends were:

- (1) Depth of relief on recompression: no difference.
- (2) Recurrences: Slight tendency for more recurrences on helium-oxygen.
- (3) Number of sites affected: no difference.
- (4) Number of signs manifested: no difference.
- (5) Treatment: helium-oxygen bends respond more easily to treatment compression and in older tables required shallower oxygen stops than did air bends. Fifty cases of helium-oxygen bends responded to depths which were not efficacious in air bends.

Workman did agree that symptoms appearing with helium usually present themselves within the first 30 minutes after decompression (1956-1962 EDU data). A diver free of symptoms 30 minutes after helium-oxygen decompression will usually continue to be free of symptoms for the duration of the decompression. On the other hand, experience with nitrogen suggests that the onset of symptoms may occasionally continue for as long as 2 hours after initiation of ascent. The majority of symptoms begin before the end of the first hour, but they may occur as long as 12 to 24 hours after ascent. In diving practice individuals cannot be brought to depths as shallow on the first stop with helium-oxygen as with air. These are the only comparative factors for which Workman has definite data. Workman also mentioned that Hempleman and associates at the Royal Naval Physiological Laboratory at Alverstoke, England, have corroborated the advantage of helium over nitrogen in determination of maximum depth allowable for nonstop decompressions. Wide person-to-person variability was also noted with helium. He indicated that even though the 1950 tables reflect only minor changes to the basic tables calculated in 1938, the helium tables are still overconservative for shallow dives^{145, 464} but not conservative enough for deep dives.¹²⁵ The slower half-time tissues must be considered for longer and deeper dives.⁴⁶³ Experimental expediencies at the time the tables were originally created were indicated as the source of these defects.

The uncertainties of diving schedules for great depths are clear.²⁷¹ A recent study by Brunner

et al.⁷⁹ reported two cases of full blown post-decompression shock after deep helium-oxygen dives of 20 minutes at a depth of 650 feet. The ratio of helium to oxygen was 90 to 10. The timing of decompression was experimental, and so the degree of conservatism is unknown. The subjects experienced the plasma loss and shock associated with neurocirculatory collapse at altitude. Some reflex changes were noted. Transient electrocardiogram changes of cor pulmonale suggest obstruction of pulmonary circulation with gas or lipid emboli. Extension of decompression time to 220 minutes prevented similar episodes in subsequent experiments.

In these well-studied cases, physiological similarity between neurocirculatory collapse of altitude and diving with helium is suggested. In general, divers who tend to be relatively tolerant to pressure changes when breathing air are also tolerant when breathing helium-oxygen.^{146, 405} There is only borderline correlation between susceptibility to pain of decompression sickness while breathing any gas and low sensitivity to pain threshold for mild electric shock.

In a recent review from the EDU Research Unit, 935 cases of decompression sickness in diving were recorded.³⁶⁵ In the report are many statistics on symptomatology and environmental background in both air and helium diving. Unfortunately, the format of the report is such that no direct comparison can be made between the degree of hazard or pathological physiology involved in equivalent air and helium dives.

Another approach to the selection of optimum inert gas for decompression is the possible simultaneous use of several inert gases. Will any constant mixture of helium and nitrogen be any better than either one of the components? One would predict from the discussion of bubble factors that there would be no optimum fixed mixture in saturation conditions. Webster⁴⁴⁶ attempted to answer this question by analyzing the Navy diving tables⁴²⁸ for air and oxygen-helium gases. The analysis suggested there may be an optimum mixture of helium and nitrogen which minimized the tendency toward decompression sickness. However, there are several errors in the analysis which shed some doubt on this prediction.

Curves were drawn by entering the diving tables and determining the time required for safe decompression from various depths with mixtures containing different percentages of helium and nitrogen. The times were plotted against percent of each gas in such a way that on the abscissae, helium percentages begin with 12 at one end of the scale, and nitrogen, with 12 at the other end. Figures 14 and 15 demonstrate these curves. It can be seen that for the shorter dive of figure 14 (30 minutes), the summed curve (dashed) 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, a time at which the body is only 50 percent saturated with helium.³¹ Durations of air diving long enough for complete nitrogen saturation are not permitted by the Navy tables so that curves of very long duration are not available. The pertinent summation of such curves for very long durations is, therefore, not possible. One could predict that analysis of such saturation curves would present

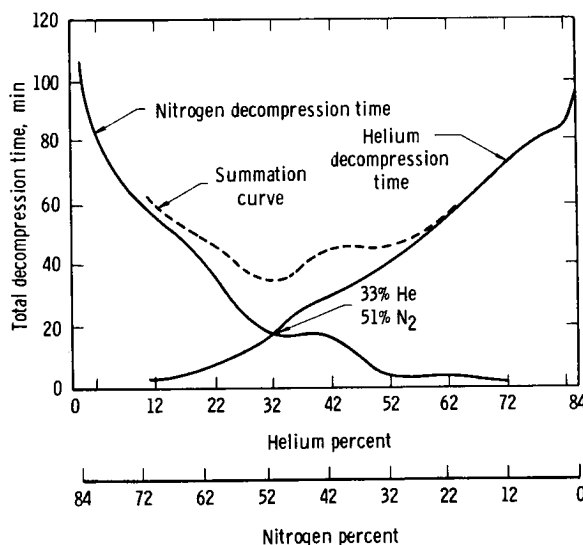


FIGURE 14.—Theoretical decompression time for dive to 180 feet for 30 minutes. (AFTER WEBSTER.⁴⁴⁶) Curves are based on the following: $O_2 = 16$ percent; $D = 180$ feet; $p_{He} = (D + 33)(\%He + 2)$ feet for helium tables (a loss of 2% O_2 in helmet is assumed); $p_{N_2} = (D + 33)(0.79)$ feet for standard tables; N_2 is assumed to include all other gases except O_2 and He.

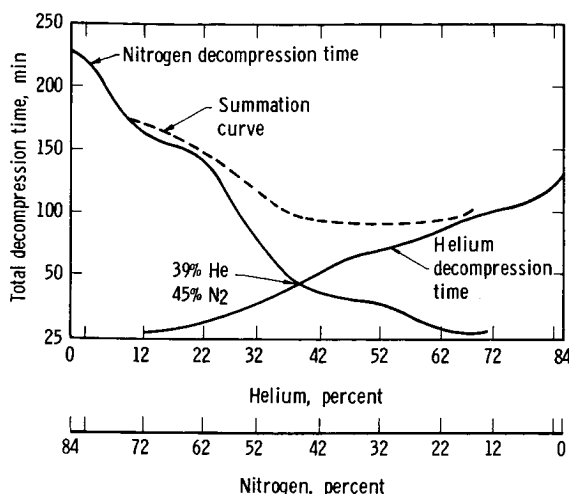


FIGURE 15.—Theoretical decompression time for dive to 180 feet for 60 minutes. (AFTER WEBSTER.⁴⁴⁶) Curves are based on the following: $O_2 = 16$ percent; $D = 180$ feet; $p_{He} = (D + 33)(\%He + 2)$ feet for helium tables (a loss of 2% O_2 in helmet is assumed); $p_{N_2} = (D + 33)(0.79)$ feet for standard tables; N_2 is assumed to include all other gases except O_2 and He.

a summation curve which had no distinct minimum and tended to be negatively sloping down through the entire mixture range, with 80 percent helium and 20 percent oxygen being the mixture offering minimum decompression time. There would probably be no optimum mixture under conditions of complete saturation. Workman has pointed out a theoretical consideration invalidating this approach.⁴⁶² He suggests that the times required for oxygen-helium and oxygen-nitrogen dives in which high fractions of oxygen are involved cannot be summed, since the gradients for inert gas uptake by the slow tissues which obligate the decompression time are not equivalent. However, it is possible that there may be an unexpected tradeoff between desaturation rates and bubble factors to give a minimum time.

The use of changing mixtures of gas in diving is a different matter which is receiving much attention. A series of dives have been performed at depths of up to 1000 feet by Bühlmann, Keller, and associates.^{84, 328, 252, 253} These investigators have made use of the fact that nitrogen and argon saturate the body tissues at a much slower rate than the desaturation rate of

helium. After diving to great depth on helium-oxygen mixtures, the gas is then switched before or during decompression to nitrogen-oxygen or argon-oxygen in a program which never allows the critical supersaturation ratios of any one of the inert gases to be exceeded in the tissues. Helium is thereby eliminated through the lungs with a maximum pressure gradient and without the danger of oxygen toxicity. Nitrogen or argon narcosis is also avoided. Keller and Bühlmann reported that a dive of 10 minutes at 700 feet in the French Navy's pressure tank at Toulon required only 2½ hours of decompression time. Similar dives by the Royal British Navy in 1956 for 4 minutes at 600 feet used 6½ hours of decompression and resulted in bends requiring an additional 5½ hours of decompression time. The dive to 1000 feet for 5 minutes was attempted on a 4-hour decompression schedule, but 2 hours was added when the divers experienced bends near the surface. Other deep dives by this group in the sea resulted in fatalities of an obscure nature. The sequential use of inert-gas mixtures would appear to have no application to the space condition where 100 percent oxygen could be used for rapid removal of inert gas prior to decompression without danger of oxygen toxicity.

Hydrogen gas, while too explosive for space operations, does present some interesting theoretical points for discussion. Hydrogen was actually used for deep diving by the Royal Swedish Navy during World War II instead of helium which was unavailable. The pioneering efforts of Arne Zetterström have been recorded.^{65, 449, 477} By keeping the oxygen content below 4 percent after the nitrogen gas was changed to hydrogen at depth, the upper concentration limit for hydrogen explosion was exceeded and the hazard was eliminated.³⁷⁰ This procedure, of course, would be impossible in space vehicles, since cabin pressures of about 5 atmospheres would be required.

Would hydrogen be expected to be safer than helium or nitrogen in decompressions? The solubility coefficient of hydrogen in water is 0.017; and in olive oil, 0.036.^{65, 139} Comparing these values with those for helium and nitrogen (table 2), it appears that the water solubility of hydrogen is actually greater than that of nitrogen.

The oil solubility appears to be halfway between that of helium and nitrogen. The diffusion coefficient of hydrogen in water is 0.8 that of helium¹³⁹ and so the permeation coefficient

$$D' = (\alpha_{\text{water}} D_{\text{water}})$$

is 1.6 times greater. Hydrogen would appear to be more dangerous under saturation conditions than helium at sites where an aqueous medium is controlling the rate of bubble formation. No figures are available for the diffusion coefficient of hydrogen in oil, but from the relative diffusion coefficients in water, the value would be expected to be slightly smaller than that of helium. Since the hydrogen solubility in oil is greater than that of helium (see above), the permeation coefficient through oil would, therefore, be somewhat greater than that of helium. Thus the bubble factors dependent on a fatty medium would lie between helium and nitrogen in representing the degree of hazard. It appears that hydrogen would definitely be no better than helium and, possibly, no better than nitrogen in reducing the overall decompression hazard.

The tragic death of young Zetterström occurred as a result of his experiments with decompression on hydrogen. After two successful dives with 72 percent hydrogen, 24 percent nitrogen, and 4 percent oxygen down to 40 and 110 meters, Zetterström switched to 96 percent hydrogen, 4 percent oxygen. He made a successful dive to 70 meters, and on the fourth dive he reached 160 meters, a world-record depth. Because of an error on board the diving boat, a guy attached to the diving platform was retrieved very rapidly to bring the diver directly to the surface from 50 meters. Zetterström died from acute hypoxia and violent decompression sickness.⁴⁴⁹

Recent preliminary studies at the Royal Navy Physiology Laboratory, Alverstoke, indicate that neon may have an advantage over nitrogen in reducing decompression sickness.⁵⁴ Unfortunately, the results are only preliminary with 10 subjects exposed to 200 feet and 20 to 300 feet. Since the narcotic tendency of neon was under study, the men breathed the neon in the 200-foot dives only until ascent was started and then switched to air. From 200 feet, according to the Miles adjustment of the Crocker tables,

the stops were: 5 minutes at 30 feet, 5 minutes at 20 feet, and 15 minutes at 10 feet. In the 300-foot dives, neon was breathed for only the first 9 minutes of decompression and then a switch was made to air. Decompression was performed according to the Damant tables III with a total ascent time of 87 minutes and the first stop at 100 feet. The attendant breathing air throughout developed bends and severe itching, while the men breathing neon had no trouble. At present the bends dose₅₀ of helium, neon, and nitrogen are being compared in rats, and it is hoped that more neon will be made available for human studies.

Unfortunately, diving experience gives us no unequivocal quantitative data comparing the relative hazards of the inert gases. Some indications point to the relative safety of helium over nitrogen in the area of severe symptoms of chokes, neurological lesions, and neurocirculatory collapse. These symptoms are not completely eliminated by helium. In the case of milder bends the evidence does tend to indicate the relative safety of helium, although the data are also equivocal. Such differences would be predicted by the bubble factors of table 9, especially the equivocal differences between the gases in bends hazard.

Human Decompression to Altitude From Helium-Oxygen Atmospheres

No animal studies are available on the relative hazards of inert gases in altitude decompressions. No published data on humans have been presented. During discussions of diving hazards with Workman,⁴⁶² it was suggested that Behnke had performed altitude decompressions with helium-oxygen mixtures at the Navy Experimental Diving Unit during World War II. Workman was kind enough to search the archives of the institution and found a single protocol outlining the results of these studies. Table 15 represents this protocol of March 1941. The first six subjects were exposed to atmospheres of 80 percent helium and 20 percent oxygen at sea-level pressure for 3.5 or 5.5 hours. They were then placed on 100 percent oxygen for varying periods of from 1 to 1½ hours; at the end of that time they were decompressed to 37 000 feet over a period of 6 to 8 minutes. According to the log, no

TABLE 15.—*Decompression to 0.20 Atmosphere Following Helium Exposures*
 [AFTER WORKMAN⁴⁶² FROM UNPUBLISHED WORK OF BEHNKE]

Time breathing 80 percent helium and 20 percent oxygen, hr:min	Time breathing 100 percent oxygen, hr:min	Decompression to 37 000 feet, hr:min	Time at 37 000 feet, hr:min	Descent to surface, hr:min	Remarks	Subject
3:30	1:30	0:08	6:00	0:07	Uneventful	1
3:30	1:30	0:07	1:57	0:13	Shoulder pain onset 1:55	2
5:30	1:00	0:06	2:46	0:08	11 min "S.I." ^a	3
		0:08	2:39	0:08	Uneventful	
5:30	1:02	0:07	0:44	0:07	Uneventful	4
5:30	1:24	0:07	0:44	0:07	Leg pain onset 0:35 ^b	5
^c 9:00	0:45	0:07	4:00	0:07	Ankle pain onset 2:00	6
^d 9:00	1:30	0:07	4:00	0:07	Uneventful	7

^a 11 minutes of surface intervals between altitude exposures.

^b Treated with overcompression; 3-minute compression to 100 feet, 8 minutes at 100 feet, 10-minute ascent.

^c Atmosphere composition was 49 percent helium, 2 percent nitrogen, and 48 percent oxygen.

^d Atmosphere composition was 77 percent helium, 2 percent nitrogen, and 21 percent oxygen.

exercise was performed at altitude. Four out of the six periods at altitude, ranging from 44 minutes to 6 hours, resulted in no symptoms. One subject experienced shoulder pains after 1 hour and 15 minutes, and after 2 minutes more at altitude returned to sea level. Subject 5 had leg pain at 35 minutes, remained at altitude for 9 minutes and continued to have difficulty after return to sea level. He was compressed in 3 minutes to 100 feet of water pressure, remained at 100 feet for 8 minutes, and then returned to sea-level pressure over a 10-minute period. Symptoms apparently were relieved by this therapeutic compression.

It must be pointed out that the 3.5-hour exposure to helium-oxygen did not fully saturate the tissues with helium, and, what is more important, did not deplete the slowly exchanging fatty tissues of nitrogen (figs. 12 and 13). Helium saturation was more complete at 5.5 hours although residual nitrogen was no doubt present in the tissues.²⁶ One of the two subjects who experienced bends was in the 3.5-hour group; one was in the 5.5-hour group. Both had almost equal periods of preoxygenation, and these periods were no shorter than those undertaken by subjects who were free of symptoms.

The last two subjects on the protocol had exposures quite similar to those expected in space cabins. Subject 6 was breathing 49 percent helium, 3 percent nitrogen, and 48 percent oxygen for 9 hours. He almost completely saturated his tissues with helium and had probably equilibrated his tissues with the 3-percent nitrogen in the atmosphere. His short preoxygenation of 45 minutes was followed by 2 hours of symptom-free rest at 37 000 feet. He experienced ankle pain, but from the protocol it appears he remained at altitude for 2 more hours and did not require compression therapy. The last subject was breathing a 77-percent helium, 2-percent nitrogen, 21-percent oxygen mixture for 9 hours with probable equilibration of tissues to both inert gases. He preoxygenated for 1.5 hours and remained at altitude for 4 hours without symptoms.

Evaluation of these results is most difficult because of the paucity of subjects in each pre-atmosphere category and the relatively long duration of exposure to altitude. It appears that under the conditions of this experiment, helium does not relieve all of the bends symptoms to altitude. It is difficult to say from these data that the incidence of symptoms is any different from what would be expected from prior exposure

to air followed by one to 1½ hours of preoxygenation. Table 12²⁴⁶ suggests that young, unselected 17- to 24-year-old subjects could expect, after 1 to 1½ hours of preoxygenation (no exercise), an 88-percent to 96-percent decrease in incidence of bends during 90 minutes at 28 000 feet; and about 80 percent decrease in incidence after only 45 minutes of preoxygenation. Since the expected incidence at 38 000 feet for the young group without preoxygenation would be about 45 percent for resting subjects,²⁴⁶ the expected incidence of bends after about 1 hour of preoxygenation from an air environment would be only about $0.90 \times 0.45 = 40$ percent. One would not expect the incidence of symptoms to increase significantly for periods longer than the 90 minutes of exposure.^{222, 223} Specific details of these nitrogenation factors will be covered in a later section.

From these data, there appears to be no advantage of 80 percent nitrogen and 20 percent oxygen over 80 percent helium and 20 percent oxygen when followed by 1 to 1½ hours' preoxygenation before decompression to altitude. The incidence of symptoms of two-sixths, or 33 percent, appears close to the 40 percent expected for nitrogen. Absence of such crucial data as age of the subjects (fig. 16),^{203, 246} the limited number of subjects, and the nonequilibrium conditions of inert-gas saturation in these

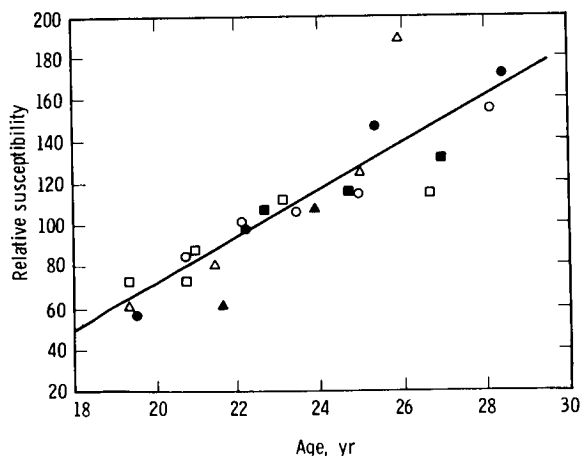


FIGURE 16.—Relationship between relative susceptibility and age. Relative susceptibility = $(10.8 \times \text{age}) - 145$. (AFTER GRAY,²⁰³)

studies preclude adequate evaluation of the helium effects.

Beard et al.³⁰ have recently presented preliminary data on decompression from helium-oxygen mixtures at altitude which were preceded by 6.5 hours of denitrogenation. The protocol closely simulated early stages of orbital flight, although it once again represented the unsteady state regarding nitrogen and helium equilibration. The data suggest that helium and nitrogen under these conditions produce bends at similar rates with a slight advantage for nitrogen under some of the test schedules. These data tend to substantiate the prediction of table 9, case 4, that the incidence of bends under near-equilibrium conditions of inert-gas saturation should be the same for nitrogen and helium.

The successful use of neon in diving by the Royal Navy has not as yet been followed by studies at altitude. The definite advantage indicated for neon by the theoretical analysis of table 9 should be tested for empirical reality.

After review of bubble growth factors and controlled decompression experience, one point remains to be covered—the relationship between the two. The bubble theory presented in the previous section represents a tool for determining those gas-dependent factors which control the rate of growth and decay of gas bubbles for local supersaturation ratios at various body sites. For any acute decompression event, the degree of danger appears to be related to the peak bubble size or pressure that can be attained. The ascent schedules used in diving also represent a degree of bubble hazard. Here, the hazard is determined, in part, by the relative rate at which tissues dispose of gas to the bloodstream or to an autochthonous site. Empirically, if the supersaturation ratios in tissues with critical half times are kept below a given level, bubbles will not develop frequently enough or grow large enough to cause symptoms. The ratio of supersaturation tolerance may be, in reality, not even an index of bubble size, but an index of the degree of embolization that the body can tolerate. However, there is no empirical evidence supporting this often-quoted hypothesis.

It therefore appears pertinent to examine the concept behind diving schedules. Focus must be kept on the role of critical supersaturation

ratios in the establishment of these tables. It is only after these concepts are understood that one can approach an overall hazard index for specific combinations of inert gas and oxygen.

DECOMPRESSION SCHEDULES AND DENITROGENATION PROGRAMS IN THE PREVENTION OF DECOMPRESSION SICKNESS

Prevention of decompression sickness in diving has been accomplished by the appropriate combination of ascent schedules and denitrogenation techniques. In aviation experience, the latter has assumed more operational practicality than the former. In the space-cabin situation, both techniques may be used to reduce the hazards of decompression sickness. In this section an attempt is made to review briefly the philosophy behind diving ascent schedules. This approach has led to current computer programs which can control ascent with great safety. These computer methods will be presented and an attempt is made to relate the approach to the space-cabin problem.

The basis for the preoxygenation-denitrogenation programs used in military aviation is then covered with an extension to recent studies defining the decompression hazard of oxygen-enriched atmospheres. Finally, an attempt is made to synthesize a possible approach to the use of these varied techniques in space operations.

Ascent Schedules in Diving

Most ascent schedules for diving have been based on the classical Haldane method.⁷² This method is based on the following assumptions by Haldane and associates:

(1) The nitrogen tension in the blood is always in equilibrium with the partial pressure of nitrogen in the air breathed.

(2) At the site of the bends development, tissue takes up nitrogen at a rate proportional to the difference in nitrogen tension between tissue and blood.

(3) When the blood nitrogen suddenly changes to a lower partial pressure, the partial pressure of nitrogen in the tissues will change exponentially with time, the half times ranging from 5 to 75 minutes.

(4) Any tissue can withstand decompression to an ambient pressure at which the absolute pressure is half that of the gases in the tissue or an ascent ratio of 2 to 1.

It should be pointed out that Haldane and his associates recognized that the rate of saturation and desaturation of some tissues was slower than they had assumed. This rule was indicated to be adequate for "obviating the risk of serious symptoms while at the same time reducing the chance of bends to a minimum" in the short dives at moderate depths (< 200 feet), typical of their day.⁷² Subsequent experience with more strenuous dives has suggested modification of the 2 : 1 ratio. These modifications have been adequately reviewed by Workman,⁴⁶¹ Crocker and Hempleman,¹²⁵ and Rashbass³⁵⁸ to name a few. Because the 2 : 1 ratio of Haldane has assumed a touch of magic in the eyes of many not familiar with diving physiology, a brief review of specific modifications is in order.

Hawkins et al.²¹⁵ felt that the ratio of 2 to 1 was too conservative for fast tissues and not conservative enough for slow tissues. On the basis of an analysis of 2143 dives to depths between 100 and 200 feet, they determined that more appropriate safe ratios for tissues of given desaturation half times would be:

Half time for tissue desaturation, min	Safe ratio
5.....	5.5 : 1
10.....	4.5 : 1
20.....	3.2 : 1
40.....	2.4 : 1
75.....	1.8 : 1 to 2.0 : 1

They revised the Navy diving tables and increased economy of time and safety by ignoring the 5- and 10-minute tissues and applying ratios of 1.8 : 1 to 2.0 : 1 for 40- to 75-minute tissue.

The nitrogen elimination curves of Behnke³² made a notable contribution to the art of diving. Behnke's data agreed with the first three assumptions of Haldane but continued to shed some doubt on the 2 to 1 ratio for the tissues of longer half time. The U.S. Navy diving tables in the 1940's and 1950's omitted the 5- and 10-minute tissues and followed the "three tissue" approach

of Hawkins et al.²¹⁵ with a slight decrease in the ratios of the 20-minute tissue to 2.45:1 from 3.2:1; 40-minute tissue to 1.75:1 from 2:1; and the 75-minute tissue to 1.75:1 from 2:1. For deep dives of long duration simulating the altitude situation, these ratios were still inadequate. The studies of Van der Aue et al.⁴³² during World War II suggested that all tissue ratios be reduced for these long dives. Subsequent studies by Van der Aue and associates led to the review of Workman,⁴⁶¹ who suggested that for long-exposure dives of emergency type, control of the 120-, 160-, and 240-minute tissues at a ratio of 1.94 to 1 ratio would be required.

It thus appears that the Haldane rule of 2 to 1 must not be taken out of context of the original diving parameters (< 200 feet) for which it was intended. These ratios do not represent p_{N_2} but treat total pressure as though air were 100 percent nitrogen. Long-duration dives require consideration of much slower tissues than were originally intended by Haldane. From experiences at altitude where the probable ratio is close to 2.7 to 1 and at great depth where the ratio may be < 1.75 to 1, it is apparent that the Haldane rule should be applied with caution. However, it must be kept in mind that with the appropriate consideration of the slow tissues and appropriate conservatism at great depth, the multiple tissue approach of Haldane does have merit. Current equations for the Haldane calculation of ascent times have been presented by Behnke³³ and Schenck.³⁸⁰

Other approaches to decompression schedules have had their drawbacks. Piccard's treatment of bubble formation³⁴² led to the idea that it is desirable to maintain constant differential pressure acting upon tissues at any depth. This results in a pressure-volume-density control of tissue tensions which should keep the tendency to bubble formation constant at all times. However, Workman⁴⁶¹ reports that for diving operations such an approach is vastly more conservative than current diving experience suggests is necessary. However, no calculations by Piccard or contrasting diving data are presented in argument.

Still another approach has been suggested by the studies of Hempleman et al.²²⁰ and Rashbass.^{358, 359} Instead of studying the rates of nitrogen equilibration in a number of tissues,

these investigators suggested that only one hypothetical tissue be considered. This tissue would have a structure and nitrogen equilibration consistent with well established ascent schedules in diving. This type of tissue is one through which nitrogen diffuses slowly. Nitrogen exchange in this hypothetical tissue is limited not by perfusion or transcapillary diffusion, but solely by linear diffusion, following the Fick equation, across a tissue slab. In other words, the tissues are considered to be immobile solvent layers as opposed to Haldane's tissues, which are regarded as well stirred fluids separated from the blood by a thin diffusion shell. The time course of the quantity of nitrogen in the tissue following a step function in the blood concentration at a time when the tissue and blood are in equilibrium is analyzed by Hill's solution of the Fick equation.²³⁴ In contrast to a limiting supersaturation ratio of the Haldane approach, the Hempleman-Rashbass method uses a finite tissue pressure head of nitrogen above ambient as critical. This was fixed at 30 feet of water by Rashbass. The ascent is controlled to prevent this pressure head in the tissues.

From the discussion in the first section of this chapter, it would appear that some of the basic concepts behind this approach may be in error. The evidence of perfusion limitation of inert-gas exchange and similar concepts appears to be directly contradicted,²⁴⁹ although the diffusion limitation may hold for critical tissues even if it does not generally hold for the body as a whole. Many of the other physiological arguments in support of this approach are not clear.²¹⁹ It is far from certain that avascular cartilage of the joints and spinal-column disks are responsible for symptoms of bends and paralysis. Also, the fact that the bends probability in goats decompressed in 150 seconds is a function of pressure P and the square root of the time t at depth ($Pt^{1/2} = \text{Constant}$) does not necessarily indicate that a limiting diffusion process is involved. Another argument brought up in favor of a diffusion-limited process is that the amount of nitrogen eliminated in the first 90 minutes of a desaturation experiment when plotted against the square root of time gives a linear plot. The suggestion that this indicates a diffusion-limited process is certainly overlooking many alternate

hypotheses. The validity of a critical tissue pressure P is also open to question.²⁷¹ Nevertheless, the method must be considered on its own merit.

How effective is this approach? Apparently, this method greatly simplifies the calculation of tables for short, shallow dives but does not appear to be satisfactory for dives of long duration.⁴⁶¹ Workman attributes failure to two factors: desaturation of the entire body is assumed to be 98 percent complete in 6 hours; and (2) for exposures of 20 to 480 minutes, inert gas uptake is considerably less by Fick's equation than actually demonstrated for the 5-, 10-, 20-, and 40-minute tissues. Dives calculated by the U.S. Navy modification of the Haldane method^{151, 201} using the decompression tables derived by Rashbass³⁵⁸ reveal surfacing tissue tensions in excess of safe values, especially in long-duration dives. The "constant differential control method" of Rashbass appears to be inadequate for the "saturation" types of decompression events to be expected in most cases in space vehicles.

Ascent schedules for helium diving were first calculated by adapting Haldane rules for the shorter tissue half times of helium.³¹⁷ The slowest tissue taken into account was that with a half time of 60 minutes. The early, rapid ascent of the nitrogen table, therefore, was reduced. The ascent ratio was calculated by considering the tissue partial pressure of helium plus the partial pressure of nitrogen at atmospheric pressure divided by the absolute ambient pressure. The addition of longer oxygen stops at 50 feet gave a table that was adequate for short-duration dives at moderate depths. However, the tables were quite inadequate for very deep dives.^{125, 316}

The Russians have attempted to analyze the permissible supersaturation ratios for helium-oxygen mixtures⁷ in diving. For the maximum depth recorded (22.5 meters or 3.25 atm), a value of 2.66 was obtained as compared with 2.40 for a depth of 19 meters (2.95 atm) for air. Brestkin⁷⁵ has attempted to analyze the changing supersaturation coefficients (SC) or the critical ratio P_0/P of helium, nitrogen, and carbon dioxide in water under varied total pressures in a dilatometer system with the production of visible bubbles as an end point. With an increase in

tension, the SC decreases as tension of gas increases up to 20 atmospheres and remains constant with further increase for helium and nitrogen. The absolute values of SC as well as the decrease in SC with pressure were greater for nitrogen than for helium. In contrast to the SC, the pressure head or $P_0 - P$ increases with P_0 . The relatively stable SC at pressures above 20 atmospheres is explained by Laplacian surface tension and radius factors. The significance of these studies to operational diving has also been discussed^{476, 76} with emphasis on the difference between physical and physiological systems.

Crocker and Hempleman¹²⁵ attempted to apply the Hempleman-Rashbass constant differential control method to helium-oxygen dives. This method also proved operationally inadequate for helium dives at great depth or for useful periods of time.¹²⁵

It is not clear at this point whether the pressure ratio or pressure head are controlling factors in the deep, long-duration dives. It is also not certain how much the critical ratios or critical pressure differences change with changes in the absolute pressure. There is a suggestion that the process of uptake and elimination of gas may not be reversible in diving operations. Formation of "silent bubbles" in tissues may well alter the elimination rate by adding an extra "diffusive barrier" in critical tissues. Another factor confusing the issue is the variable amount of fat in divers (2 to 20 kg).³⁷ For saturation dives on helium, estimates of the slowest tissues range up to half times of 180 to 200 minutes with 98 percent saturation in 18 to 24 hours, well beyond the estimates based on gas measurements following saturation. It appears clear, however, that by making use of the sequential change of inert gases during ascent²⁵³ and pushing the percentage of oxygen to its physiological limit, a maximum tissue-to-lung gradient of helium can be maintained, the tissues can be desaturated at a maximum rate, and ascent time can be minimized.

Computer Programs in Diving

Several computer approaches have been used in diving operations. The French have applied a modification of Haldane's approach to helium-

oxygen scuba dives.⁶³ They have programed on an IBM 1620 computer an equation which gives the pressure of any inert gas in a tissue of known half time after inhaling the gas at a given pressure for a given time. Approaching the decompression the same way, they can arrive at a tissue pressure after a given period of desaturation. By then comparing the supersaturation ratios with critical ratios derived from symptom experience on known tables, they have programed ascents to avoid the critical ratios. The critical ratios assumed are given in table 16. Thus, the computer program can be used to calculate the tension of dissolved helium in each of the four half-time tissues during preoxygenation, during descent with changing percentage of oxygen in the mixture, during bottom time, and during ascent. The computer can indicate duration of stop at 3-meter intervals. During the past few years the program has proved useful for shallow dives and for a limited number of dives up to 150 meters. No mention was made of saturation dives with a helium-oxygen mixture which is of immediate pertinence to the space-cabin problem.

Computer programs have merit in planning operational diving decompressions, but become somewhat cumbersome during the actual operation. Repetitive diving and emergency situations beyond the preplanned schedule are most difficult to control by these methods. In recent years, however, several analog approaches have been presented which deserve special mention. The possible use of similar techniques in space operations is evident.

In 1953, conversations between Hugh Bradner of the Radiation Laboratory of the University

TABLE 16.—Critical Supersaturation Ratios and Tissue Half-Times in Helium-Oxygen Scuba Diving

Depth of dive, m	Half time of limiting tissue, min	Critical supersaturation ratio
11.....	120	1.7
12 to 20.....	60	1.8
20 to 35.....	30	2.0
35 to 55.....	7	3.0

of California and Groves and Munk at the Scripps Institute of Oceanography at La Jolla, Calif., led to the development of a hydraulic analog of the tissue-desaturation mechanism.²⁰⁸ Bradner reviewed the concept of supersaturation ratios and perfusion limitations of inert-gas exchange²⁴⁹ and suggested an analog computer based on Henry's law, a linear device which would indicate when tissue saturation was greater than surrounding pressure by a given factor. Groves and Munk²⁰⁸ presented several designs of a small analog device to be carried by the diver and modeling the uptake and release of nitrogen by critical body tissues. The diver was to merely regulate his ascent by keeping his depth within a Haldane ratio of his critical tissue. The gage automatically accounts for irregular depth-time history of repetitive dives and allows continuous optimum ascent instead of uneconomical staged ascent. A schematic diagram of this device is seen in figure 17. The chamber consists of a capillary through which sea water can enter. An evacuated bellows is compressed proportionally to the pressure in the chamber. This gives a "constant time-constant" gage. This means that the time constant of the chamber with fixed volume and capillary orifice determines the pressure changes in the fixed aneroid indicator. If P and P_i are the pressures of the

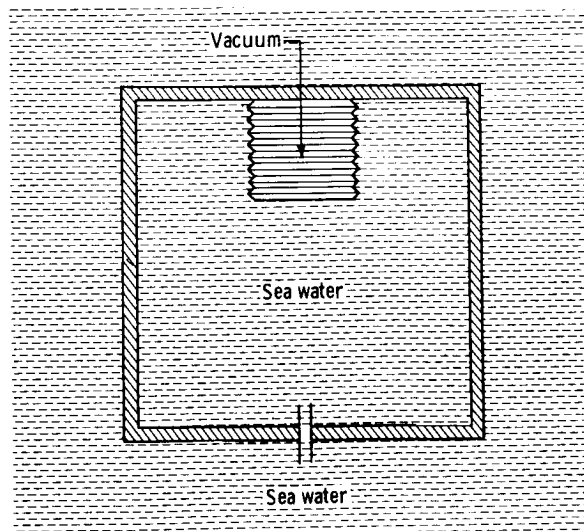


FIGURE 17.—Schematic diagram of one state of a diving gage having linear response. (AFTER GROVES AND MUNK.²⁰⁸)

outside sea water and the i th chamber, respectively, then the rate of change in pressure in the i th tissue analog becomes

$$\Delta P_i = k_i(P - P_i) \quad (17)$$

where k_i is dependent on the dimensions of capillary and bellows. It has the dimension of time^{-1} and $\ln_e 2/k_i$ is referred to as the half time of the i th chamber.

One of the problems of this approach is to determine which of the i th chamber is limiting on ascent. At any time during ascent any one of the several half-time tissues may be limiting. Expressed another way, for any one of the chambers, for example, the j th chamber, the ratio of pressure P_j to the supersaturation ratio ψ_j will be larger than for any other chamber. At any time in the dive only that chamber with the maximum $q_j = P_j/\psi_j$ determines the rate of ascent.

Several mechanical-hydraulic approaches to this problem were suggested. However, it was reported that no operationally useful ascent meter was forthcoming from this effort.⁴¹⁵ The Foxboro Co. did produce a single time-constant version of the analog device.¹⁷⁹ An Italian firm has attempted a single-chamber device with little operative success.⁷³ Wittenborn⁴⁵⁸ has also designed a similar device.

In 1963 Bradner and MacKay⁷³ presented electrical analog models of the Groves-Munk concept. The body was considered to be made of six half-time tissues arranged in the almost geometric series of 5, 10, 20, 40, 80, and 120 minutes. The critical supersaturation ratios of each tissue ψ_i for 200-foot dives were 2.7, 2.3, 2.0, 1.7, 1.6, and 1.6. For hypothetical 1000-foot dives, the corresponding ratios of 2.6, 2.2, 1.9, 1.6, 1.6, and 1.6 were used. Ascent curves were generated so as to keep the then critical tissue (j th tissue) from exceeding its q_j value. The corresponding ascent equations were also outlined. In one example, a 1000-foot dive with 4 minutes of bottom time requires 102 minutes for ascent. This is considerably less than the 275 minutes determined by the Keller-Bühlmann calculations.³²⁸ The 102-minute ascent is not operationally valid in that the ratios were held constant for all depths and 2 atmospheres of p_{O_2} were used.

It is also of interest that neither of the 4- nor 120-minute tissues were ever limiting in this deep dive of short duration. These investigators suggest that switching to gas mixtures of different oxygen or inert-gas concentrations at different points in the dive may reduce the ascent times even further. In principle, if the two characteristic tissues are the same for two gases, then the total decompression time will not be changed. For unequal time characteristics and solubilities, this need not be true. The characteristic of the analog device must be modified for each change of gas.

For the past several years Stubbs of the Royal Canadian Air Force⁴¹⁵ has been developing a practical diving gage of analog type similar in principle to the Groves-Munk gage. Instead of using the half time of sea-water flow through a critical orifice as the tissue analog, Stubbs uses gas taken from the breathing regulator. Four Bourdon tubes represent the half times of four tissues. The device uses the range of 2 to 1 to 3 to 1 for the Haldane supersaturation ratios. The pneumatic tissue analogs have been connected in various series and parallel arrangements to simulate best the tissue condition. The series system has been found to be most effective. The most striking advance is the use of a mechanical link which allows the tissue or chamber with the highest P_i/ψ_i ratio at that time to control the ascent. The diver merely keeps a dial "bug" representing the critical pressure in this limiting chamber at or below a pointer representing ambient pressure. This allows the ascent to be continuous and never exceed the bends limit.

The device has been patented in Canada and will be manufactured by Hunttec Ltd., Toronto. It has been tested in numerous dry dives and has resulted in considerable economy in time and safety.⁴¹⁶ For example, in short dives of less than 200 minutes, there has been a 17- to 35-percent savings in ascent time. For longer dives of 5 or 6 hours, there has been a threefold reduction in ascent time from 12 hours prescribed by the old tables to 4 hours with the pneumatic computer.

An electrical analog similar in principle to that used by Bradner and MacKay⁷³ and capable of continuous control of the rate-limiting tissue

has also been devised by Stubbs. This device allows prediction of repetitive dive schedules and long-range time predictions in diving operations. This combination of pneumatic diving gage and electrical analog appears to be the most significant advance in diving technology in many years.

In discussions with Stubbs it became apparent that the analog device could be used to simulate altitude decompressions for any gas mixture. The critical factors would be choice of half time and critical supersaturation ratio for each of the four tissues. Altitude decompression experience suggests that a ratio of 2.7:1 may suffice in spite of the rare episodes noted at ratios of 2:1 to 2.4:1 during flight operations. The critical tissues probably have half times of 100 minutes to 260 minutes.²⁶ Stubbs suggests that he would first start his programs with Haldane ratios of 1.5 and work up to higher ratios with increasing clinical experience. Stubbs is currently studying helium-oxygen dives and hopes to move into the altitude problem when the current program is completed. From his experience with the program for helium diving, Stubbs suggests that fourfold advantage of helium over nitrogen in case 1 of table 9 appears reasonable. Comparative studies of helium and nitrogen on the analog computer should prove interesting. The fact that the 100- and 240-minute tissues were used for helium as well as nitrogen is of interest in this regard.

Several new computer programs for decompression^{194, 392, 289} from saturation deep dives have recently become available, and work is underway to validate the systems.

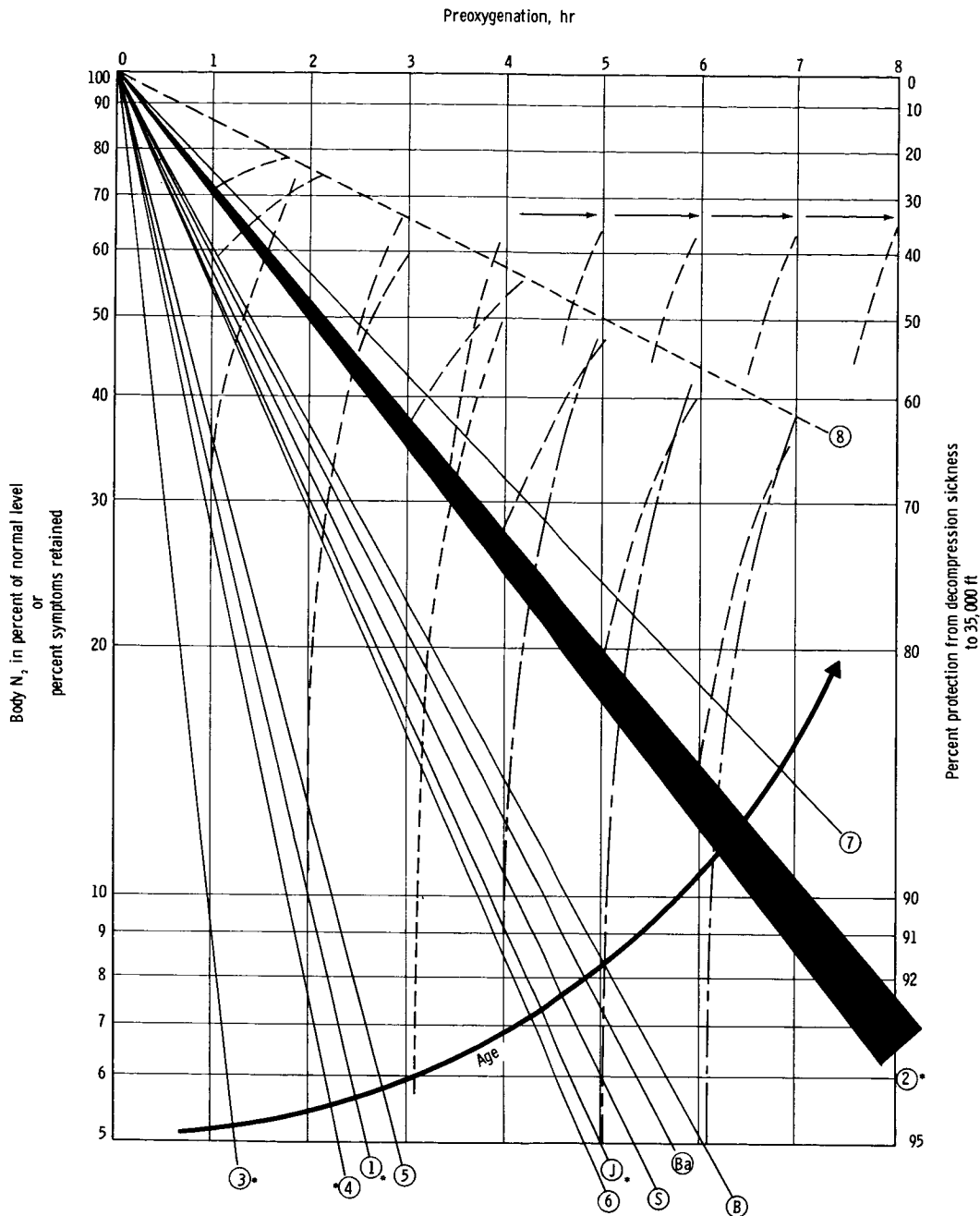
In summary, it should be stated that the bubble-growth factors and desaturation curves are related through three factors: solubility and diffusivity of gases at critical sites of the body, and the perfusion efficiency of the blood flow through these areas. The "tissue components" having specific half times do not represent individual organs per se, but tissue sites where diffusivity and solubility relationships are coupled to perfusion factors to give a uniform characteristic of passage of gas from tissue to bloodstream. That the bubble-growth and gas-exchange factors meet in some common ground is not surprising. The initial supersaturation

ratio and the rate of gas depletion from the specific tissues, coupled with the local physical factors determining bubble growth and decay, control the number and size of bubbles forming during any time interval at any body site. The number, size, and degree of coalescence of bubbles, as well as the persistence time and tissue sensitivity to pressure and ischemic change, ultimately determine symptom frequency and pattern. Information gleaned from desaturation theory must be linked with bubble theory for a rigorous analysis of the total physiological problem. Desaturation theory must be correlated with clinical symptomatology to allow practical prediction of ascent schedules and decompression regimens.

Denitrogenation Schedules in Decompression to Altitude

The role of denitrogenation in altitude decompression has been of interest to aviation physiologists for several decades. The early work of Behnke³² on nitrogen elimination in diving was followed by studies of Boothby and his associates in altitude decompression.^{32, 68, 69} The protection by denitrogenation against bends at altitude received much study during World War II. The results of these studies have been analyzed in great detail by Jones²⁴⁶ and Bateman.²⁵ Much of the data below has been taken from these excellent summaries.

Correlation between the amount of residual tissue nitrogen after preoxygenation^{16, 31, 68, 246, 294} and the incidence of decompression symptoms is a well-known phenomenon. For bends-susceptible subjects, the half times of tissue denitrogenation and protection against decompression sickness appear to be equal.²⁴⁶ The half time of the second tissue component for nitrogen (68 to 73 minutes) seems to correlate best with the half time of symptom reduction by preoxygenation upon exposure with exercise to 35 000 feet. For younger subjects (18- to 21-year olds), the half times of both the symptoms and nitrogen depletion from critical tissues are reduced to about 20 minutes. There is considerable variation from person to person and age to age (fig. 16). Most of the pertinent data available have been summarized in figure 18. The stability of the probability of group perform-



- Ⓐ Behnke³⁸
 - Ⓢ Stevens et al.⁴¹²
 - Ⓝ Jones²⁴⁶
 - ④ Average curve, ③ Fastest curve, of 18 yr old group
 - Ⓐ Bateman,²⁶ Average individual protection rate
 - Ⓑ Slowest individual protection rate
 - Clark et al.¹⁰⁰ ⑤ 17 yr, ⑥ 27 yr, ⑦ 35 yr, age group
 - Percent symptoms retained, 38,000 ft
 - Broken lines indicate loss of protection during 1 hr air breathing.
- Average reported N₂ elimination } Groups
 ① Fastest curve ② Slowest curve } < 24 yr

FIGURE 18.—Compilation of all data bearing on rate of protection by preoxygenation and rate of nitrogen loss from critical tissues. (AFTER JONES.²⁴⁶)

ance is striking and can be used to generate tables of the degree of protection afforded to any group by preoxygenation of any duration against specific altitudes (tables 17 and 18). The left ordinate in figure 18 gives the body nitrogen in percent of normal. The percent tissue nitrogen retained and the percent symptoms retained are synonymous. Curves (1) and (2) represent the highest and lowest percent of residual nitrogen and percent bends protection found in the three groups^{39, 246, 412} with an age range of 17 to 24 years. Curves (3) and (4) represent the fastest and average half times in an 18-year-old group. Curve (Ba) represents the average; curve (8), the slowest individual protection rates found by Bateman.²⁵ These curves were for protection at 35 000 feet with moderate exercise. Curves (5), (6), and (7) represent the data for the percentage of symptoms retained at 38 000 feet for 17-, 27-, and 35-year olds, respectively.

The effect of exercise rate on incidence of bends is seen in figure 19. There is a steady increase in incidence from rest to about 10 deep knee bends every 15 minutes.

Tables 17 and 18 represent protection factors from figure 18. These tables are conservative and are designed to cover groups which eliminate nitrogen slowly. Table 17 applies to 35 000 feet and table 18 to 38 000 feet with moderate exercise at altitude. The average nitrogen elimination curves of groups older than 24 years are used in the tables for the category "probable protection." The slowest curve (2 of fig. 18)

TABLE 17.—Protection^a of Groups^b Compared to Ascent Without Preoxygenation
[AFTER JONES²⁴⁶]

Preoxygenation, hr	Minimum protection, percent	Probable protection, percent
0.5.....	16	26
1.0.....	29	45
1.5.....	41	59
2.0.....	50	70
2.5.....	58	77
3.0.....	61	83
3.5.....	70	87
4.0.....	75	91
4.5.....	79	
5.0.....	82	
5.5.....	85	
6.0.....	86	
6.5.....	89	
7.0.....	91	

^a Zero protection equals incidence of decompression sickness of group without preflight oxygen when ascending to altitude at 4000 feet per minute.

^b For group prediction and not for individual prediction.

appears in the table as the "minimum protection" category. The young group of table 18 eliminated nitrogen very rapidly; the average elimination rate of this group is faster than the fastest rate in individuals older than 24 years. Unless age or nitrogen-elimination characteristics of a group are known, prediction should be made with "minimum protection" category. "Protection" is given in percentage of improvement over the

TABLE 18.—Protection Afforded by Various Intervals of Preoxygenation for 90-Minute Flights at 38 000 Feet. At Rest and With Moderate Activity

[AFTER JONES²⁴⁶]

Preoxygenation, hr	Minimum protection (exercise), ^a percent	Probable protection (exercise), ^a percent	Young, unselected, 17 to 24 years (exercise), ^a percent	Young, unselected, 17 to 24 years (rest), percent
0.5.....	15	24	42	65
1.0.....	29	42	55	88
1.5.....	40	54	61	96
2.0.....	50	61	63	99
2.5.....	56	66	65	
3.0.....	62	69	66	
3.5.....	65	71	66	
4.0.....	68	72	66	
4.5.....	69	73	66	

^a Ten 9-inch stepups each 5 minutes at altitude.

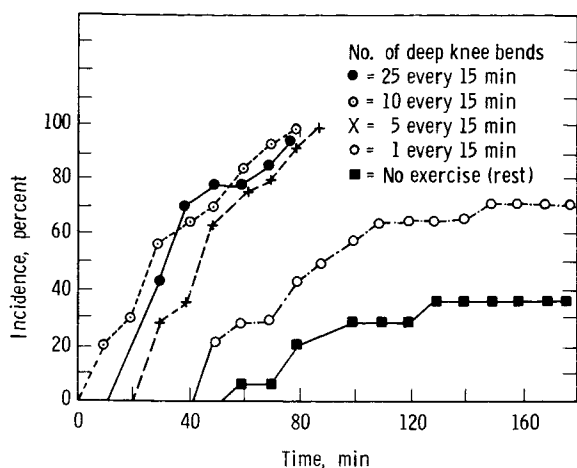


FIGURE 19.—Comparison of cumulative incidence of decompression sickness in group of fourteen subjects exposed in random fashion to variable degrees of exercise during simulated flights at 35,000 feet. Exercise was deep knee bends. (AFTER FERRIS AND ENGEL.¹⁶⁹)

expected condition of preflight oxygenation for that group and ascent to altitude no faster than 4000 ft/min. For example, if at an altitude of 35 000 feet a group experiences 70 percent symptoms, and 50 percent forced descents with no preoxygenation, after 1 hour of preoxygenation one would expect from table 17, “a minimum protection” for the group of —

$0.70 \times 0.29 = 20.3\%$; $70 - 20.3 = 49.7\%$ symptoms
 $0.50 \times 0.29 = 14.5\%$; $50 - 14.5 = 35.5\%$ descents.

With the dashed curves of figure 18 and from table 19 can be noted the rate of regaining body

nitrogen and loss of protection by 1 hour of breathing air following various lengths of preoxygenation at sea level. As expected, the slower nitrogen eliminators lose protection more slowly.

The group-to-group variations are interesting. The difference may be related to adiposity, but is probably dependent on the higher rate of perfusion of critical tissues in the youngest group. Presence of slight hypoxia will increase the denitrogenation rate.²⁴⁶ Above 30 000 feet, where slight hypoxia is often present, denitrogenation rates are more rapid. Below this altitude there is no increase above the sea-level rate and possibly some decrease.³⁰⁰ Exercise during denitrogenation will, of course, increase the rate.¹⁶ There is a limit to protection by preoxygenation when decompressing with exercise.

It has been noted that exercise at 38 000 feet will apply a definite limit to the protective effects of preoxygenation at sea level.²⁴⁶ In table 18 it is seen that beyond 1 hour of preoxygenation there is very little improvement in the bends tolerance of the rapidly denitrogenating group undergoing exercise. High carbon dioxide levels in the exercising muscles may well be responsible for the limit of preoxygenation protection in bends-resistant individuals at altitudes above 38 000 feet. The phenomenon is not seen below this altitude or in bends-sensitive groups.

There are two other factors that modify the determination of preoxygenation time. The first is the fact that the longer an individual preoxygenates, the longer he can stay at altitude

TABLE 19.—Protection ^a Retained When Preoxygenation Is Interrupted With Air Breathing

[AFTER JONES ²⁴⁶]

	O ₂		Air		O ₂		Air		O ₂		Air		O ₂		Air		O ₂		Air		
Time, hr.	1	1/2	1	2	1/2	1	3	1/2	1	4	1/2	1	5	1/2	1	6	1/2	1	7	1/2	1
Minimum protection, percent	29	26	20	50	40	33	64	54	46	75	62	53	82	68	60	86	74	62	91	74	62
Probable protection, percent	45	33	25	70	52	39	83	62	46	91	67	50	95	70	52	97	72	54	97	73	54

^a Zero protection equals incidence of decompression sickness of group without preflight oxygen when ascending to an altitude of 35 000 feet at 4000 feet per minute.

before onset of symptoms.^{225, 247} Since denitrogenation for 1 hour results in an increase of 15 minutes in latent period, the true denitrogenation period would really be 75 minutes instead of 60 minutes. This prolonged effective preoxygenation time is countered by the second factor, the tendency for development of "silent bubbles" at "prebends altitudes."⁹⁹ The study of Gray²⁰⁴ suggests that in the period at 20 000 to 30 000 feet on the way to higher altitudes, the formation of "silent bubbles" can be assumed to reduce the effectiveness of preoxygenation from one-half to three-fourths the sea-level equivalent. These two factors will, therefore, cancel one another in gradual ascent to altitude and reduce the latency-time distortion from 15 to 10 min/hr. In rapid ascents, however, the full latency factor should be kept in mind. When denitrogenating on 100 percent oxygen above 38 000 feet, the slight hypoxia and rapid circulation may give an equivalent of about 20 additional minutes of sea-level preoxygenation per hour. The role of the vasoconstrictive aspects of the hyperventilatory hypocapnia is still not clear in this situation.

The protection half time for chest symptoms (chokes) of 35 minutes is considerably longer than that observed for joint symptoms in the same group.¹⁰⁰ The reason for this difference observed at an altitude of 38 000 feet may be that the slower tissue is involved in chokes. There appears to be no exercise limit as seen in joint symptoms for the same group. This suggests that the muscle insertions which may be partly responsible for joint symptoms of bends are probably not the major source of bubbles in chokes.

In general, the correlation of preoxygenation and symptom reduction has been poor in predicting individual susceptibility to decompression sickness.^{25, 26, 100, 246, 412} Operational inadequacy of the denitrogenation prediction probably results from gross variation in perfusion of critical tissues and from differences in adiposity. Many tissues, as classified by gas exchange and vascularity, must have a more rapid or slower gas-exchange rate than the bulk of tissues. When such tissues are present in small amounts they may be masked in the denitro-

genation curves by the relative mass of differently vascularized tissues. In predicting the protection rate or level, this limiting tissue might differ radically from the average or modal tissue. In group data, these "limiting tissue" effects cancel out with the resultant strong correlation between group denitrogenation and group protection. This correlation is far too weak in a single individual for an adequate prediction of bends protection from denitrogenation data.

From the data presented above, it would appear that prior equilibration to any atmosphere with a lower partial pressure of nitrogen than air at sea level would protect against the bends. Such is the situation in space cabins where reduced total pressures and increased partial pressures of oxygen bring about relatively low partial pressures of inert gas. Can symptoms be related to partial pressure of nitrogen and other gases in tissue? What is the actual incidence of bends after prolonged equilibrium exposures to altered inert-gas concentration, and how does this incidence compare with that predicted from denitrogenation theory? Can these data be used to predict the protective effects of any inert gas substituted for nitrogen in these altered atmospheres?

Bateman²⁵ attempted to answer the first question by developing an overall equation which related the likelihood of symptoms appearing at a given time to the "product of the bubble size and the initial supersaturation divided by the square root of the time measured from the instant of decompression." The bubble-size factor is clear. The supersaturation ratio could represent the original driving force of the gas and the $1/t^{1/2}$, an empirical factor, could be a function of the residue of that driving force remaining after a diffusive process has limited removal of the gas from the tissues. Bateman attempted to relate this postulate to tissue gas factors. The following is a slight modification of his approach to the problem of predicting the likelihood of symptoms from this postulate.

The removal of nitrogen from a given region following decompression to a given altitude is assumed to follow the equation

$$p_{N_2} = (p_{N_2}^0 - p_{N_2}^x) \cdot e^{-kt} + p_{N_2}^x \quad (18)$$

where

p_{N_2} partial pressure of nitrogen at time t

$p_{N_2}^0$ initial partial pressure of nitrogen

$p_{N_2}^\infty$ value approached after indefinitely long decompression

k time constant of the desaturation process

According to equations (1), (2), and (3) and the subsequent discussion, a bubble will grow when the sum of the partial pressures of the gases exceed the total hydrostatic pressure, the pressure of surface tension factors being neglected, or when $P_B > H$. This can be expanded to the condition

$$p_{N_2} + p_{CO_2} + p_{O_2} + p_{H_2O} > P_A + P_T$$

The supersaturation S at the bubble site is defined as

$$S = (p_{N_2} + p_{CO_2} + p_{O_2} + p_{H_2O}) - (P_A + P_T) \quad (19)$$

Assuming $p_{H_2O} = 47$ mm Hg; $p_{CO_2} = 45$ mm Hg; and $P_T = 30$ mm Hg (capillary blood pressure for bubbles forming in capillaries)

$$S = (p_{N_2} + p_{O_2} + 62) - P_A \quad (20)$$

Substituting equation (18) into equation (20), the

degree of supersaturation at the bubble site after time t is obtained by

$$S = (p_{N_2}^0 - p_{N_2}^\infty)e^{-kt} + p_{N_2}^\infty + p_{O_2} + 62 - P_A \quad (21)$$

The initial supersaturation S_0 at $t=0$ is:

$$S_0 = (p_{N_2}^0 + p_{O_2} + 62) - A \quad (22)$$

By combining constants and substituting equation (19) for the ΔP , equation (7) can be rewritten to indicate the rate of bubble growth in a capillary

$$\frac{dV_g}{dt} = \frac{KS}{P_A + P_T - (p_{O_2} + p_{CO_2} + p_{H_2O})} = \frac{KS}{P_A - p_{O_2} - 62} \quad (23)$$

where

$$K = \left(\frac{\alpha_g D_g A R T}{\Delta x} \right) = \text{Constant}$$

By substituting equation (21) for the supersaturation S

$$\frac{dV}{dt} = \frac{K[(p_{N_2}^0 + p_{N_2}^\infty) \cdot e^{-kt} + p_{N_2}^\infty + p_{O_2} + 62 - P_A]}{P_A - p_{O_2} - 62} \quad (24)$$

Integrating from $t=0$ to time $= t$

$$V - V_0 = \frac{P_A - p_{O_2} - 62(p_{N_2}^\infty + p_{O_2} + 62 - P_A)t + \frac{1}{k}(p_{N_2}^0 - p_{N_2}^\infty)(1 - e^{-kt})}{K} \quad (25)$$

where V_0 = volume at $t=0$. The basic postulate of Bateman was that the likelihood of symptoms X could be determined by

$$X = \frac{VS_0}{\sqrt{t}} = \frac{V}{\sqrt{t}}(p_{N_2}^0 + p_{O_2} + 62 - P_A) \quad (26)$$

By ignoring the small initial volume of the bubble V_0 , and substituting equation (25) for V , the likelihood of symptoms can be determined:

$$X = \frac{p_{N_2}^0 + p_{O_2} + 62 - P_A \left[\frac{1}{k}(p_{N_2}^0 - p_{N_2}^\infty)(1 - e^{-kt}) - (P_A - p_{N_2}^\infty - p_{O_2} - 63)t \right]}{(P_A - p_{O_2} - 62)\sqrt{t}} \quad (27)$$

This equation and postulate were tested by Bateman against the data for likelihood of symptoms at depth and altitude upon exposure to any final ambient pressure P_A . As desaturation constants for the equation, he chose two values: for fast denitrogenation, $k=1$; for slow denitro-

generation, $k=0.2$. These constants indicate that the time required for the $k=1$ subject to eliminate $1-1/e$ or 0.64 of the initial nitrogen is 1 hour; for $k=0.2$, 5 hours.

Empirically, substitution of the $P_A - p_{O_2} - 62$ factor by $P_A + 30$ as seen in equation (28) gives a closer fit to the data, especially in avoiding

$$X = \frac{p_{N_2^0} + p_{O_2} + 62 - P_A \left[\frac{1}{k} (p_{N_2^0} - p_{N_2^\infty}) (1 - e^{-kt}) - (P_A - p_{N_2^\infty} - p_{O_2} - 63) t \right]}{(P_A + 30) \sqrt{t}} \quad (28)$$

The modified Bateman equation has been used to generate values of X in the curves of figure 20. The symptom threshold was set at 650 since, at the time the equation was written, the most susceptible individuals were thought to show very few symptoms upon sudden decompression from 44 feet of sea water after saturation dives. That this threshold should be lowered to between 500 and 600 is suggested by the data of Duffner and Snider¹⁴⁷ in table 14, where only 33 feet of water appeared to be the threshold for susceptible divers after 12 hours at depth.

In a few susceptible persons, symptoms of decompression sickness are also seen in decompressions to 25 000 feet or lower.¹⁸⁵ That only

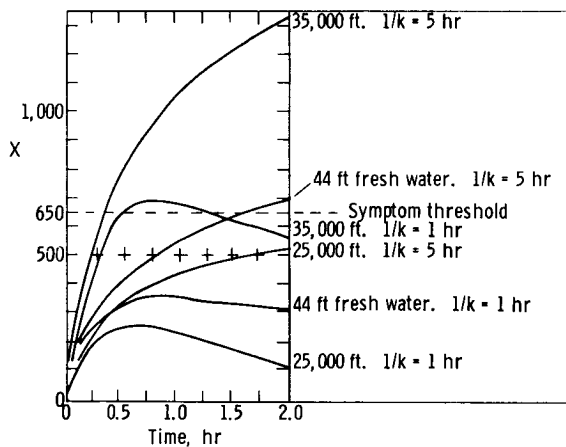


FIGURE 20.—Effects of sudden decompression reproduced by modified equation (28). Values of X calculated from equation (28) for cases of sudden decompression as indicated on right. A desaturation constant, k , of 1.00 is assumed typical of persons highly resistant to decompression sickness, and a value 0.200 ($1/k=5$ hr) is taken to characterize the more susceptible persons. (AFTER BATEMAN.²⁵)

too great an expansion of bubbles at high altitudes. As the predecompression altitude is increased and absolute pressure of nitrogen is decreased, the carbon dioxide and oxygen factors would be expected to play an increasingly larger role. The modified equation (28) represents this empirical correction for high-altitude decompression.

the most resistant subjects ($1/k=1$ hr) tolerate decompression to 35 000 feet without symptoms and that susceptible subjects invariably get bends are shown by these calculations.

Bateman then calculated the decompression ratios that will just permit the threshold value of X to be reached for slow and fast denitrogenators decompressed while saturated at different absolute pressures of air. These values, seen in figure 21, indicate that the ratio of 2.7 is adequate for slow desaturators when decompressing from sea level. As would be expected from Piccard's theory in the first section of this chapter, these ratios increase with altitude and become increasingly dependent on p_{CO_2} and p_{O_2} factors.

A more practical presentation of the threshold decompression ratio is seen in figure 22. Here the values on the abscissa give absolute pressures of saturation exposure with corresponding altitude and depth figures; the ordinate gives threshold pressures for safe, rapid decompression. The initial partial pressure of nitrogen for threshold decompressions may be obtained by multiplying each pressure by 0.8. This graph indicates that from sea level, the more resistant individual can decompress to 35 000 feet and the more susceptible to only 25 000 feet without symptoms. From an altitude of 7500 feet (500 mm Hg), the more resistant individual can decompress to 43 000 feet and the more susceptible to 35 000 feet. Unfortunately, the lower end of the curve which is of great importance to the present study is not complete. It may well be that the increasing importance of p_{CO_2} and p_{O_2} in decompression from high altitudes is not adequately covered by this semiempirical equation.

Bateman,²⁴ however, feels that the equations should be valid for space-cabin studies at higher altitudes of equilibration. He claims that there was no need for the calculation of values for higher saturation altitudes during World War II.

To arrive at a first-order prediction of the hazard of decompression from space cabins of mixed-gas type and set a basis for evaluating empirical data to be presented, one can calculate the X values for decompression to 35 000 feet (3.5 psi) for 1 hour from the following equilibrium conditions: (1) 15 000 feet on supplemental oxygen to give sea-level alveolar equivalent, and (2) 18 000 feet on a mixture of 50 percent oxygen and 50 percent nitrogen. The alveolar values for p_{N_2} and p_{O_2} will be used to approximate the tissue levels. From the alveolar gas equation (eq. (8) in ref. 309), the alveolar nitrogen and oxygen were obtained. For 15 000 feet, assuming an alveolar $p_{O_2} = 103$ mm Hg, the $p_{N_2}^0$ would equal $P_A - 47 - 40 - 103 = 239$ mm Hg. For 18 000 feet, on 50 percent oxygen and 50 percent nitrogen, the values of $p_{O_2} = 123$ mm Hg, $p_{N_2}^0 = 169$ mm Hg. The $p_{N_2}^\infty$ is 0 for 100 percent oxygen at altitude. One can convert the equation to common logarithms by changing k values to $k' = k/2.303$. The value for $k = 1.0$ becomes $k' = 0.434$, and the value for $k = 0.2$ becomes $k' = 0.0868$. The exponential factor e^{-kt} becomes $10^{-k't}$. For fast desaturators ($k = 1.0$), equilibrated at 15 000 feet with sea-level alveolar p_{O_2} , equation (28) reads:

$$X = \frac{238 + 103 + 62 - 179 \left[\frac{1}{1.0} (239 - 0) (1 - 10^{-.43(1.0)}) - (179 - 0 - 103 - 63) 1.0 \right]}{(179 + 30) \sqrt{1.0}} = 148$$

In the same manner, for exposure of slow denitrogenators ($k = 0.2$) the same exposure would give $X = 229$. The calculation can be made for case 2 with equilibration at 18 000 feet with 50 percent oxygen and 50 percent nitrogen. The value of X for fast equilibrators ($k = 1.0$) will be 96; for the slow equilibrators, 134.

This calculation would suggest that the likelihood of symptoms in fast denitrogenators would be 1.5 times greater in the 15 000-foot group than in the group equilibrated at 18 000 feet on 50 percent oxygen and 50 percent nitrogen. For

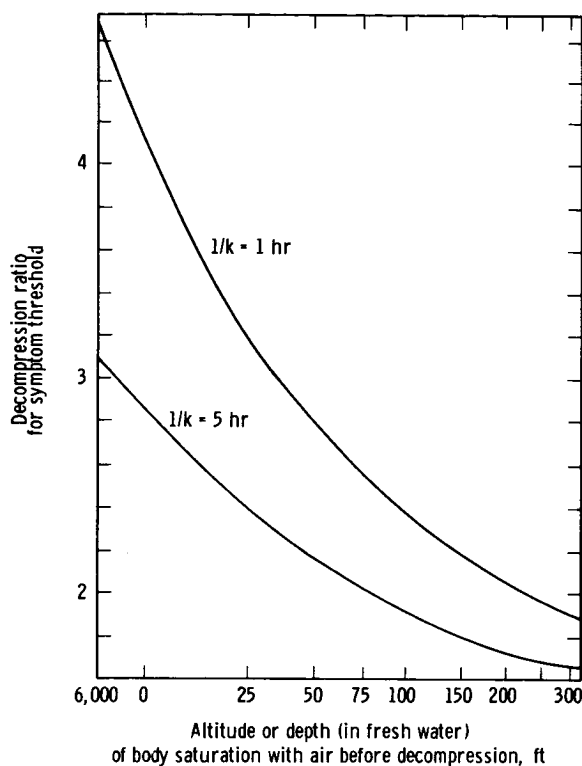


FIGURE 21.—Theoretical threshold decomposition ratios. Threshold decomposition ratios for rapidly (upper curve) and slowly (lower curve) desaturating persons initially equilibrated with air at various absolute pressures indicated by depth and altitude values on axis of abscissae. Curves represent decomposition ratios at which maximum value of X attained according to equation (28) is 650, threshold value. (AFTER BATEMAN.²⁵)

the slow denitrogenators, the likelihood of symptoms would be about 1.7 greater in the 15 000-foot group than the 18 000-foot group. In both cases, however, the X values fall far short of the threshold of 500 to 650 for expected symptoms in some subjects. From figure 20 it can be seen that subjects equilibrated at 15 000 feet ($X = 148$ to 299) would be expected to have the same frequency of symptoms as rapid denitrogenators decompressing to 25 000 feet from sea level. From the reviews of Ferris,¹⁶⁹ Cook,¹¹² and Nims³²⁹ the expected frequency of bends at

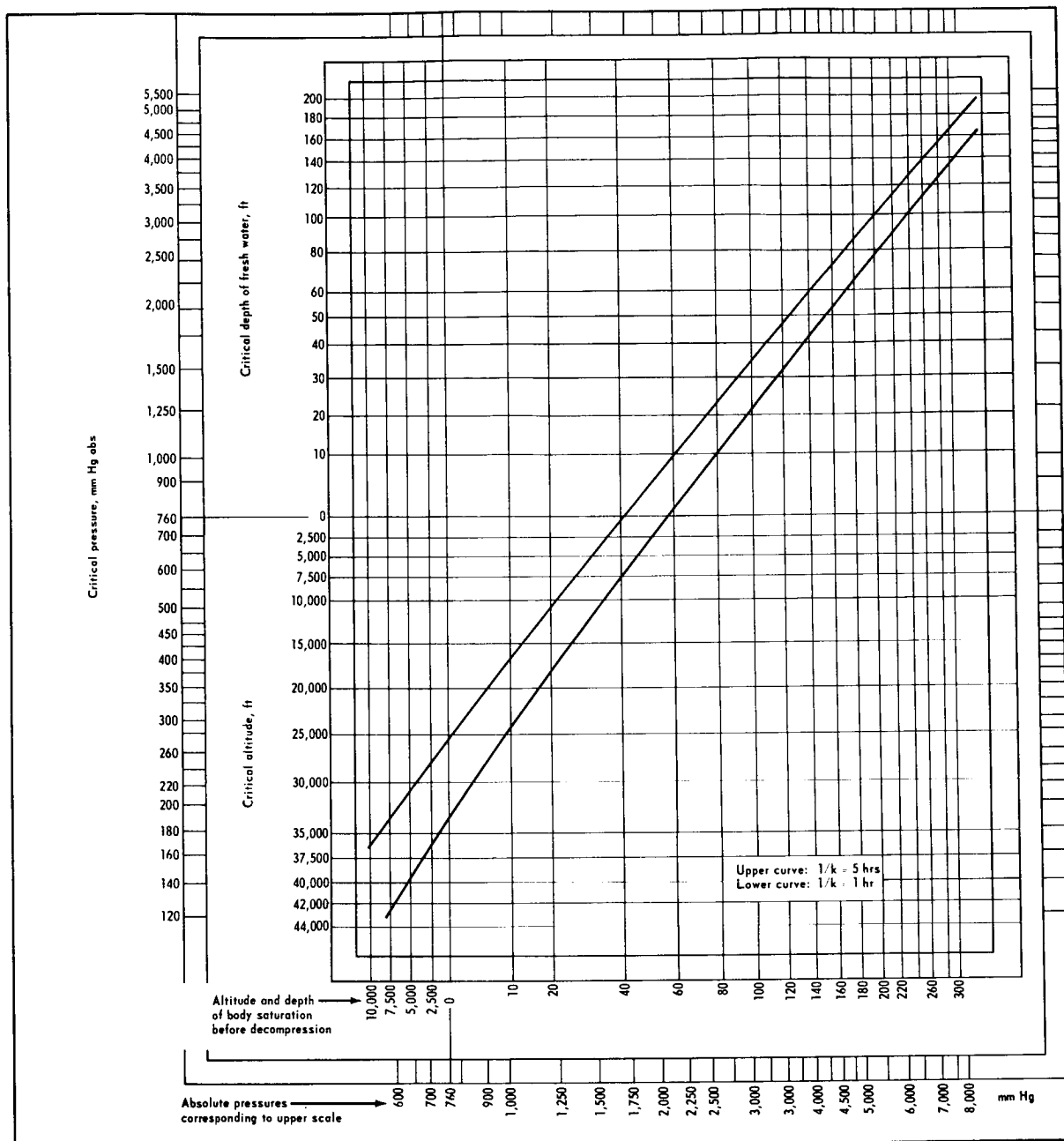


FIGURE 22.—*Threshold decompression curve.* (AFTER BATEMAN.²⁵)

this low altitude can be determined. Subjects at rest at 25 000 feet had about 0 to 1.5 percent symptoms; subjects exercising at five deep knee bends/min every 3 minutes during 20 minutes at altitude, 15 to 18 percent. Symptoms at rest were all mild; with exercise some moderate symptoms were noted. If the Bateman equation

and the concept of symptom likelihood holds for both resting and exercising subjects, then one could predict that for subjects equilibrated at 15 000 feet to tissue nitrogen of 239 mm Hg, decompression to 35 000 feet at rest should give from 0 to 1.5 percent symptoms; and with exercise, from 15 to 18 percent symptoms. In a like

manner, the subjects equilibrated at 18 000 (50 percent oxygen and 50 percent nitrogen) should have about 0 to 1 percent symptoms at rest and about 7 to 11 percent symptoms with exercise. Similar calculations for final suit altitudes of 27 000 feet (5 psi) predict symptom rates about one-third of those at altitudes of 35 000 feet. Initial atmospheres at 5 psia of 70 percent N_2 and 30 percent O_2 with p_{N_2} of 77 mm Hg will reduce the expected symptom rate considerably.

What empirical data are available to check these predictions? In 1944, Bateman and his associates reported on studies of subjects decompressed to 35 000 feet after spending 6 hours at 15 000 feet with alveolar oxygen equal to sea level. These are essentially the conditions calculated in the first examples above. During ascent, a standard exercise regimen was initiated at 20 000 feet. It consisted of five deep knee bends and five arm bends (with 3-pound weights) every 3 minutes. This exercise was so strenuous that it was often difficult to distinguish between joint pain and fatigue from exercise and from bends. For this purpose, secondary ascent to 40 000 feet was often attempted at the end of a questionable run. An arbitrary scoring system was used which gave the degree of immunity as a function of time of onset, severity, and duration of symptoms.

Details of the bends scoring are given in the footnote to table 20. The results are shown on row A of table 20. The 40-percent oxygen represents normal alveolar p_{O_2} . The 30-percent oxygen in row B represents alveolar p_{O_2} reduced to 5000 feet equivalent on air. The 40- and 70-percent oxygen of row C at ground level represented a still higher p_{N_2} . It can be seen that subject JB was far more sensitive to bends than the other three subjects. In four out of six runs on 40 percent oxygen at 15 000 feet, symptoms were absent or negligible. Only JB had symptoms. Increase of nitrogen in the 30-percent oxygen run caused symptoms in LC. Subject JB happened to have one of the slowest denitrogenation rates ever recorded. His curve is (8) in figure 18. After 6 hours at 15 000 feet on 40-percent oxygen, he still had 65 percent of original sea-level nitrogen in his tissue in contrast to the expected equilibrium level of 40 percent. Prolongation of his equilibrium time to 12 hours (row D) increased his tolerance considerably.

Prediction of expected incidence of symptoms from the Bateman equation gave about 15 to 18 percent for this type of experiment. The small number of subjects precludes adequate test of the equation, but the general level of symptoms is in the predicted range. Rows B, C, and D of table 20 indicate how close to the symptom

TABLE 20.—*Degree of Immunity to Decompression Sickness Following Various Forms of Desaturation*
[ADAPTED FROM BATEMAN ²⁵]

Test	Procedure before decompression					Scores at 35 000 ft (exercise) ^a			
	Oxygen inhaled, percent	Duration, min	Altitude, ft	p_{N_2} at equilibrium, mm Hg	Fraction of sea level, p_{N_2}	Subjects			
						RS	LC	RH	JB
A.....	40	360	15 000	233	0.39	360 +	360 +	344	98
	40	360	15 000	233	.39	319 +	360 +	360 +	131
B.....	30	360	15 000	272	.46		348		106
C.....	40	360	1 000	419	.71	143 +	156	171	90
	57	360	1 000	290	.49	137 +	351	335	167
D.....	40	720	1 000	419	.71				113
	59	720	1 000	285	.48				271

^a Scoring system: 4 points are allotted for every minute free of pain; 3 points for every minute of grade 1 pain; 2 points for grade 2 pain; and 1 point for grade 3 pain. Maximum score for 90 minutes is 360.

threshold the tissue nitrogen content did lie in the 15 000-foot experiments. Analysis of the Bateman equation and these data suggest that the tissue nitrogen equilibrated at about 240 mm Hg may be a threshold value for symptoms in all but the extremely sensitive at 35 000 feet with the most severe exercise. The small number of subjects demands a guarded prediction.

Another set of experiments was performed by Balke and associates at Mount Evans, Colo.¹⁵ A brief review of the results has been presented by Clark et al.⁹⁹ The susceptibility to bends and chokes was tested at 38 000 feet with exercise of five deep knee bends every 3 minutes. During control tests from ground level (747 mm Hg), all subjects (aged 20 to 51; mean 33.39 years) experienced third-degree bends or chokes in an average time of 18 minutes. After subjects lived 3 to 4 days on air at an altitude of 10 000 feet (525 mm Hg total pressure; 420 mm Hg p_{N_2}), third-degree bends were not observed when subjects were subsequently decompressed further to 38 000 feet in a mobile chamber. Second-degree bends occurred after an average of 50 minutes. The pains were not severe enough to force descent. The same was true at a lower conditioning altitude of 6000 feet (625 mm Hg total pressure). Two days at 14 000 feet (total pressure 446 mm Hg; p_{N_2} = 355 mm Hg) resulted in only two out of seven subjects experiencing slight pains, with symptoms disappearing at altitude at the end of the 1-hour test. Exposure to 42 500 and 56 000 feet for a total time of 30 to 40 minutes after equilibration to 14 000 feet resulted in no symptoms when subjects simulated work involved in piloting an airplane. These studies suggest that equilibration to tissue nitrogen of 440 mm Hg p_{N_2} may protect subjects from the more serious grade 2-3 bends upon subsequent exposure to 38 000 feet while undergoing mild to moderate exercise at this altitude and may reduce incidence of symptoms to about 30 percent.

In 1957 Marbarger et al.³⁰¹ reported studies of 15 subjects with nonequilibrium desaturation at altitude before decompression to 38 000 feet while performing five deep knee bends every 3 minutes for 30 minutes. Control subjects breathing air at sea level all experienced bends

within 16.9 minutes. After breathing an oxygen-enriched mixture (105 mm Hg p_{O_2} ; 260 mm Hg p_{N_2}) for 4 hours at an altitude of 18 000 feet, 47 percent of the subjects experienced bends within the 30-minute test period. Four hours of desaturation at 12 000 feet on 105 mm Hg p_{O_2} and 380 mm Hg (p_{N_2}) resulted in the same percent symptoms. Denitrogenation on 100 percent oxygen at 18 000 feet for 2 hours gave 60 percent symptoms after the same test exposure. Even though the total nitrogen present in the tissues at the end of the 4-hour exposures on the nitrogen-oxygen mixtures was greater than in the short preoxygenation with pure p_{O_2} , the symptom rate was lower in the former. The extra 2 hours on the nitrogen-oxygen mixture probably allowed slower critical tissues to desaturate more adequately.

Marotta et al.³⁰³ studied the effects of different times of equilibration with air at 12 000-foot altitudes (380 mm Hg p_{N_2}) on subsequent bends upon exposure to 38 000 feet. Exercise at test altitude consisted of five deep knee bends every 3 minutes for 30 minutes followed by five deep knee bends every 2 minutes for the next 30 minutes. Immediate descent followed onset of symptoms. As expected, there were wide variations from person to person and for the same person in the time of onset of symptoms. As the time at 12 000 feet increased from 0 to 8 hours, the mean time before onset of symptoms lengthened from 18 to 32 minutes. After 8 to 12 hours at 12 000 feet, the mean time decreased to 25 minutes, possibly a result of "silent bubbles."²²³ Also, the chronic mild hypoxia may have had some biochemical effect. The reduction of symptoms by equilibration to lower p_{N_2} was not as marked as that noted by Balke.¹⁵ In contrast to Balke's subjects, who were in excellent physical shape and exercised freely at equilibration altitudes, these subjects were sedentary and equilibrated at rest. Of interest is the note that the site of joint pains did not change significantly with the duration of equilibration.

A recent experiment on bends protection by equilibration at altitude was performed by Damato et al.¹³⁰ at the Air Crew Equipment Laboratory. These studies, sponsored by NASA, attempted to compare the symptoms present in

12 men brought to an altitude of 35 000 feet after different preoxygenation and equilibration regimens. At altitude, subjects engaged in a Master's Step Test consisting of 10 stepups on a 9-inch platform every 5 minutes for 3 hours. This appears to be slightly less exercise than that in previous bends stress tests after equilibrium desaturation at altitude. Subjects were standardized as to general bends tolerance by being brought to an altitude of 33 750 feet with no previous oxygenation and exercising. As a result, 26 out of 28 subjects experienced symptoms severe enough to force descent. Henry et al.²²⁴ had previously studied the same decompression sequence with 156 subjects and 290-man runs and had found only 33 percent forced to descend because of symptoms. This suggests that the subjects of Damato et al. were highly bends prone. The mean age of 18.4 (17 to 23) of Henry's subjects as compared to 25.4 (19 to 40) in Damato's group may partially explain the difference in sensitivity.²⁰⁴

Table 21 reviews the test conditions employed in this study. Conditions 1 to 5 represent the preoxygenation phase of the study. Subjects denitrogenated for 2 to 3 hours and decompressed to altitude in from 40 to 120 seconds.

It is seen in table 21 that 10 out of 12 of those preoxygenating for 2 hours experienced bends regardless of time of decompression. The incidents of forced descents was 5 to 7 out of 12. The poor response to preoxygenation (see tables 17 and 19) corroborates the results of the standardization test that a high bends-prone group of slow denitrogenators was being studied. In test 5 where 3 hours of preoxygenation were used, only 1 out of 12 experienced symptoms which required descent at 132 minutes.

In conditions 6 to 9, subjects were equilibrated in an atmosphere of 50 percent oxygen and 50 percent nitrogen for 12 to 24 hours before decompression. Only in condition 6 was this equilibration period preceded by preoxygenation for 2 hours. All decompression took place over a 60-second period. In condition 7 where only 12 hours of equilibration were used, 10 out of 12 subjects had symptoms and 3 out of 12 were forced to descend. In 3 of these 10 cases, subjects experienced bends, 4, 5, and 7 hours after onset of equilibration at an altitude of 18 000 feet. This again corroborates the high-risk nature of the group. Heavy physical exertion, unusual for these subjects, was reported on the day prior to the test. It is doubtful that this

TABLE 21.—Incidence and Time of Onset of Bends Under Various Test Conditions
[AFTER DAMATO¹³⁰]

Tests	Conditions			Symptoms		Forced descent	
	Preoxygenation time (sea level), hr	Equilibration time, percent ^a	Decompression time, sec ^b	Ratio	Time of onset, min	Ratio	Time, min
1 ^c				12 : 12	8 to 81	10 : 12	11 to 62
2.....	2	0	40	10 : 12	13 to 119	7 : 12	22 to 126
3.....	2	0	80	10 : 12	40 to 152	5 : 12	65 to 154
4.....	2	0	120	10 : 12	16 to 134	6 : 12	44 to 148
5.....	3	0	40	1 : 12	106	1 : 12	132
6.....	2	12	60	1 : 12	21	1 : 12	86
7.....	0	12	60	10 : 12	0 to 44 ^c	3 : 12	0 to 132 ^b
8.....	0	18	60	1 : 12	18	0 : 12	
9.....	0	24	60	4 : 12	0 to 114	1 : 12	20

^a Breathing 50 percent oxygen and 50 percent nitrogen at 18 000 feet.

^b In runs involving equilibration, decompression from sea level to 18 000 ft was 60 seconds. *T*, expressed in tables, is decompression time from 18 000 to 35 000 ft.

^c 0 indicates onset of bends symptoms and/or forced descent occurring during decompression to, or arrival at, 35 000 ft.

precondition, without any reported joint or muscle injury, would have a specific influence on the symptomatology. The symptoms at 18 000 feet might well be a reflection of the poor cardiovascular condition of these subjects which may also have been reflected in the "overexertion" of the previous day.

Prolongation of the equilibration to 18 hours (condition 8) resulted in reduction of symptoms to 1 out of 12 with no descents. The prolonged denitrogenation time of 12 to 18 hours suggests that many of these subjects could be classed in the slow denitrogenator groups (curves (2), (7), and (8) in fig. 18). The extreme variability of the subjects and symptoms is indicated by condition 9 in which 4 out of 12 subjects experienced symptoms after 24 hours of equilibration. Three of these four experienced no bends after 18 hours equilibration in condition 8. This would suggest that after 18 hours there was probably little or no change in tissue nitrogen and that no inert-gas variables were present. It is of interest that exposure to 2 hours of oxygen prior to a 12-hour equilibration (condition 6) reduced symptom rates to 1 out of 12 with descent required. The extra 2 hours of denitrogenation probably had little effect on the absolute level of tissue p_{N_2} , but brought 9 out of 12 subjects below the symptom threshold. Since the final equilibrium level of p_{N_2} is 190 mm Hg, 2 hours of preoxygenation on 100 percent oxygen should be equivalent to 608/418, or 1.5 times this duration under equilibration conditions at a p_{N_2} of 190 mm Hg. The 2 hours of oxygen would, therefore, be equivalent in denitrogenation effect to 3 hours of 50 percent oxygen and 50 percent nitrogen at 18 000 feet. The fact that 2 hours of preoxygenation followed by 12 hours of equilibration (15 hours of effective equilibration) gave symptom rates equivalent to 18 hours at 18 000 feet suggests that the 12- to 18-hour period placed subjects in a broad threshold zone with minor physiological variables playing as significant a role in symptoms as the final equilibration level of p_{N_2} . Formation of "silent bubbles" at 18 000 feet is no doubt one of the major factors in question.

How do these results compare with previous predictions? The equivocal results in this study are probably a function of the wide range of age

and physical conditioning. One can predict with relative certainty that with a uniform group of well-conditioned individuals such as an astronaut group, 8 to 12 hours of equilibration at 18 000 feet with 50 percent oxygen and 50 percent nitrogen without preoxygenation should be adequate protection against bends upon exposure to moderate exercise at 35 000 feet. Even though the astronaut group falls in the upper age bracket of the Gray study (fig. 16), the general excellence of cardiovascular conditioning would probably put them in the bends-tolerant category of younger subjects who are rapid denitrogenators.

The Bateman equation (19) predicted for the category of slow denitrogenators ($k=0.2$), a symptom likelihood, X , of 134 when equilibrated at 18 000 feet with 50 percent oxygen and 50 percent nitrogen. This was interpreted from figure 19 to represent about one-half the incidence of bends expected of a rapidly denitrogenating ($k=1.0$) subject after decompressing from sea level to 25 000 feet. For 1 hour at altitude and at rest, this incidence would be 0 to 1 percent; with moderate exercise, 7 to 11 percent. The 1 out of 12 incidence experienced in this experiment under equilibrium conditions falls within the expected incidence.

It is obvious that more data are required to substantiate fully the Bateman equation for equilibrium conditions with slow and rapid denitrogenators. If the Bateman equation is correct, rapid denitrogenators would be expected to have, at equilibrium, 96/134 or 0.7 times the incidence of symptoms of slow denitrogenators. This would give an overall prediction that within 12 hours of exposure to 18 000 feet with 50 percent oxygen and 50 percent nitrogen, a well-conditioned astronaut when exposed to moderate exercise at 35 000 feet would have a 5- to 8-percent chance of experiencing bends. Two hours of preoxygenation should reduce this equilibration time to about 9 hours; 3 hours of oxygen should reduce the equilibration time to 6 hours; and 4 hours of oxygen, to 3 hours. By preoxygenating for 5 hours, a well-conditioned astronaut should be able to step into an atmosphere of 50 percent oxygen and 50 percent nitrogen at an altitude of 18 000 feet, be almost fully equilibrated with the p_{N_2} of this environment, and

expect the 5- to 8-percent incidence of bends predicted by the Bateman equation and its corollaries.

An excellent tabular summary of American and Russian decompression episodes following altered gaseous environments has been published by Wilson.⁴⁵³ Many of the isolated exposures not discussed in this section may be found in this table.

A recent study has been presented by Degner et al.¹³⁶ attempting to correlate the incidence of bends with the level of nitrogen dissolved in the blood prior to decompression. The hypothesis that this level would be significant arises from the theory of Piccard³⁴² (see first section of ch. 2) which stated that a critical number of molecules had to be present in any volume of fluid in order to initiate growth of a bubble beyond the size at which surface tension forces would cause spontaneous collapse. The hypothesis was tested by exposing subjects to a gas and pressure profile simulating orbital work.

Thirty-two subjects of different ages and work background, but all of whom passed USAF Class III flying examinations, were put through several simulated flight profiles (fig. 23). Subjects began by breathing 100 percent oxygen through an aviator's mask at ground pressures of 14.5 psi. This continued for 1.5 to 4 hours and was followed by an "orbit phase" with decrease in pressure (within 2.3 minutes) to 5 psi at 100 percent oxygen for 2½ more hours. The pressure was again decreased within 1.6 minutes to 3.5 psia. Immediately, three sets of five deep knee bends and five pushups were performed at 5-minute intervals simulating execution of "transfer phase" from ascent vehicle to laboratory. The third stage (lab stage) involved 4 to 12 hours of exposure to several gaseous environments: 1A at 5 psi (260 mm Hg) with $p_{O_2} : p_{N_2} = 246 \text{ mm Hg} : 1.9 \text{ mm Hg} = 95 : 1$; 2A, 2B, and 2C at 7 psi (365 mm Hg) with $p_{O_2} : p_{N_2} = 167 \text{ mm Hg} : 183 \pm 3 \text{ mm Hg} = 46 : 50$. The fractional water plus carbon dioxide content was close to 0.04 and the temperature was 23° to 26° C. It took 10 minutes to reach the new composition from previous 100 percent oxygen. Subjects spent their time in these simulated cabin environments at sedentary activity.

The last stage of each flight, "reconnaissance,"

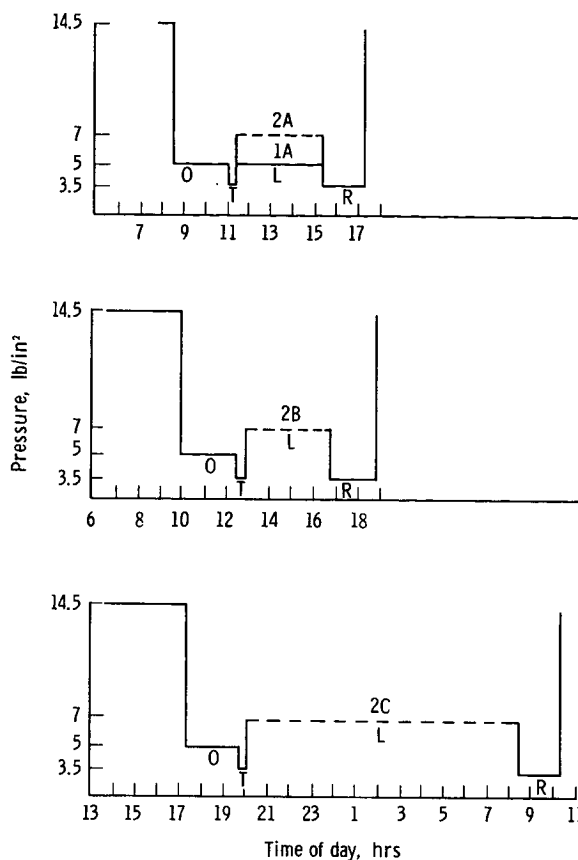


FIGURE 23.—Sequence of pressure stages in four types of simulated flights (solid line, breathing of pure O₂ with the body exposed to air or complete exposure to 95:1::O₂:N₂; dashed line, complete exposure to 46:50::O₂:N₂). (O=orbit; T=transfer; L=laboratory; R=reconnaissance.) (AFTER DEGNER ET AL.¹³⁶)

lasted 2 hours during which, over a period of from 2 to 3 minutes, the pressure was reduced to 3.5 psia and the same exercises as in "transfer" were performed at 15-minute intervals. Oxygen masks were donned at the start of this stage and used throughout the flight by groups 2A and 2B. In flight 2C, following the 12 hours of "lab" and for 0.5 hour before decreasing the pressure, oxygen was breathed through a mask so as to remove some of the reaccumulated nitrogen before exercising at 3.5 psia. The only stage of flight 1A during which oxygen masks were used was in the first preoxygenation stage at 14.5 psia.

Blood samples for nitrogen determination were taken from the antecubital vein without stasis

and with care to avoid air bubbles. Decompression sickness was scored according to a formula which added the products of the grade (1 to 3) of pain multiplied by the duration (min) for each grade and divided the sum by the total number of minutes of exposure. For example, if there was no pain for 4 minutes, grade 1 pain for 2 minutes, and grade 2 pain for 3 minutes, and grade 3 pain for 1 minute followed by descent, the score would be: $(4 \times 0) + (2 \times 1) + (3 \times 2) + (1 \times 3) = 11$ grade \times minutes/10 minutes = score of 1.1.

Table 22 indicates the results of this complicated study which simulates as closely as possible the operational problem of early orbital

transfer. The authors summarize these results as follows:

Almost 90 percent of the symptoms were referred to knee or knee and ankle joints. Once pain was reported it generally became more intense, remaining at the same locations and recurring during subsequent stages. Among the 31 subjects of Flight 2A, the results of those suffering bends are listed according to the flight stage then with reference to the level of bends [table 22 columns and lines, respectively]. Although bends were not reported in the "laboratory" stage of this flight, each of the eight men who suffered during transfer had a higher level of bends while reconnoitering. The other flights also had progressive increases in level of bends. In order to show the average intensity and duration of bends caused by *each stage* of a flight, it was decided to remove from consideration those who reported bends in preceding stages. Thus, in the first stage of Flight 2A there were

TABLE 22.—Average Grade of Bends for Stages in 4 Types of Simulated Aerospace Flights
[AFTER DEGNER ET AL.¹³⁶]

Subject ^a	Type 1A				Type 2A				Type 2B	Type 2C	
	Orbit	Transfer	Lab.	Reconnaissance	Orbit	Transfer	Lab.	Reconnaissance	Reconnaissance	Transfer	Reconnaissance
16.....	1.22	2.00	2.00	^b 2.04	0.41	1.00	0	1.07	0.99	0	0
24.....					0	.69	0	1.00	0	0	0
12.....					0	.61	0	^b 2.20		0	0
9.....	0	0	0	0	0	.54	0	^b 2.07	0	0	0
8.....	^b .47				0	.46	0	2.00		0	0
17.....					0	.38	0	^b 2.15			
1.....	1.35	2.00	^b 2.03		0	.15	0	2.00	^b 1.68	.31	^b 2.25
19.....	1.22	2.00	2.00	^b 3.00	0	.15	0	1.00	0	0	0
3.....	0	0	.11	.75	0	0	0	1.90	1.00	0	0
32.....	0	0	0	.38	0	0	0	1.53	0	0	0
2.....	0	0	0	0	0	0	0	1.12	0	0	0
23.....					0	0	0	1.07	.60	0	0
5.....	0	0	.38	^b 2.14	0	0	0	.97	0	0	0
13.....					0	0	0	.92		0	0
31.....	0	0	0	.98	0	0	0	.90	0	0	0
27.....	0	0	0	.85	0	0	0	.76	0	0	0
26.....	0	0	.06	1.96	0	0	0	.75	0	0	0
6.....	0	0	0	0	0	0	0	.58	.71	0	0
14.....					0	0	0	.14		0	0
11.....	0	0	.15	^b 2.25	0	0	0	0		0	0
28.....	0	0	0	0	0	0	0	0	.54	0	0
18.....	0	.77	0	0	0	0	0	0	0	0	0
21.....	0	0	0	1.00	0	0	0	0	0	0	0
n.....	22	21	21	20	31	31	31	31	24	30	30
\bar{X}194	.322	.320	.768	.013	.128	.00	.778	.230	.010	.075
n'.....	22	18	17	13	31	30	23	23	24	30	29
\bar{X}'194	.043	.041	.247	.013	.099	.00	.463	.230	.010	.00

^a Subjects 4, 7, 10, 22, and 30 did not report bends at any stage of the 4 flights; subjects 15, 20, 25, and 29 took flights 2A, 2B, and 2C only and never reported bends.

^b Grade 3 bends.

31 men with a total bends level of only 0.41, entirely due to subject 16. Deducting this subject leaves 30 men in the next state, of whom seven reported a total grade of 2.98 for an average bends level of 0.0993. The numbers and conditional means listed in the final two lines [table 22] were obtained by this method of elimination, permitting comparison of effects of different flight stages.

The first "orbiting" stage of 1A showed a higher level of bends than that of 2A. Aside from loss of indicated subjects by a single refusal and by departure from this station the only difference was that in 1a for this stage onward the flight was in "shirtsleeves," thus permitting more freedom of movement than in 2A where O₂ masks were used except in the "laboratory." An important difference between the two flights was the protective effect of the 7 psia as opposed to the 5 psia pressure. On the other hand, during reconnaissance only four new cases appeared in 1a as compared with 11 new cases in 2A. Longer prebreathing of O₂ was beneficial, since bends were not reported in the first three orbiting stages of 2B and only appeared in the final stage. Removal from consideration of subject 1 for preceding bends showed that one-half hour's prebreathing of O₂ at the end of the laboratory stage prevented bends even during reconnaissance in 2C.

In general, results could be predicted from the discussion of previous experiments. Whenever other considerations were equal, the frequency and level of bends seemed to be correlated with the expected level of residual nitrogen in the tissues and with the degree of exercise. Measuring the p_{N_2} in the blood at various times and applying the appropriate decay equations for nitrogen, the curves of nitrogen depletion and reaccumulation in the blood were drawn (fig. 24) as a basis for bends prediction. One would, of

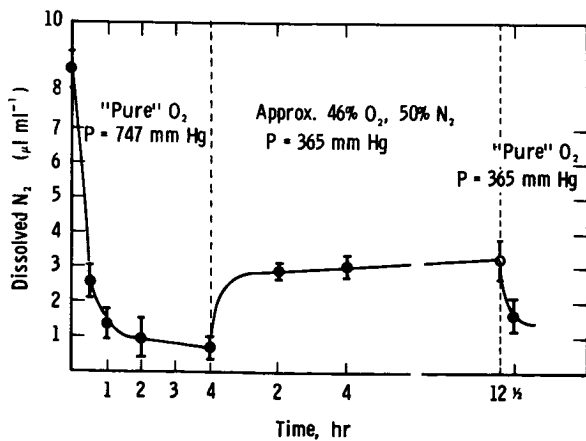


FIGURE 24.—Elimination and accumulation of dissolved nitrogen in antecubital venous blood of men while breathing different partial pressures of oxygen and nitrogen. (AFTER DEGNER ET AL.¹³⁵)

course, expect some correlation between the blood p_{N_2} level, the average residual tissue p_{N_2} level, and the incidence of symptoms. It must be remembered, however, that the p_{N_2} in antecubital venous blood is a poor measure of residual p_{N_2} in the critical, slowly desaturating tissues where bends pains are probably occurring.

In another approach to the analysis, these investigators attempted to correlate the symptom score from the critical volume of blood required to contain the threshold number of molecules for maintenance of bubble stability. This was calculated by the Piccard equations (ch. 2, first section). Figure 25 indicates the hyperbolic relationship between critical volume and bends level. It can be seen that above the range 2000 to 4000 μ^3 of critical volume (as predicted by Piccard for altitude decompression,³⁴²) there was a constant minimal incidence of bends. Below this critical volume, there was a progressive increase in bends score. These results do not necessarily indicate that bubbles of bends originate in the blood nor do they indicate the validity of Piccard's hypothesis. It is probable that this threshold represents only a second-order correlation between blood p_{N_2} and tissue p_{N_2} . From the

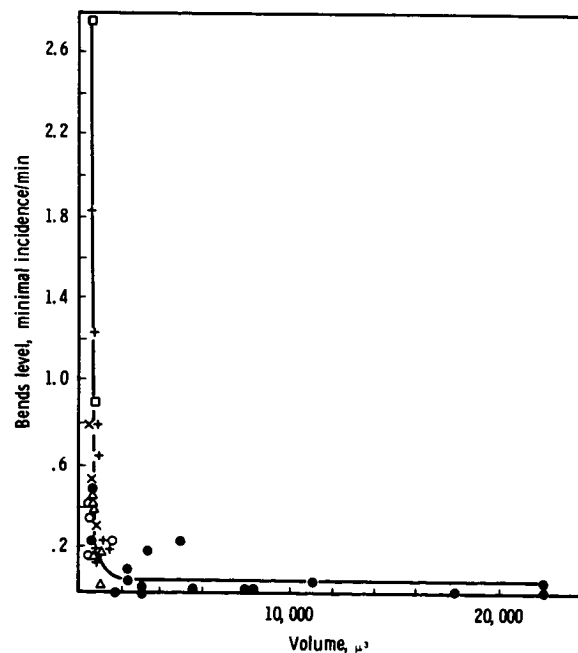


FIGURE 25.—Relationship between level of bends and the volume of blood required to form a nitrogen seed bubble. (AFTER DEGNER ET AL.¹³⁶)

discussion in Chapter 2, first and second sections, it would appear that the blood p_{N_2} would be a valid measure of bends tendency either in the steady state or in the transient state when only the slowly exchanging tissues are contributing significantly to the nitrogen gas of the venous blood. During transient periods of less than 2 hours following marked change in p_{N_2} of the inspired gas, the measure of blood p_{N_2} may lead to erroneous predictions regarding bends tendency.

In flight 1A, exposure to orbital altitude of 5 psi (27 000 ft) and "transfer" altitude of 3.5 psi (35 400 ft) occurred before adequate denitrogenation was available. The high incidence of severe bends during subsequent decompression of the "reconnaissance" phase of the mission 7 hours later was no doubt associated with both "silent" and not-so-silent bubbles formed previously. The recommendations regarding denitrogenation schedules appear valid even though justification of the physical basis for the recommendations appears weak. A review of the previous discussion would suggest that a minimum of 2 hours preoxygenation should precede decompression to 5 psi associated with moderate activity. From curve (Ba) of figure 18 it would seem that at least 4 hours of preoxygenation at sea level or 3 hours at sea level and several hours at 7 psi with 50 percent nitrogen or 5 psi with 30 percent nitrogen should precede exposure to moderate exercise in a suit at 3.5 psi. This would probably reduce to less than about 5 percent the expected incidence of bends in a well-conditioned astronaut population. Such a prediction, extrapolated from indirect data, certainly requires empirical confirmation.

Is there a limit to denitrogenation procedures, and can the last 5 percent of symptoms be eliminated in exercising individuals? As was suggested in the discussion of preoxygenation, there is a limit above 38 000 feet in rapid denitrogenators (table 18). Heavy exercise, at a time when the effective tissue nitrogen has already been drastically reduced, could lead to bubbles with greater percentage of carbon dioxide and oxygen than of nitrogen. Such a bubble could be responsible for the last few percent of symptoms with exercise at high altitudes and would be

resistant to prolonged denitrogenation procedures. The phenomenon is not very evident at 35 000 feet with exercise even in the rapid denitrogenators. Somewhere in the range of 35 000 to 38 000 feet there is a threshold for this effect.

Will equilibration with 100 percent oxygen at a pressure of 5 psi used in Gemini and Apollo programs give 100 percent protection against bends in subjects exercising heavily in the altitude range of 35 000 to 38 000 feet? There appears little direct evidence to this point. Equilibration with 100 percent oxygen at 5 psi followed by decompression has not been studied enough to answer this question.

Can helium eliminate the last 5 percent of symptoms when substituted for nitrogen in a 50-50 mixture at 7 psi? The limited empirical data presented in the previous section on altitude decompression after helium-oxygen exposure with near saturation led to the conclusion that there would be little reduction in bends incidence by substitution of helium for nitrogen. There may even be a higher level of residual symptoms.³⁰ Person-to-person variability in diving operations is greater with helium than with nitrogen. This in itself would tend to increase the potential for unusual bends sensitivity in any relatively uniform population. Analysis of bubble theory (table 9) and Navy diving experience suggests that there may be a slight reduction in the more serious neurocirculatory sequelae with helium or neon. Evidence on this point is equivocal. The expected incidence of these serious sequelae appears to be so low after equilibration at reduced partial pressure of nitrogen at 7 psi that further reduction by other gases may be of only academic interest.

What do the semiempirical approaches have to offer in predicting the incidence of bends after helium? From the Bateman equation (28), it would appear at first glance that helium may reduce the X -factor quite considerably. The range of time constants used by Bateman to represent the critical denitrogenation process was 1.0 and 0.2 hours⁻¹. These single constants were arrived at by examination of denitrogenation data which indicated that some persons are protected from decompression sickness

by inhalation of oxygen for 30 minutes or less and others by 2½ hours or more. These were not the extremes, but they encompassed the majority of cases. Comparable figures for helium are not available. In the second section of chapter 2, half times of the several exchange components in the body were compared for helium and nitrogen. Whereas the half time of more than 50 percent of the stored nitrogen is more than 147 minutes, the half time for the slower half of the stored helium is only about 50 minutes in some studies and around 100 minutes in others. Momsen³¹⁷ used 60 minutes as the critical half time in setting up helium diving tables, but this was not adequate for long, deep dives. Stubbs⁴¹⁵ suggested that for his computer program a value of 100 to 260 minutes should be used for the effective half time of helium desaturation in the slower tissues. It is, therefore, uncertain as to which range of half times should be used in the Bateman equation for helium.

In addition to this uncertainty regarding critical time constant for helium, it also appears that the altered bubble peak factors of helium (table 9) would change the other empirical constants in the Bateman equation. These constants, it appears, take into account the relation between desaturation rates, local supersaturation ratios, and bubble growth factors for nitrogen. There has been no test of a helium equation against empirical data. This is necessary for alteration of the constants. At this point it must be said that any attempt to extrapolate the Bateman equation to helium would be unwarranted. The Piccardian approach of Degner et al.¹³⁶ also offers no clear answer to this problem. The empirical data of Beard et al.³⁰ will have to stand alone until further confirmation is available from both theoretical and empirical studies. These cover only the transient state.

As for neon, absence of definitive physiological data precludes an adequate extrapolation from any desaturation scheme for nitrogen or helium. The findings of Jones,²⁴⁹ which indicate that only perfusion factors and tissue-blood solubility ratios limit inert gas exchange, do not help in this extrapolation since the coupling of solubilities and perfusion for neon are not known. Physio-

logical studies on neon are certainly in order, especially in view of the recent success in preliminary studies of this gas by the Royal Navy.⁵⁴

There are several aspects of experimental design which warrant comment as an epilogue to this discussion. The first is the choice of exercise regimen to be used in evaluation of cabin atmospheres. The second is the evaluation of the level below symptom threshold at which asymptomatic subjects find themselves after an experimental decompression.

As noted in figure 19, and throughout this section, exercise level has a profound effect on incidence bends symptoms and probably to a lesser degree on chokes and neurocirculatory symptoms. Therefore, the design of the provocative aspects of the tests must simulate as closely as possible the operational exercise levels in different phases of each space mission. Piloting the craft presents no problem. Extravehicular operations, however, should be simulated using arm and leg motions that are as close to the operational situation as possible. Deep knee bends or step-ups will probably exaggerate the incidence of leg symptoms expected in even the most severe orbital maintenance tasks. Locomotion or work in space suits should be used whenever possible to simulate tasks in orbit or on a planetary surface. The incidence of specific symptoms after various preoxygenation and altitude equilibration regimens is an important factor in evaluation of the mission hazard index. Standard exercises such as stepups, deep knee bends, and weight lifting may be adequate for a rough evaluation of atmosphere selection criteria, but could give a false picture of the specific operational hazards which may be encountered by the astronaut population in various space tasks. Individual idiosyncrasies in symptom patterns may require testing of specific astronauts when unusual work regimens are needed in preparation for hazardous or emergency operations where adequate denitrogenation procedures cannot be employed.

Detection of subclinical bubbles in asymptomatic subjects after decompression has been a goal long sought by investigators in this area. Diving technology has used secondary altitude decompressions to elicit symptoms from "silent bubbles" present at sea level after ascent.²⁶¹ A

reasonable substitute has not been available for primary altitude decompression. It may well be worthwhile to consider the use of ultrasound as a method of bubble detection. The acoustic physics of bubbles has been a topic of interest to workers in the field of cavitation, hydrodynamics, and acoustics.^{94, 313, 424} Recently, a practical ultrasonic bubble detector has been developed for detection of bubbles in studies of biphasic flow and cavitation.²¹⁷ Such a device could be adapted to study of "silent bubbles" in decompression sickness. MacKay^{271, P. 41} has recently mentioned his experience with ultrasound devices in detection of bubbles. A pulsed 15-megacycle (100 μ) echo-exploring device was employed to detect bubbles "an appreciable fraction" of the 100- μ wavelength in diameter. Sound intensities of 0.001 watt/cm² were used. Stubbs⁴¹⁵ has reported the preliminary use of ultrasound in detecting silent bubbles for evaluation of the effectiveness of his analog diving computer. This technique may be of value in the study of the kinetics of bubble formation *in vitro* and *in vivo*. When properly calibrated, it could possibly be used to define at any body site the local physical conditions necessary for bubble formation. Knowledge of this fact would greatly enhance our understanding of the decompression process and lead to a more effective calibration of computer devices for generating decompression curves and hazard indices.

ANALYSIS OF INERT GASES IN "EXPLOSIVE" DECOMPRESSION AND IN THE EBULLISM SYNDROME

In the previous sections of this chapter, no mention was made of two conditions that may modify the analysis of inert gas factors. "Explosive" decompression to altitude adds the potential for new inert-gas factors associated with sudden overdensation and disruption of the lungs. The inert-gas effects of exposure to very high altitudes must also be considered. Current space-suit concepts suggest that a fully operative suit will now allow exposure of an astronaut to effective altitudes above 40 000 feet. The analysis in the first section of this chapter is probably valid up to altitudes of 60 000 feet. Even gradual ascent to altitudes above approximately 60 000 feet com-

pounds the problem of low-altitude decompression by presenting the vaporization of body fluids as an added factor. In this section, explosive decompression and ebullism are examined for inert-gas dependence.

"Explosive" Decompression

In addition to the external trauma which may occur following perforation of a space suit or in the vicinity of a cabin puncture, there is the possibility of serious internal injury. In general, the critical limiting factor in human tolerance to "explosive" decompression is the physical damage that may occur in the lungs. The theoretical analyses of Fliegner,¹⁷³ and, more recently, of Haber and Clamann²¹⁰ and Luft,²⁹¹ indicate that the mechanical effects upon the body are dependent upon the change in absolute pressure, the ratio of initial pressure to final pressure, and the rate of decompression. The pressure transients during the event can be defined in terms of two principal determinants, the time characteristic t_c and a pressure factor P_1 . The time characteristic has the general form

$$t_c = \frac{V}{AC} \quad (29)$$

where

- V volume of pressure vessel
- A effective aerodynamic orifice
- C velocity of sound

This relationship is plotted in figure 26.

A more rigorous analysis of this relationship has been recently presented by Mavriplis.³¹⁰ If

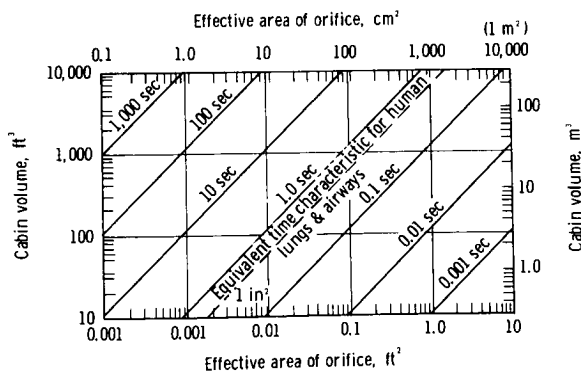


FIGURE 26.—Time characteristics of decompressing pressure vessel. (AFTER LUFT AND BANCROFT.²⁹²)

the critical ratio of about 2 to 1 is exceeded, the escape flow will be constant at the speed of sound regardless of pressure head. The term "explosive" decompression, although common in the literature, is, therefore, a misnomer in conditions of cabin decompression. "Rapid" decompression would be more physically correct, though less onomatopoeic.

Under conditions of polytropic flow, the pressure factor P_1 is a function of the initial pressure P_i and the final pressure P_f in the vessel as follows:

$$P_1 = f\left(\frac{P_i - P_f}{P_i}\right) \quad (30)$$

Figure 27 represents this relationship. The total decompression time or duration of transient t_d is the product of the time characteristic of the system t_c defined by equation (29), and the pressure factor P_1

$$t_d = t_c P_1 \quad (31)$$

In decompression to space conditions, the very low final pressure prolongs the duration of decompression because of the slow process of terminal equilibration. Under these circumstances, the initial part of the transient provides a more mean-

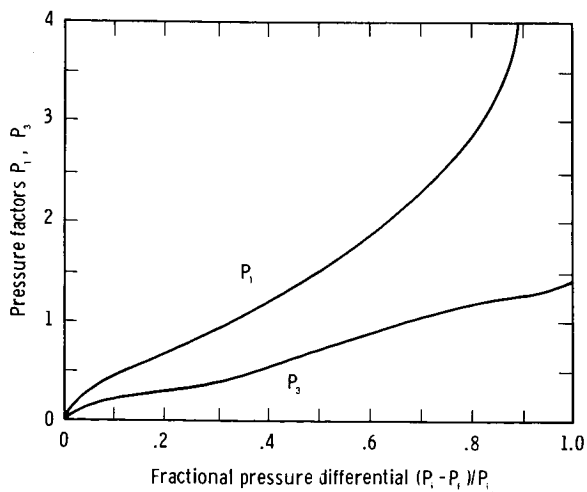


FIGURE 27.—The pressure factor P_1 for the total time of decompression and P_3 for the "constant rate time," as derived from the pressure ratio $(P_i - P_f)/P_i$. (REDRAWN AFTER HABER AND CLAMANN.²¹⁰)

ingful period than the total duration. For the initial period, the constant rate time t_{cr} can be calculated from the pressure factor P_3 which may be read from the curve on figure 27. For the appropriate decompression ratio

$$t_{cr} = t_c P_3 \quad (32)$$

As demonstrated by Luft and coworkers,^{291, 292, 293} if the time characteristic of the human lung and airway is greater than the time characteristic of the pressure suit or cabin in which an individual is confined during the decompression, a transient differential pressure will build up between the lungs and ambient atmosphere. This is illustrated diagrammatically in figure 28.

It has been shown by Adams and Polak¹ that dog lungs may become disrupted by pressure differentials of over 80 mm Hg. Under some conditions even lower pressures are required.³⁵² Henry feels that the threshold for humans is only 50 mm Hg.²²⁶ If this pressure differential is exceeded during decompression, the lungs may be damaged. The dashed line in figure 26 represents the time characteristic of the human lung with open glottis on a background of the general volume-to-orifice relationship. Since the volume

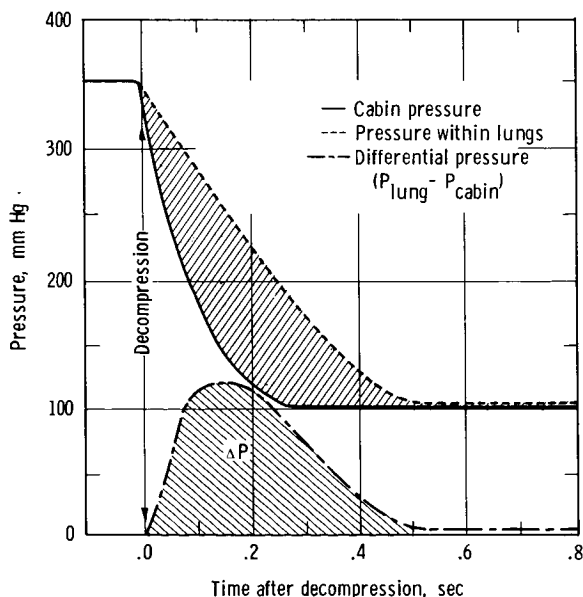


FIGURE 28.—Time characteristics of overpressure in the limbs. (AFTER WEBB.⁴⁴⁵) (MODIFIED FROM LUFT.²⁹¹)

of the lungs varies with respiration, it is obvious that the time characteristic of the lungs may also vary, depending on the phase of expiration. The pressure differential across a lung and degree of hazard would, therefore, be maximal with a narrow glottis in full inspiration. Many of these relationships have been recently reviewed in great detail by Luft.²⁹⁰

One aspect of this discussion is pertinent to the present problem. That is the critical V/A ratio of the cabin relative to that of the human respiratory tract required for injury or death.

Little information is available from human studies. The results of animal studies are recorded in table 23 compiled by Luft.²⁹⁰ The maximal V/A ratios of the cabins that produced death were around $3 \text{ m}^3/\text{m}^2$. Ratios for LD_{50} were about $1.2 \text{ m}^3/\text{m}^2$; and for LD_{100} , $0.12 \text{ m}^3/\text{m}^2$. The V/A ratio for human pulmonary tree calculated by Luft and Bancroft²⁹² from intrathoracic pressure transients is $180 \text{ m}^3/\text{m}^2$. For dogs, Violette⁴³⁶ gives a value of 100. This indicates that the dogs may tolerate somewhat lower V/A cabin ratios than humans. However, this dif-

TABLE 23.—*Mortality in Relation to Decompression Time in Experimental Animals*
[AFTER LUFT²⁹⁰]

Reference	Species	Decompression		$P_i - P_f$ mm Hg	P_i/P_f , mm Hg	Decompression time, sec	V/A , m^3/m^2	Mortality, percent
		Initial pressure, P_i , mm Hg	Final pressure, P_f , mm Hg					
Corey ¹²¹	Rat.....	760	21	739	36.2	0.630	36.2	0
Eggleton ¹⁵⁵	Rabbit.....	760	122	638	6.2	.200	18.0	0
Eggleton ¹⁵⁵	Rat.....	760	122	638	6.2	.200	18.0	0
Kolder ²⁶⁷	Rat.....	735	73	662	10.0	.180	15.0	0
Kolder ²⁶⁷	Rat.....	735	73	662	10.0	.041	3.3	10
Kolder ²⁶⁷	Rat.....	735	73	662	10.0	.015	1.2	50
Stickney ⁴¹³	Rat.....	738	32	706	23.1	.019	1.14	50
Kolder ²⁶⁷	Rat.....	735	73	662	10.0	.0014	.12	100

All experiments are comparable in the range of decompression from approximately 1 atmosphere to less than 0.2 atmosphere.

ference may well be due to the different experimental techniques used to obtain the values. From figure 26 it can be seen that a cabin time characteristic t_c of about 4.0 milliseconds would be required for an LD_{50} exposure. Translated into current space cabins, this would suggest that in a 50-ft³ cabin of the Project Mercury type, a wall hole in excess of 1.0 ft² would have been required to kill an astronaut with open glottis by "explosive" decompression.

Experience with human exposure to decompression at high cabin V/A ratios is very limited. Most deaths have occurred in subjects with pathology such as blebs which decrease the overpressure tolerance of the lungs, and with closed glottis during the exposure. Well-documented, danger-

zone decompressions with open glottis have been limited to those recorded in table 24. It can be seen that only the first exposure of Sweeney⁴¹⁸ would have had a cabin V/A ratio ($1 \text{ m}^3/\text{m}^2$) well within the expected lethal range. Luft²⁹⁰ has calculated for these experiences the overpressures to be expected in the lung for closed airways at midrespiratory volume. Even under these conditions, the pressure ratio P_i/P_f would have been small enough in the first case with low V/A ratio to have prevented the critical overpressure of 80 mm Hg from being reached.

What are the gas-dependent factors that determine the medical hazard of "explosive" decompression? There appear to be two major factors: hemorrhage from the disrupted lung; and intro-

TABLE 24.—*Rapid Decompression Tolerated by Man*
[AFTER LUFT²⁹¹]

Reference	<i>n</i>	Altitude, ft	Initial pressure in cabin, <i>P_i</i> , mm Hg	Final pressure, <i>P_f</i> , mm Hg	<i>P_i</i> - <i>P_f</i> , mm Hg	<i>P_i</i> / <i>P_f</i>	Time, sec	<i>V</i> / <i>A</i> , m ³ /m ²	Δ <i>P_L</i> , mm Hg ^a
Sweeney ⁴¹⁸ ...	10	27 000 to 45 000	253	112	141	2.23	0.005	1.0	48
Sweeney ⁴¹⁸ ...	15	8 000 to 35 000	565	179	386	3.16	.090	13.4	153
Döring ¹⁴¹	13	9 800 to 49 100	526	90	436	5.83	.230	23.0	220

^a Δ*P_L* is the overpressure which would occur in the lungs if the airways were closed at midlung volume; critical pressure is 80 mm Hg.

duction of gas emboli into the venous side of the pulmonary circulation with subsequent infarction of critical sites in the systemic circulation. It appears that an inert-gas factor would play a role at two points in the overall sequence of events. The inert gas may determine the flow characteristics of gas through the pulmonary tree or the glottic orifice as well as determine the size characteristic of the gas bubbles being sent to the peripheral systemic circulation.

Gas-Dependent Factors in Lung Expansion During "Explosive" Decompression

The flow of gas through the respiratory tree, as mentioned above, is a critical factor in lung damage during "explosive" decompression. A rigid analysis of the flow factor has been performed by Bowen et al.⁷¹ in their mathematical model of the fluid-mechanical response of the thoracoabdominal system to blast overpressure and "explosive" decompression. An analysis of the gas-dependent factors in their model leads to the conclusion that the rate of pressure change in the lung with respect to ambient $\left(\frac{dP}{dt}\right)_{t=0}$ is a function of the product of the reciprocal of the square root of the average molecular weight of the gas *M* and a gas-flow factor involving the specific heat ratio γ . This relationship is shown in the following equation

$$\left(\frac{dP}{dt}\right)_{t=0} \sim \frac{1}{M^{1/2}} \left(\gamma \left[\gamma \left(\frac{2}{\gamma+1} \right)^{\frac{\gamma+1}{\gamma-1}} \right]^{1/2} \right) \quad (33)$$

The lower the rate of pressure change in the lung with respect to ambient, the more dangerous is the atmosphere. This same relationship would define the hazard from external blast overpressure. For isothermal processes, the value of $\gamma=1$ can be used. For adiabatic processes the values of γ are obtained from the *C_p*/*C_v* ratio of table 1. As discussed in chapter 1, the value for the inert gases lies in the 1.67 range, except nitrogen at 1.4. The value of oxygen is 1.4.

It is still not absolutely clear whether adiabatic or isothermal processes predominate in the lung in "explosive" decompression or blast overpressure. The rapidity of the process suggests adiabatic conditions. It must be remembered, however, that the alveoli of the lung present a large surface for heat exchange and high humidity. This would allow for rapid condensation of water vapor to counteract the adiabatic cooling. Hitchcock²³⁵ has measured the temperature change in the lung during "explosive" decompression and found it to be minimal. Sensor lag obviously complicates the measurement to an unknown degree. The lung model of Bowen et al.⁷¹ used a value of $\gamma=1.2$ for air as a polytropic compromise in an unknown situation. It is felt, by this group, however, that the isothermal process probably predominates.¹⁷²

In the analysis of the space-cabin situation, calculations are presented for the currently proposed environment of 50 percent inert gas and 50 percent oxygen. Both the isothermal and 50 percent isothermal-50 percent adiabatic specific heat ratios are presented in table 25. For the isothermal condition, $\gamma=1$. Table 25 represents

TABLE 25.—Relative “Explosive” Decompression and Blast Overpressure Hazards From Atmospheres at 7 psia With 50 Percent Inert Gas and 50 Percent Oxygen

Factor	Gas mixture in cabin						
	He-O ₂	Ne-O ₂	A-O ₂	Kr-O ₂	Xe-O ₂	N ₂ -O ₂	O ₂
1/M ^{1/2}	0.34	0.20	0.17	0.15	0.13	0.18	0.18
γ(50 percent adiabatic).....	1.25	1.25	1.25	1.25	1.25	1.20	1.20
Isothermal expansion (γ=1) $\left(\frac{dP}{dt}\right)_{t=0}$34	.20	.17	.15	.13	.18	.18
Relative hazard index (N ₂ -O ₂ =1).....	.53	.90	1.1	1.2	1.4	1.0	1.0
Polytropic expansion (50 percent adiabatic) $\left(\frac{dP}{dt}\right)_{t=0}$26	.15	.13	.11	.10	.13	.13
Relative hazard index (N ₂ -O ₂ =1).....	.50	.87	1.0	1.2	1.3	1.0	1.0

the calculations of $\left(\frac{dP}{dt}\right)_{t=0}$ for these gas mixtures and the relative hazard index with nitrogen-oxygen=1. The relative hazard index is calculated from the reciprocal of the $\left(\frac{dP}{dt}\right)_{t=0}$ factor. The nitrogen-oxygen and the 100-percent oxygen (7 psi) atmospheres would have the same degree of hazard.

It can be seen that the major gas factor is 1/M^{1/2}. The thermodynamic nature of the expansion has little effect on the relative hazard of the inert gas. Helium-oxygen appears to be about 0.5 as hazardous as nitrogen-oxygen or 100 percent oxygen; neon-oxygen appears to be about 0.9 times as hazardous. The relative degree of hazard then increases with increasing molecular weight for the other gases. It should be pointed out that these are the maximum differences expected.

Most second-order factors would probably tend to decrease the relative molecular-weight dependence. For example, the rate of gas escaping from the cabin is also dependent upon molecular weight. However, when one reviews the cabin V/A ratios required for lethality in animals, it is evident that the cabin pressure will have essentially reached ambient well before the flow of gas out of the respiratory tree has ceased. Any overlap of these flows would reduce the dependence upon molecular weight. Therefore, a prediction would be made that the smaller the cabin hole, the less gas dependent is the decompression hazard.

One must also keep in mind that the huge cabin hole required to kill a crewman by “explosive” decompression will probably involve enough external trauma to the crew in present-day cabins to render lung damage of secondary importance. Blast overpressures caused by meteoroid penetration, military action, or internal explosions are still problems which, although probably rare, are within the considerations presented above.³⁷⁰ The weighting of this factor in evaluation of the overall gas-dependent hazard must, however, be kept in the proper perspective.

The only animal studies that bear on the effect of specific gases on the lethality of “explosive” decompression were presented by Witherspoon et al.⁴⁵⁶ The presence of an 80 percent helium and 20 percent oxygen environment had the same effect as air on the lethality to mice undergoing “rapid decompression.” Unfortunately, neither the time of decompression to 35 000 feet, nor the V/A ratio of the pressure vessel was noted. Little can, therefore, be concluded about the absence of the protective effect of helium in potentially lethal exposures.

Gas-Dependent Factors in Gas Emboli After Lung Disruption

Both “explosive” decompression and air blast can introduce ambient gas into the lungs.^{188, 236, 370, 397, 450} These bubbles pass to the systemic circulation and lodge in the arterial tree. It does not seem likely that the passage of a bubble through a tear in the wall of pulmonary veins is

directly related to the gaseous composition of the bubble. However, the dynamics of the bubble at its terminal site appears from the discussion in the first section of this chapter to be gas dependent. One might predict that the duration of effective embolization and infarction is somewhat related to the total pathology produced. The longer a bubble retains its size, the more severe the medical hazard. What gas-dependent factors are actually involved?

When a bubble lodges in an artery, it may block the flow to a variable degree. In a nonbranched site the bubble probably blocks the flow completely. The rate of decay of this type of bubble is probably perfusion limited. The rate of decay will not depend on the gas composition but on the amount of blood passing the bubble surface. If a bubble lodges at a branching point, it may well have up to one-half of its surface exposed to the blood passing into the unblocked channel of the bifurcation. There is a distinct possibility that the rate of bubble decay is related to the permeation coefficient of the gas in blood. Surface tension will supply the driving force. The bubble would follow the decay dynamics outlined by Epstein and Plesset¹⁵⁹ and discussed in the first section of this chapter. One would, therefore, expect that the $\alpha_{\text{blood}}D_{\text{blood}}$ factor suggested in the discussion of the case 3 bubble in the first section of this chapter would determine the rate of bubble collapse in diffusion-limited sites. The relative bubble factor for inert gases is presented as phase 1 in case 2 of table 9. In the present situation, however, the lower is the value for $\alpha_{\text{blood}}D_{\text{blood}}$, the greater the hazard.

It would thus appear that neon should cause the bubble to linger the longest, with decreasing durations expected with nitrogen, helium, argon, krypton, and xenon. The empirical data on the relative hazard of intravenous injection of different gas mixtures²⁰⁰ are not valid in the present context where arterial embolization is at question. Of course, 100 percent oxygen with its great solubility in blood would be the most advantageous gas to be breathing at the time of embolization.³⁵³ Again, it must be stated that the expected low frequency of dangerous "explosive" decompression or blast hazard in a space vehicle would cause this factor to have a low weight in the overall evaluation of gas-dependent hazards.

Ebullism Syndrome

Exposure to altitude where the total ambient pressure approaches the effective vapor pressure of fluids at body temperature gives rise to the profuse evaporation associated with the formation of vapor bubbles in tissues, blood vessels, and body cavities. In his excellent theoretical analysis of this phenomenon, Ward^{442, 443} pointed out the physicochemical considerations which define the site and nature of vapor bubbles throughout the body. Ward recommended that the syndrome be named "ebullism," and this name has been accepted by the scientific community.

The interesting history of the syndrome has been reviewed by Wilson.⁴⁵⁴ The presence of vapor bubbles in animals exposed to low pressures was first pointed out by the early experiments with Torricelli tubes, von Guericke vacuum hemispheres, and Boyle pumps. Van Musschenbroek was the first to point out tissue swelling.³²⁴ This phenomenon was repeatedly reported by Bert and other investigators, but was not carefully studied until 1936 when Armstrong¹² attempted to analyze the nature of the intravascular bubbles forming at 58 000 feet. These animal studies have been followed up by many investigators. The excellent dog series by Hitchcock and his coworkers have been well reviewed and summarized,²³⁶ and reviews of Soviet studies have also been presented.^{221, 397}

The first reported case of swelling of the human hand after 9 minutes at 58 000 feet was given by Henry et al.²²⁷ in 1944. These findings have been repeated many times. The excellent study of this phenomenon by Wilson⁴⁵⁴ reviews these human exposures and adds some plethysmographic data on deliberate exposure of hands to 3 to 20 mm Hg. The data of the Russians, summarized by Ivanov et al.,²⁴⁴ agree in general with these findings.

An exhaustive review of the experimental data on ebullism is quite beyond the scope of this report. It would be appropriate, however, to review the general aspects of the syndrome. At altitudes as low as 43 500 feet during vigorous inspiration or "negative valsalva maneuvers," evidence of transient interpleural vaporization can be shown by X-ray and at 61 000 feet (50

mm Hg), vapor may form at this site during normal inspiration. As pointed out by Ward,^{442, 443} body fluids begin vaporization at 63 000 feet. Selection of the site is determined by such local factors as temperature, hydrostatic pressure, tissue elasticity, solute concentration (Clausius-Clapeyron factors), and the presence of gas nuclei. As would be expected from these considerations, the large venous channels at the center of the body temperature core are sites of early bubble formation resulting in vapor lock of the heart. Vapor pockets forming in the loose subcutaneous tissue are often seen, as are vapor bubbles, on the aqueous humor of the eye and in the brain.

The survival and functional capabilities of animals exposed to altitudes above 100 000 feet (8 mm Hg) are currently being studied in great detail. Clamann⁹⁸ has reported that decompressions up to 130 000 feet (2 mm Hg) result in violent evolution of water vapor with swelling of the whole body in dogs. Preliminary results indicate that in 36 dogs, some kept as long as 90 seconds at 2 mm Hg, not a single fatality was observed. The animals were unconscious, gasping, and had bradycardias down to 10 beats/min from the normal rate of 159 beats/min, probably a vagal response to distortion of the mediastinal structures.⁴⁷¹ Most also had paralysis of hind limbs, yet after 10 to 15 minutes at sea level they walked about normally. No permanent pathological lesions were seen on subsequent autopsy.

Many of the dogs reported decompressed by Clamann were included in the report of Dunn et al.¹⁴⁹ The results were summarized by Koestler et al.²⁶⁶ as follows: 125 dogs were decompressed at pressure levels of 2 mm Hg and less; 92 dogs were autopsied within 30 minutes, 3 to 5 days, and 1 to 3 weeks after the rapid decompression (RD). The major findings were summarized:

The most interesting finding was the absence of major pathological damage except in the lungs unless the exposure time exceeded 120 seconds. By varying the exposure time and the time of decompression (altitude of less than 2 mm Hg), it was possible to separate the pathological effect of anoxia versus time of decompression. In all dogs the severity of lung damage increased with the duration of the anoxic exposure. In groups with comparable exposure times, the dogs decompressed in 1 second exhibited pulmonary conges-

tion, edema, and hemorrhage, while those decompressed in 0.2 second showed predominantly more petechial hemorrhage, and emphysematous changes. Denitrogenation appeared to reduce the incidents of severity of lung damage. . . . Animals autopsied at later dates showed evidence of all lesions, especially in the lungs. For the exposures of more than 120 seconds, gross examinations of the brain and other organs showed increasing amounts of congestion and hemorrhage.

Squirrel monkeys trained in a specific behavioral task known as "learning set" have recently been decompressed to 130 000 feet (2 mm Hg) for intervals up to 90 seconds and retested 1 week and again 2 months after exposure.³⁷² Of the 20 animals decompressed, there were 2 fatalities. One that had been exposed for 11 seconds and had subsequently died was still alive at 4 minutes after recompression, but no attempt was made at resuscitation. An autopsy showed atelectasis and possibly a visceral tear with hemorrhage. An autopsy of an animal that died after exposure for 90 seconds revealed no air in the subpleural cavity (during underwater examination in water), but showed basilar pulmonary atelectasis with subpleural petechial hemorrhage. Many of the survivors of 90 seconds of exposure showed various defects in locomotion, hearing, vision, and food retrieval, and lost more weight than the other groups. Of interest, however, is the fact that among the survivors there was no loss of proficiency in learning set.

Koestler et al.²⁶⁶ have very recently completed the first phase of decompression studies on trained chimpanzees under sponsorship of NASA. The results have been summarized as follows:

Eight chimpanzees, used in nine separate tests, were decompressed from 179 mm Hg (breathing 100 percent O₂) to less than 2 mm Hg in 0.8 second and remained at this altitude from 5 to 150 seconds. After recompression to 179 mm Hg (again breathing 100 percent O₂), the subjects were kept at this altitude for 24 hours. Performance by all animals, on a complex operant schedule presented during and following rapid decompression, reached a baseline level of performance within a 4-hour post-decompression period. No central nervous system damage (as measured by performance) could be detected and all subjects survived in good health.

Perhaps the most important result of this series of tests is that *all* subjects survived the experimental conditions. The fact that the animals were capable of performing a complex task and achieving a level of performance equal to or superior to their preexposure performance provides clear-cut

evidence of a functional capability not previously anticipated. The best and most cautious generalization that can be made at this time from the experimental findings is that the chimpanzee can survive, without apparent central nervous system damage (as measured by performance), the effects of decompression to a near vacuum up to 2.5 minutes and return within approximately 4 hours to baseline levels of functioning. Further research, in which the replication of longer duration exposures (90, 120, 150 seconds) is accomplished (perhaps with several different primate species), should determine the reliability of these findings and suggest the degree to which subhuman results may realistically be extrapolated to man.

It should be remembered, however, that because of the great species specificity of critical sites and times of onset, restraint should be used in extrapolation of these data to humans.²⁴³

What is the major cause of death during decompression to ebullism altitudes? From the animal studies it can be inferred that cardiovascular collapse will be most precipitous. After exposure to subebullism altitudes, there is a dramatic fall in blood pressure followed by rebound with subsequent anoxic failure. At ebullism altitudes, one can expect vapor lock of the heart to result in complete cardiac standstill after 10 to 15 seconds, with increasing lethality for exposures of more than 90 seconds.²³⁷ Vapor pockets have been seen in the heart of animals as soon as 1 second after decompression to 3 mm Hg.²⁴³

What is the role of the inert gases in vapor bubble formation of ebullism? Henry²²⁷ suggested that the subcutaneous swelling he observed in the hand was probably initiated by a small nucleus of gas produced by the decompression. Armstrong^{11, 12} actually measured the composition of gas bubbles in the blood of goats after a 4-minute climb to a simulated altitude of 50 000 feet. Table 26 indicates his findings. From the altitude involved, it is not clear whether these findings represent the

TABLE 26.—*Composition of Intravascular Gas Bubbles at 50 000 Feet*
[AFTER ARMSTRONG¹¹]

Location	Composition, percent			
	O ₂	CO ₂	N ₂	Total
Jugular vein.....	6.7	28.3	65.0	100.0
Right ventricle.....	11.4	28.3	60.3	100.0

composition of inert gas in vapor bubbles or the composition of gas bubbles expected to be produced at subebullism altitudes.

Because the decrease in subcutaneous pocket volume is much slower on recompression than is the expansion upon decompression, Hitchcock and coworkers suggested that air must enter the pockets.²³⁷ Kempf et al.²⁵⁷ analyzed the gas pockets in the subcutaneous compartments of dogs during "explosive" decompression to 30 mm Hg. The internal pressures measured by strain gages rose to about 20 mm Hg above ambient and then increased to 26 mm Hg above ambient. The absolute pressure measured by mercury manometers reached 67 mm Hg. Analysis of gas within subcutaneous compartments of dogs is recorded as indicating "a high concentration of water vapor and small amounts of carbon dioxide." These authors felt that the rising pressure was caused by carbon dioxide diffusing into the bubble. They expressed surprise at finding no nitrogen or oxygen. The sampling time of 60 seconds after exposure may have been too short for the other gases to enter in significant amount, although the studies below suggest otherwise.

The Soviets have been interested for some time in this problem as indicated by the excellent study of Balakhovskiy and Fomenko.¹⁴ These investigators measured the changing humidity and p_{CO_2} within subcutaneous pockets ("emphysematous bubbles") of rabbits and rats. As would be expected, the relative humidity quickly reaches the maximum level of the humidity sensor at 95 percent. Figure 29 represents the curve of p_{CO_2} made during one of these experiments.

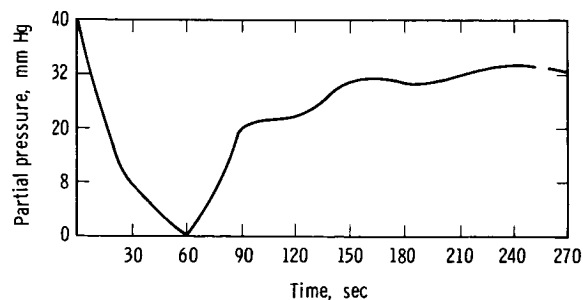


FIGURE 29.—*Changes in the partial pressure of carbon dioxide in the emphysematous bubble.*
(REDRAWN AFTER BALAKHOVSKIY AND FOMENKO.¹⁴)

A substantial drop of p_{CO_2} is noticed during the development period of the "emphysematous bubble." The authors point out that in small air bubbles injected subcutaneously at sea level there is a rapid carbon dioxide buildup, but in altitude emphysema there is an actual lag in carbon dioxide buildup caused by rapid water vapor entry.

These authors also analyzed the gaseous composition of the bubbles at the point of maximum volume of the pocket. Table 27 represents the

findings. Analysis of the variability of composition suggests that a sampling error is not at fault. As discussed in the first section of this chapter, the specific tissue site and fat composition may well be a major factor in determining the gas composition of connective tissue pockets.

A more recent Soviet study defines the change of inert-gas composition of subcutaneous pockets of rats decompressed to 7 to 8 mm Hg over a period of 50 seconds. Analyses performed at sea level are seen in table 28.

TABLE 27.—*Chemical Composition of Gas From Emphysematous Bubbles*
[AFTER BALAKHOVSKIY AND FOMENKO ¹⁴]

Gas	Bubble composition, percent					
	1	2	3	4	5	6
Rats						
O ₂	13.1	15.4	6.3	18.6	7.4	20.8
CO ₂	33.3	20.6	41.9	30.8	48.3	1.2
N ₂	53.6	64.0	51.8	55.6	44.3	78.0
Rabbits						
O ₂	6.6	19.7	6.3	2.0	14.5
CO ₂	68.0	2.3	62.4	64.0	27.5
N ₂	25.4	78.0	31.3	34.0	58.0

Again, there are large variations from pocket to pocket. Examination of the gases, measured by the Scholander method, revealed that within the first 10 seconds, nitrogen was predominant. At the end of a minute, carbon dioxide became predominant. The differences between the findings of the two series of Russian investigators may well be explained by a difference in sampling time. It is puzzling why Kempf et al.²⁵⁷ found no nitrogen or oxygen at the end of 60 seconds. Species differences of this magnitude would be most improbable.

The dynamics of subcutaneous vapor pockets in ebullism can be summarized by stating that there is first a rapid conversion of liquid water to the vapor phase which reaches a peak at about 1 minute and probably continues for several minutes at a slower rate. There is an original rush of carbon dioxide, nitrogen, and oxygen into the pocket. Gradually, carbon dioxide becomes the dominant gas. From the pressure data of Kempf et al.,²⁵⁷ it appears that at the

end of 60 seconds, 5/56, or about 10 percent, of the pressure within the vapor bubble may be secondary gas.

The above analysis suggests that the rate of formation of vapor bubbles and pockets is probably somewhat dependent on the inert gas. The growth rate of intravascular vapor bubbles in the great veins and right side of the heart would probably depend on the permeation coefficient $\alpha_{\text{blood}} D_{\text{blood}}$. The relative bubble factors for the inert gases are seen in phase 1, case 2 of table 9, in which the substitute value $\alpha_{\text{water}} D_{\text{serum}}$ is used. Neon appears to be the safest gas, followed by nitrogen, helium, and argon. The high level of water vapor and possibly carbon dioxide in the intravascular bubbles would reduce the sensitivity of bubble growth to the inert-gas factor. However, it should be remembered that the carbon dioxide concentrations presented by the Soviets for subcutaneous pockets are probably higher than those to be expected in intravascular vapor bubbles. In

TABLE 28.—*Gas Composition at Subcutaneous Rat Pockets After Decompression to 7 to 8 mm Hg*

[AFTER KOVELENKO AND YURKOV ²⁶⁸]

Composition, percent		
CO ₂	O ₂	N ₂
Decompression time = 10 sec		
14.22	17.00	68.78
8.00	18.60	73.40
13.51	17.70	68.79
8.40	17.90	73.70
5.35	18.59	76.06
19.43	3.60	76.97
5.45	18.65	75.90
.....
^a 10.62	^a 16.00	^a 73.37
Decompression time = 20 sec		
31.91	13.13	54.96
38.85	15.80	45.35
38.90	11.04	50.06
28.23	12.00	59.77
39.15	10.75	50.10
32.83	11.33	55.84
39.80	25.05	35.15
23.30	26.26	50.44
^a 34.12	^a 15.67	^a 50.21
Decompression time = 40 to 50 sec		
77.70	5.14	17.16
41.05	23.10	35.85
89.50	3.65	6.95
78.55	1.10	20.35
61.53	17.87	20.60
77.53	10.12	12.35
54.54	10.80	24.66
48.48	18.80	32.72
^a 66.11	^a 11.32	^a 22.57

^a Average.

any case, the relative $\alpha_{\text{blood}} D_{\text{blood}}$ factors represent the maximum inert-gas dependency to be expected.

For subcutaneous emphysematous pockets, the same physical analysis and relative ranking of bubble factors would be expected as discussed in case 4 of table 9 for connective tissue gas

pockets. The high level of water vapor and carbon dioxide, possibly up to 90 percent of the pressure, would no doubt dilute the absolute effect of the inert-gas dependence.

A third gas-dependent site is the interpleural space and lung. The atelectasis seen in animals is probably caused by vapor formation in the pleural space compounded by trauma to the lung surface during an "explosive" decompression to ebullism altitudes.^{236, 396} Another factor is suggested by the findings that only those animals in which respiration had ceased before recompression showed complete atelectasis. It is conceivable that the stream of water vapor entering the alveoli displaces the gas content and then recondenses on recompression to cause severe collapse.²⁹⁰

The same inert-gas factors would be expected to hold here as for the subcutaneous pockets. The fact that the effective "braking action" against atelectatic absorption of gas from a traumatized lung is inversely proportional to the α_{blood} of the inert-gas mixture would be only a side issue in the present discussion.^{128, 369} The braking effect would hold only in the unsteady state where the blood is unequilibrated with respect to alveolar gas pressure.

In the ebullism syndrome, the intravascular bubbles are much more physiologically significant than the subcutaneous or atelectatic aspects; consequently, the $\alpha_{\text{blood}} D_{\text{blood}}$ factor should be weighted more heavily. It can then be concluded that neon would probably be safer than nitrogen, and nitrogen safer than helium, but the overall dependence of lethality on the inert gas would be much less than that seen in decompression sickness at lower, nonebullism altitudes.

Because of the seriousness of the cardiac vapor lock in ebullism, it might be pertinent to suggest that a more detailed understanding of biphasic flow through tubes and vessels of various types is needed. Several theoretical studies of nucleate boiling under unusual acceleration conditions in space vehicles and nuclear power systems seem to offer much along this line.^{97, 197} The physics of biphasic flow and the role of zero gravity on this flow^{47, 192, 402, 429, 437, 414} are also of immediate significance to the biological problem. Discussion of these interesting subjects is, however, beyond the scope of this review.

SUMMARY OF INERT GAS FACTORS IN DECOMPRESSION

In the selection of an optimum inert-gas environment for space vehicles, decompression sickness is a major consideration. An environment of 100 percent oxygen appears to be ideal for subsequent decompression. After equilibration at 100 percent oxygen there is a possibility of mild bends symptoms after severe exercise at space-suit altitudes of about 35 000 feet. They could be caused by carbon dioxide and oxygen bubbles, but there are no adequate data on this point. Prior to equilibration in 100 percent oxygen, tissue nitrogen remains a hazard. Pre-flight denitrogenation rates and predicted bends incidence during the unsteady state of saturation can be selected from figure 18 and tables 17, 18, 19.

Rough extrapolation of World War II data to current problems indicates that equilibration with an atmosphere of 50 percent oxygen and 50 percent nitrogen may be expected to reduce the incidence of bends after exercise at 35 000 feet (3.5 psi) to about 7 to 10 percent in a physically unconditioned population between 20 and 40 years old. At rest or during piloting operations, the incidence of symptoms should fall far below 1 percent. Well conditioned astronauts could probably expect an incidence of less than 7 percent under moderate exercise conditions. The incidence of bends for a similar decompression to a suit altitude of 27 000 feet (5 psi) should be one-third that predicted for a suit at 35 000 feet. Equilibration to an atmosphere of 5-psia 70 percent O₂-30 percent nitrogen should reduce the symptom rate considerably for both suit altitudes. Will other inert gases substituted for nitrogen in this or other mixtures have any advantage over nitrogen in decompression sickness?

It must be concluded that there are inadequate data for predicting in a definitive way the relative decompression hazard of the different inert gases in any mixtures. A first-order approximation of the relative hazard at any one of several body sites can be calculated with the assumption that the local supersaturation ratios for each gas are equal (table 9). A review of data on tissue desaturation times and critical supersaturation ratios for total body systems suggests that the coupling between these factors, tissue/blood

solubility ratios, and permeation coefficient factors are lacking for gases other than nitrogen. Data for other inert gases such as those for nitrogen in table 12 would clarify the tissue desaturation problem, but would not provide a complete answer about hazard index. The critical supersaturation ratios for each tissue would still be required.

Semiempirical approaches similar to that of Bateman would be useful in combining bubble theory and practice. Much more empirical data are needed for modification of the Bateman equation for other gas mixtures. The hydraulic analog approach of Groves and Munk²⁰⁸ or Stubbs,⁴¹⁶ even though it eliminates the local bubble-growth factors, could become a useful tool for predicting the decompression hazard of any inert gas-oxygen combinations used individually or in sequence. Each gas mixture would require a separate multichamber analog. An electrical analog approach such as that used by Bradner and MacKay⁷³ and Stubbs⁴¹⁶ should be able to tie together any sequence of analogs for individual mixtures and present a powerful tool for optimizing decompression schedules in complex profiles of future space missions. Once again, any analog device has to be calibrated against empirical data regarding pertinent critical supersaturation ratios and tissue half times at altitude.

In the absence of such data as these, there are several predictions which can set the pattern for future study:

(1) From the point of view of decompression sickness, helium, neon, and nitrogen are the only inert gases worth considering.

(2) With regard to bends alone, there is no evidence from extrapolation of empirical data³⁰ or from theoretical considerations that helium will be any better than nitrogen in altitude decompressions. Only preliminary data are available on favorable aspects of neon in decompression.^{388, 52} Operationally, neon may prove to have a tissue-blood solubility ratio and desaturation pattern for critical tissue that would synergize with its favorable permeation coefficient to minimize bends in any gas mixture suitable for space cabins.

(3) The very rare though serious neurocirculatory collapse syndrome will be even more

rare after decompression from equilibrium conditions of reduced p_{N_2} at 7-psi pressure. Unfortunately, there is little information on the effect of exercise on this condition. One would expect at least one order of magnitude less collapse symptoms than bends symptoms, or less than a 0.5-percent incidence on decompressing from a 7-psia cabin with a 50-percent oxygen and 50-percent nitrogen mixture even after exercise at 35 000 feet.^{3, 61, 169} How much less cannot be determined because of inadequate data. In an astronaut population which consists of well conditioned individuals, the expected incidence would be reduced even further.

The comparative effects of specific inert gases in this syndrome can be determined only from theoretical considerations. If one considers the basic cause of the syndrome as bubbles forming autochthonously in adipose tissues and if only permeation factors are considered (table 9, cases 1 and 2), neon and helium are of great advantage in reducing the incidence of this syndrome. When one considers bubbles forming intravascularly in nonfatty or in muscular tissue, the theoretical advantage of helium and neon over nitrogen fades. This is seen from consideration of bubble factor in case 3 of table 9 and from the relatively uniform and rapid desaturation rates expected from aqueous tissues. Empirical evidence from diving supports a less-distinct difference between helium and nitrogen in serious neurocirculatory symptoms. The evidence sug-

gests that tissue desaturation factors and critical supersaturation ratios at bubble sites may overwhelm the consideration of permeation coefficients in determining the overall hazard. The chokes syndrome may fall into the same category of low dependence on the specific inert gas.

(4) It is possible that the favorable permeation coefficient of neon may be supported by favorable tissue desaturation rates and critical supersaturation ratios to give an overall advantage to this gas in space cabins. Study of this gas in decompression events is certainly indicated, especially in view of the preliminary success of this gas in diving.^{54, 388}

(5) "Explosive" decompression and ebullism do have gas-dependent factors limiting their physiological expression. In the case of "explosive" decompression, there is a small but definite advantage of helium over nitrogen as an oxygen diluent (table 25). Because this advantage would be exercised only in case of blast overpressure or a massive disruption of the cabin wall when other traumatic factors would come to the fore, the weighting of this advantage in the overall selection process should be very light. Gas factors also play a role in the ebullism syndrome. Because water vapor and carbon dioxide predominate in the vapor pockets or bubbles in the syndrome, the small advantage which neon holds over helium or nitrogen should not weigh heavily in the overall selection criteria.

Metabolic Effects of Inert Gases

THE METAZOAN has evolved on this Earth in the presence of a relatively high partial pressure of nitrogen and only trace amounts of the other inert gases. Table 29 gives the concentration of inert gases in the atmosphere. One might expect that the physical presence of these gases at specific

TABLE 29.—*Composition of Dry Air*
[AFTER COOK ¹⁰⁹]

Gas	Mole, percent	Weight, ^a percent
N ₂	78.084	75.521
O ₂	20.946	23.139
A.....	.934	1.288
CO ₂033	.050
Rare gases.....	.003	.002
Total.....	100.000	100.000

Gas	Ppm by volume	Ppm by weight ^a
Ne.....	18.18 ± 0.04	12.67
He.....	5.239 ± 0.004	.724
Kr.....	1.139 ± 0.01	3.295
H ₂	0.5	.035
Xe.....	0.086 ± 0.001	.390
Rn.....	6 × 10 ⁻¹⁴	46 × 10 ⁻¹⁴

^a The weight values have been calculated from the values given for "Mole, percent" and "Ppm by volume."

intracellular concentrations may have directed biochemical evolution to account for this composition in optimization of cellular mechanisms. Alteration of this balance can, therefore, be expected to induce an adaptive biochemical response which may or may not be detectable. This chapter covers the adaptive response of the organism to changes in the inert-gas environment. It is hoped that this review will provide a framework for analyzing physiological changes which may become manifest if long-term exposure to these altered atmospheres becomes an operational necessity in space vehicles.

Chapter 1 presented a review of the physico-chemical properties of the different inert gases and general implications of these properties to biochemical reactions within an organism. This chapter covers the physiological manifestations that these biochemical properties determine. Much of this material has been reviewed by Rinfret and Doebbler³⁶⁴ and Cook and Leon.¹¹³ These studies form the background for the present discussion. No attempt has been made to be exhaustive in this review. Emphasis is placed on those aspects of the metabolic response to inert gases which may be of consequence to long-range space missions.

Of historical interest is the early study of Schloesing and Richard,³⁸¹ who reported in 1896 that the partial pressure of argon in swim bladders of fish is 20 times that in sea water and raised the question of a concentration mechanism. Haldane²¹¹ favored a purely physical mechanism by which inert gases entered the swim bladder. Recent studies by Wittenberg⁴⁵⁷ suggest that oxygen is actually secreted in the bladder in the form of tiny bubbles into which the inert gases diffuse during the formation of the bubbles.

In the late 1920's Hershey^{228, 229} published the results of studies on mice breathing mixtures of oxygen with nitrogen, argon, or helium. He described oxygen toxicity in the absence of these gases and pointed out that while 80 percent helium and 20 percent oxygen had no effect on mice, 80 percent argon and 20 percent oxygen "permitted life for only 92 hours." Fidar's comments on this work are most interesting, for they presented a review of the experimental difficulties and biases of the day. He looked on these gases as "acting like vitamins." During the 1920's, the ideas of Thompson, Cooke, Hildebrand, Sayers and Yant, and others brought the use of helium gas in diving to reality. These

studies and their consequences were reviewed in detail in chapter 2. In the 1930's, therapeutic studies of Barach^{18, 19, 20} and his coworkers and the ideas of Orcutt and Waters³³³ on the mechanism of action of the inert gases in physiological systems were of great value in stimulating interest of the medical community on the therapeutic uses of helium and other gases.

Most recently, the use of xenon as an anesthetic agent has rekindled an interest in the chemical properties of inert gases. The pioneering studies of Lazarev et al.,²⁸⁰ Lawrence et al.,²⁷⁶ and Cullen and Gross¹²⁶ are outstanding in this area. Since chronic exposure to relatively low pressures of the several inert gases in space cabins may have long-range metabolic effects, it would be well to review the general problem of inert-gas narcosis and its metabolic ramifications.

INERT GAS NARCOSIS

As was indicated in chapter 2, the early use of helium as an inert diluent in diving was prompted by the narcotic effects of nitrogen at depths greater than 150 feet. The "rapture of the deep" syndrome was first attributed to high pressures of nitrogen or oxygen by Damant.¹²⁹ These first reports were followed by the studies of Behnke and his coworkers^{38, 40, 41, 42} who thought that nitrogen was the most probable agent involved, but suggested that carbon dioxide retention and other factors may be involved. The studies of Bean^{28, 29} indicated that carbon dioxide does indeed build up in the lungs at great depths and that at a depth of 7 to 10 atmospheres, the carbon dioxide content of the alveolar air is as high as 10 percent in sea-level equivalents. The increased gas density and defective mixing of alveolar gas at depth was hypothesized to be the major physical factor involved. The possibility of the carbon dioxide buildup being secondary to hypoventilation from the increased respiratory resistance factor has been reviewed in great detail by Lanphier,²⁷⁴ Bühlmann,^{82, 83} and Wood et al.⁴⁶⁰

Current evidence suggests that while carbon dioxide narcosis does contribute to the syndrome at great depth, it is not the prime factor. The findings of Rashbass³⁶⁰ that forced hyperventilation at 250 feet will produce a marked decrease in alveolar carbon dioxide, but will not affect the narcosis is a strong point in favor of true nitrogen

narcosis. The neurophysiological and pharmacological studies of Carpenter,^{90, 91, 92, 93} Bennett and his coworkers,^{48, 49, 50, 51, 52, 53, 55, 56, 57} Taylor⁴²⁰ and of Barnard²¹ also point to nitrogen narcosis as being a definite entity with early depression of nervous activity at the level of the cortex and reticular formation and subsequent effect on the lower centers and peripheral nervous system. That a narcotic synergism exists between carbon dioxide retention, oxygen pressure, and elevated p_{N_2} has been confirmed by Frankenhaeuser et al.¹⁸³ It would seem that all three entities are responsible for the clinical syndrome at depth and that such secondary factors as the degree of exercise and adequacy of respiratory equipment may well determine the extent of contribution by each of these entities. In space cabins where failure of carbon dioxide absorption systems is always a potential hazard, this synergism between carbon dioxide narcosis and inert-gas "intoxication" must be kept in mind. But first, the possibility of inert-gas intoxication in space cabins must be examined with specific focus on critical partial pressures and physiological mechanisms.

The symptoms of nitrogen narcosis on air become first perceptible at pressures as low as 2½ atmospheres,³⁵⁵ though the usual threshold is considered at 4 atmospheres absolute pressure (100 feet of sea water), and quite serious conditions occur at 7 to 8 atmospheres (200 to 300 feet). Behnke and Yarbrough⁴¹ showed that for a mixture of 80 percent argon and 20 percent oxygen, this serious narcosis is seen at only 4 atmospheres. Argon, therefore, has twice the narcotic potency of nitrogen. Helium and hydrogen, on the other hand, are much less potent than nitrogen^{65, 276} and require much greater pressures (> 600 ft) for narcosis.^{51, 212, 253, 275} At the Linde Corp., no narcotic manifestations were noted in men at partial pressures of helium up to 20 atmospheres, and in neon, up to 16 atmospheres.^{212, 386} Mice can in fact tolerate 122 atmospheres of a 99.6-percent helium and 0.4-percent oxygen mixture and remain conscious.³¹¹ At these higher pressures, carbon dioxide retention again confuses the issue. Some adaptation to nitrogen narcosis is possible.³²⁷

Behnke and coworkers³⁸ first suggested that the narcotic effect of nitrogen was greater than

that of helium because its solubility in lipid was greater (table 2). An analogy was drawn comparing nitrogen to the aliphatic anesthetic agents, the activity of which, according to the old Meyer-Overton law, appeared to be related to the ratio of solubility in fat to solubility in water (table 2). Since argon has the same lipid-water solubility ratio as nitrogen, but twice the fat solubility and twice the narcotic potency, it was argued that lipid solubility itself may be the key factor.⁴² The lipid solubilities of krypton and argon (table 2) suggest that 80 percent krypton at sea level would be equal in narcotic effect to 6 atmospheres of air, and that 80 percent xenon at sea level would be equivalent to 25 atmospheres of air. This hypothesis was tested by Lawrence et al.²⁷⁶ A human breathing 50 percent krypton gas in oxygen at sea level reported only dizziness. Mice exposed to 58 to 60 percent xenon for 30 minutes to 1 hour developed convulsive head movements, paralysis of the limbs, and ataxia with complete recovery upon return to air. Similar studies on lower animal forms are claimed to have been carried out by Lazarev before 1941.^{278, 280} It, therefore, appears that in the absence of carbon dioxide narcosis and oxygen toxicity, a true narcosis is possible with an inert gas.

Cullen and Gross¹²⁶ then studied the anesthetic qualities of xenon and krypton in animals and man. Rats, mice, and rabbits were tested in a mixture of 80 percent inert gas (composed of 95 percent krypton and 5 percent xenon) and 20 percent oxygen, and in a mixture of 80 percent nitrous oxide and 20 percent oxygen. No unequivocal evidence of narcosis was found. Three humans inhaling mixtures of 80 percent krypton and 20 percent oxygen reported changes in voice quality, desire to breathe more deeply, and ill-defined dizziness or discomfort, but no significant narcosis. Mixtures of 80 percent xenon and 20 percent oxygen, on the other hand, produced minimal narcotic effects in rabbits with some loss of lid reflex, apparent diminution in response to painful stimuli, and tendency to remain in induced unnatural positions. Recovery was complete.

The narcotic effects of xenon on humans were studied in great detail. Six humans inhaling mixtures of 50 percent xenon and 50 percent oxygen were shown to have a 15-percent increase

in pain threshold. Each subject reported subjective sensations of dizziness and incipient loss of consciousness. A mixture of 70 percent xenon and 30 percent oxygen produced narcotic effects and incipient loss of consciousness in two other men. Orchidectomy was performed on one of the two men, an 81-year-old patient. There was no evidence of pain, and first-plane, third-stage anesthesia was reported. Vital signs were normal, and both jaw and pharyngeal muscles were relaxed. Recovery was normal. The patient began to recover 2 minutes after xenon gas was stopped and was oriented after 5 minutes. The other patient underwent a Fallopiian tube ligation with similar good results. Cullen and Gross¹²⁶ compared xenon to ethylene in anesthetic capacity and noted their similar solubility coefficient in oil of about 1.5. Nitrous oxide also has similar anesthetic properties and has a solubility coefficient of 1.46.

The Soviets have also used xenon anesthesia clinically.^{80, 279} They demonstrated that 60 percent xenon shows the "Shane effect," a prolongation of thiopental anesthesia. Abdominal laparotomy at this pressure of xenon was impossible because of residual muscle tension.

These early studies have been followed up by many others describing electroencephalographic changes^{140, 320, 346} in xenon anesthesia. Increasing partial pressures of xenon in monkeys and dogs lead to deeper anesthesia with the same electroencephalographic changes noted with other general gaseous anesthetics. Pittinger and coworkers^{347, 348} studied the partition of this agent in the body organs and found the brain is practically saturated with the agent within 6 minutes. In general, the kinetic properties of this gas are not unlike those of nitrous oxide, ethylene, cyclopropane, and other gaseous agents which move most rapidly to lipid structures.

Studies have recently been completed by Gottlieb and Weatherly¹⁹⁵ and Schreiner³⁸⁸ on the responses of the frog sciatic nerve-gastrocnemius muscle complex to compressed inert gases. At 200 psig, neither helium, neon, nitrogen, nor argon reduced the ability of the muscle to produce tension, or of the nerve to provide stimulation. In these compressed gaseous environments, the muscle did not fatigue

faster than in air at ambient pressure. While krypton at 200 psig has no effect on the isolated frog sciatic nerve, it may have a slight inhibitory effect on the ability of the muscle to produce tension. Xenon, on the other hand, exerts at 100 psig a readily reversible, mild depression of nerve excitability. This depression increases rapidly with increasing pressure of xenon. At 100 psig, xenon exhibits a rapid and apparently irreversible direct effect on the frog muscle, inhibiting its ability to contract. The critical p_{Xe} required to interfere with normal muscle function appears to lie between 68 and 100 psig. Nitrous oxide, in comparison, has an effect similar to that of xenon. It can be expected that under pressures in excess of those used in these studies, the other gases of the helium group may also exert effects similar to those demonstrated for xenon. These studies indicate that the frog gastrocnemius muscle is more readily subject to inert-gas inhibition than either the myoneural junction or the conducting systems. In man, nitrous oxide and xenon will produce narcosis below pressures that are shown to damage the frog sciatic gastrocnemius muscle. Present knowledge indicates this to be also true for nitrogen and argon. Whether this pattern holds true for neon and helium remains to be explored.

Further studies by this group on instrumented unanesthetized rats did not reveal electroencephalographic evidence of inert-gas anesthesia when the animals were exposed to 206- to 220-psig neon, argon, or nitrogen in the presence of 14.7-psia oxygen. Under the experimental conditions employed, behavioral responses to nitrogen and argon under pressure could be clearly discerned. However, no corresponding electroencephalographic changes such as those observed in xenon anesthesia were noted. It is not possible without further experimentation to attribute the behavioral changes to centrally mediated direct effects of the compressed gases since, at the pressures employed, the density of the respired media was sufficiently high to have possibly caused physiological changes from hypercarbia not readily reflected in the electroencephalogram.

The molecular mechanism of inert-gas narcosis or anesthesia is still an open question.¹⁶⁶ Correlation of narcotic potency and lipid solubility

suggests, but does not prove, that lipids are specifically involved in the process.³²³ In studies of xenon *in vitro*, Pittinger et al.^{345, 348} showed no difference in the respiration or oxidative phosphorylation of guinea-pig brain tissue with glucose or pyruvate as substrates. Unlike the case of barbiturates, inhibition of oxidation or uncoupling of phosphorylation do not appear to be involved. If the proteolipid mitochondrion is the site of activity, its basic function is not affected in these *in vitro* conditions.

Carpenter^{90, 91, 92, 93} demonstrated that the inert gases do inhibit firing of nerves *in vitro* and suggested that correlation between this activity and lipid solubility of many "inert" gases could be linked through the reciprocal of the fugacity of the gas. Wulf and Featherstone⁴⁶⁸ suggested that there was a correlation between lipid solubility and the molecular volume of a gas. The magnitude of the van der Waals forces, which are indices of the volume occupied by the atoms and the attractive forces between them, appeared to also correlate well with anesthetic potency. An additional correlation was found between anesthetic potency and the molar refraction or polarizability of the molecules. Therefore, it appears that anesthetic potency correlates well with several interdependent physicochemical properties: reciprocal of fugacity, molecular volume, molar refraction, and van der Waals constant. Since lipid solubility is directly related to these properties, it is not surprising that it has long been regarded as the key factor. It would appear, however, that these physical properties may be involved in a mechanism quite unrelated to lipid solubility *per se*.

A recent approach to a mechanism of anesthesia has been the clathrate hypothesis of Pauling³³⁷ and Miller.³¹⁴ The nature of inert-gas clathrates is discussed in chapter 1. Correlation between polarizability or van der Waals forces and the potential for clathrate formation is well known.⁴⁴¹ Pauling hypothesized that inert-gas hydrates forming in the aqueous phase or aqueous interfaces in the nervous system interfere with electrical conduction of the structures and prevent normal nervous activity. The problem of instability of the hydrates in pure water may be overcome by including the clathrate potential of protein side chains and the para-

crystalline water around proteins as part of a mixed hydrate complex. The inert gas within such a complex could change the impedance of the system and alter its function. Miller³¹⁴ feels that the paracrystalline "ice cover" may be a key factor in the process and that a change in water structure may in itself alter the function of nervous tissue by changing conductive impedance or "plugging pores" in membranes in the manner suggested by Mullins.³²³ Both theories suffer from the instability of hydrates at 37° C; from the fact that many anesthetic gases do not form hydrates (i.e., diethyl ether, propane, and others); and from the fact that a number of gases that do form hydrates do not have anesthetic properties.⁵⁸

A recent combination of the lipid and the clathrate theories comes from the study of Clements and Wilson.¹⁰² By following changes in surface tension, these investigators studied the affinity of narcotic agents for artificial interfacial lipid and protein films. Inert gases at partial pressures in the anesthetic range cause a 0.39-dyne/cm change in the interfacial tension. This is visualized as a tendency to expand the film and to replace water at the interface. The fact that the protein films are affected in the same way suggests that alteration of the water interface of the film may be the key factor. Such a mechanism thereby relates the hypotheses of Sears and Fenn,³⁹⁸ Mullins,³²³ Pauling,³³⁷ and Miller³¹⁴ with the supporters of the older Meyer-Overton lipid solubility theory. The paper of Agin et al.⁴ also adds to the physical complexity of the problem.

The recent studies of Schoenborn and his co-workers^{382, 383} suggesting that xenon combines selectively and reversibly with specific sites on hemoglobin must also be considered in discussion of proteolipid membrane effects. The combination of 1 atom of xenon with 1 molecule of hemoglobin can cause the aggregation of about 30 molecules of water and thereby alter the function of the membrane complex.^{384, 167, 168} Studies of the polarizability and adsorption of inert gases on molecular sieves have also been presented as a possible model for the physiological effects of these gases.⁵⁸ Further studies of this phenomenon are needed to define the specific interactions involved.

From the discussion in chapter 1, it would ap-

pear that covalent bonding of the type seen in the xenon halides would not have a role in anesthesia. The xenon halides are far too unstable in aqueous systems to play an obvious role in the narcotic mechanism. Since dogma regarding the chemical inertness of these gases has failed to meet the challenge of time, predictions about chemical impossibilities with this group of agents must be made with caution.

There is only one experiment that suggests a narcotic effect in humans of helium in an 80-percent mixture with 20 percent oxygen at sea level.¹⁰⁶ Subjects breathing this mixture for 30-minute periods were reported to have shown a larger percent alpha rhythm than those breathing air. The significance of this older study is not clear and the findings have never again been repeated.

Since the discussion of chapter 2 suggests that xenon and krypton are the worst gases for decompression and since helium and neon, the best candidates, are not expected to be anesthetic agents under pressures indicated for space cabins, why dwell on the mechanism of narcosis? The reason will become obvious when some of the nonnarcotic, metabolic effects of helium are discussed. These effects have often been mentioned as possible deterrents to the use of this gas in long-duration space missions. This discussion of narcosis puts them in the proper context.

INERT GASES IN CELLULAR METABOLISM

Helium.—Of the inert gases other than nitrogen, helium has been the most adequately studied. Table 30 summarizes most of the work published prior to 1961. A discussion of the most pertinent of these studies follows. The review of Cook and Leon¹¹³ is used as a basis for this discussion.

In 1950 Cook¹¹¹ reported that helium, when substituted for nitrogen in air, had no effect on yeast, wood termites, or *Drosophila* tested in a Warburg apparatus. It did stimulate greater oxygen consumption and carbon dioxide production in larvae of meal worms and mice when tested in more open systems. Of interest was the fact that in adult meal worms or in their starved larvae, no increase in oxidative metabolism was noted. In the poikilothermic lizard, no

TABLE 30.—*Effects of Helium on Intact Organisms and Isolated Systems*
 [AFTER RINFRET AND DOEBBLER³⁶⁴]

Test system	Partial pressure, atm	Effect
Man.....	0.8	No effect
Mouse.....	.8	Increased CO ₂ production, increased O ₂ use
Mouse.....	> 54.0	Narcotic effect
<i>Drosophila melanogaster</i> (fruit fly).....	.8	No effect on O ₂ use; development accelerated
<i>Zoötermopsis nevadensis</i> (wood termite).....	.8	No effect on O ₂ use
<i>Tenebrio molitor</i> (meal worm).....	.8	Increased O ₂ use, increased CO ₂ production (larvae), decreased CO ₂ production (adults and starved larvae)
<i>Tenebrio molitor</i> (meal worm).....	.8	Accelerated development; ⁴⁷ no effect on development ⁷³
<i>Mormoniella vitripennis</i> (chalcid wasp).....	.8	No effect on development
<i>Cnemidophorus tessellatus</i> (lizard).....	5.0, 10.0	.8 Decreased CO ₂ production
<i>Coleonyx variegatus</i> (gekko lizard).....	.8	Decreased CO ₂ production; no effect, O ₂ use
Yeast.....	.8	No effect on O ₂ use
Frog.....	> 82.0	No effect
Frog spinal cord preparation.....	> 82.0	No effect
Frog peripheral nerve.....	> 82.0	No effect
Turtle atria.....	> 82.0	No effect
Sea urchin egg.....	> 61.0	No effect
Mouse brain slice.....	.8	Increased O ₂ use; decreased anaerobic glycolysis
Mouse muscle slice.....	.8	Increased O ₂ use; decreased anaerobic glycolysis
Mouse liver slice.....	.8	Increased O ₂ use; decreased anaerobic glycolysis
Mouse diaphragm.....	.8	Increased O ₂ use; decreased anaerobic glycolysis
Mouse ventricle slice.....	.8	Increased O ₂ use; decreased anaerobic glycolysis
Mouse sarcoma slice.....	.8	Increased O ₂ use; no effect on glycolysis
Mouse liver homogenate (hexose diphosphate substrate)	.8	Increased O ₂ use; increased anaerobic glycolysis

increase in oxidative metabolism was produced. With argon-oxygen mixtures, the same pattern of results was found in all of these experiments but changes were less pronounced. These results were not all confirmed in other laboratories.¹⁸² A more recent evaluation of these results was presented by Cook and Leon.¹¹³ Most of these differences could be accounted for by the far greater thermal conductivity of helium. Table 1 indicates that helium conducts heat about six times faster than does an equal molecular concentration of nitrogen. The acceleration of metabolism by argon cannot be explained on this basis.

Increased heat loss in homoiotherms would be expected to cause an increase in metabolic rate to maintain the body temperature constant. The experimental design of the studies of Cook et al.¹¹⁵ and Young and Cook⁴⁷⁴ was involved with this problem. Oxygen consumption of mice

was measured in vessels equipped with manometers in a room where temperature was controlled at 22° C. In comparing young mice, adult thyroidectomized mice, and hyperthyroid mice, it was noted that the ability of helium to accelerate the metabolic rate was inversely proportional to the level of the initial metabolic rate regardless of the nature of the factor determining this initial level. Therefore, in young and hyperthyroid mice where the upper limit of metabolism is approached, helium is relatively ineffective. Thyroidectomized mice, because of their low initial metabolism, can respond to the thermal stimulus.

The atmospheric factor in this thermally conditioned increase in metabolic rate has been studied by Cook and Leon.¹¹³ The temperature drop in carcasses of rats of two different body weights, 250 grams and 188 grams, is seen in figure 30. The slightly different ambient tem-

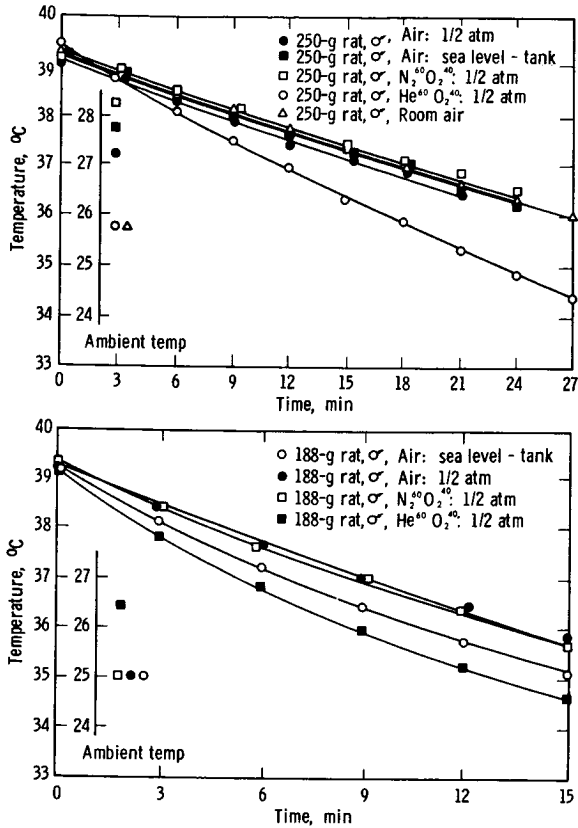


FIGURE 30.—The rate of heat loss by rat carcasses in various gas mixtures and at various pressures. One chamber was used in all cases. The ambient temperature scale on the left represents the chamber temperature 6 inches from the animal. (AFTER COOK AND LEON.¹¹³)

peratures of each study are also noted. As would be expected from ratios of body surface area to volume, there is a greater tendency for the smaller animal to lose heat. Total pressure changes in the chamber have a smaller effect than does the thermal conductivity factor of helium. Smaller animals are relatively less affected by the molecular factor than are larger animals. This heat-loss factor appears to explain the metabolic changes found in the homoiotherms, but does not explain the findings in the more primitive creatures. The effects of inert gas on the air-conditioning requirements are discussed in chapter 4.

What other biochemical effects would explain the metabolic differences in tissues and insects? Cook and his coworkers¹¹⁵ found that, in Warburg flasks, tissues of the mouse such as sar-

coma, diaphragm, liver, and ventricle showed increases in oxygen uptake and carbon dioxide production of about 30 percent. In an attempt to determine the site of action, South and Cook,⁴⁰⁷ using mouse liver slices and homogenates, found that cyanide inhibition of the cytochrome system was somewhat alleviated by helium-oxygen mixtures. There was no change in RQ. Since fluoride inhibition of the glycolytic cycle at enolase prevented an increase in oxygen consumption when either pyruvate or lactate was added, it was concluded that helium had its action above enolase in the glycolytic cycle and that relief of cyanide inhibition by helium was not related to normal respiration. Further studies of the helium effect were performed under anaerobic conditions. Helium paradoxically inhibited carbon dioxide production by both liver slices and diaphragm. In liver slices incubated with fluoride, a greater depression of carbon dioxide production than could be attributed to the fluoride effect was noted. In the presence of fluoride, hexose diphosphate was able to reverse the helium depression. On the basis of these anaerobic studies, the site of helium activity was noted to be above the aldolase reaction. However, no evidence was presented on the specific site of oxidative acceleration by helium in aerobic or anaerobic conditions.

Further extension of this work has only confused the issue. Cook and South,¹¹⁴ in a comparison of various mouse tissues, found an inverse relationship between oxygen consumption and the ability of helium to accelerate metabolism. Also under anaerobic conditions, the degree of depression of carbon dioxide production by helium was inversely related to the rate of carbon dioxide production in nitrogen. Comparative effects of other gases shed little light on the problem.⁴⁰⁶ The order of increasing ability of gases to increase oxygen consumption by the liver is helium, xenon, argon, nitrogen, and hydrogen. The order of increasing effectiveness in anaerobic depression of carbon dioxide production is helium, xenon, hydrogen, and argon. There appears to be no correlation with narcotic potency in either the intact animal or in isolated nerves (see above). The findings of Levy and Featherstone²⁸³ that xenon had no effect on oxidative phosphorylation of brain mitochondria may possibly fit the

hypothesis that the gas acts primarily in the early glycolytic cycle.

The following general conclusions were drawn by Cook and his coworkers:

(1) Helium does not alter the specific substrate utilized by the tissue.

(2) The gas interferes in some way with the cyanide-cytochrome bond but may not affect cytochrome oxidase in the absence of cyanide.

(3) The citric acid cycle is not subject to the influence of helium in 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 an acceleratory effect of helium. The location of the anaerobic inhibition lies above aldolase reaction, and that of the oxidative acceleration between the aldolase and enolase reactions.

Further work on subcellular fractions may well indicate more definitely the site of helium action and reconcile the equivocal findings of different laboratories.

Several years ago, an attempt was made by Allen to determine if nitrogen gas was required for the development of mammalian organisms.⁸ Fertile hen eggs incubated at 1 atmosphere pressure in a mixture of 20 percent oxygen and 80 percent helium showed the same retardation of growth as seen in 100 percent oxygen. The addition of nitrogen to the extent of 10 percent of partial pressure did not relieve the inhibitory effect. Fertile eggs incubated in 100 percent oxygen at p_{O_2} of 150 mm Hg showed the same lack of development of the cardiovascular system as seen in 100 percent oxygen at 1 atmosphere. A Soviet report at the same period suggested that replacement of nitrogen by helium affects the development of chick embryos only when the temperature control of the incubator is inadequate to overcome the thermal conductivity factor.⁷⁰

Hiatt has continued these studies with support from NASA.^{231, 232} Using standard room temperatures and humidities, he finds that he can hatch only one-half as many chicks in a mixture of 79 percent helium and 21 percent oxygen as in air. The chicks in helium atmospheres under these conditions are 5 to 10 percent

smaller in size. When raised in helium atmospheres, these chicks grow at the same rate, but require 15 percent more food. Hiatt feels that the thermal conductivity and excessive heat loss could explain these findings in the intact embryo.

Hiatt and Weiss also made preliminary studies on the oxygen consumption of tissue homogenates of 8-day chick embryos by the Warburg technique.²³² Homogenates from eggs which have been incubated in helium and oxygen and protected from nitrogen even during the preparation for the Warburg flasks show an increase in metabolism over the controls incubated in air. However, if they are exposed to air for just 1 hour during preparation, their metabolic rate drops below that of the controls. It appears that these tissues incubated in helium are particularly vulnerable to nitrogen on first exposure. Similar effects have been observed on whole animals (rats and chicks). It has also been found that such embryos have a depression of their oxygen consumption after exposure to 2000 R X-ray irradiation which is similar to the effect on the air incubated embryos.⁴⁶⁷ The findings of Cook and his coworkers described above have, therefore, been generally corroborated in embryonic tissue.

A recent study by Schreiner and Doebbler³⁹⁰ suggests that the helium group gases under pressure inhibit the reaction rate of tyrosinase, and the extent of reaction parallels the narcotic potency in intact animals. This and other oxygenases require further study.

One must conclude from these studies that in isolated mammalian tissue, helium shows distinct metabolic effect which may or may not operate through the same molecular mechanism as does the narcotic effect in isolated nerves or in intact animals. A combination of the clathrate mechanism with the proteolipid film mechanism (see above) may be involved. Modification of the hydration shell about enzymes or about the proteolipid membranes of the various intracellular organelles associated with enzymatic activity could explain some of the metabolic changes. It is obvious that further work needs to be done in this area.

Neon.—The biochemical effects of neon have received little study. From the data of tables 1 and 2, it would appear that the physical prop-

erties of neon-oxygen mixtures would be more similar to nitrogen-oxygen and argon-oxygen than to helium-oxygen. Wittenberg⁴⁵⁷ has studied neon while investigating the mechanism of gas concentration in swim bladders of fish. Molnar et al.³¹⁵ have also used neon in their attempt to relate the inhibition of nitrogen fixation by gaseous agents to the physical properties of the gas. The only published study of gross mammalian response to neon-oxygen mixtures was presented by Young et al.⁴⁷⁵ These investigators anesthetized dogs lightly with Pentothal and after appropriate control periods, presented varying mixtures of neon, nitrogen, and oxygen through a tracheal tube from an anesthesia machine. Gas mixtures were 1 percent neon, 20 percent oxygen, and 79 percent nitrogen; 5 percent neon, 20 percent oxygen, and 75 percent nitrogen; 10 percent neon, 20 percent oxygen, and 70 percent nitrogen; and 80 percent neon and 20 percent oxygen. No mention is made of the source or purity of the gas. Six dogs were used in 11 runs. Definite increases in tidal volume and minute volume were seen in animals breathing 5 to 10 percent neon. Five percent neon gave increases in tidal volume from 13 to 62 percent; 10 percent neon gave almost 50 percent increases. Simultaneous decreases in respiratory rate were noted in these animals. Eighty percent neon gave inconsistent changes in respiratory rate while producing a 17-percent increase in tidal volume in one animal and a 5-percent decrease in another.

Guinea pigs exposed to an atmosphere of 80 percent neon and 20 percent oxygen were reported to be "quite inactive" and appeared to have slightly lower respiration rates compared to the animals breathing air. Animals breathing the 5-percent neon mixture showed normal activity, but they had respiration rates 5 percent greater than air breathers, though the values were erratic from animal to animal.

Hemograms of the guinea pigs appeared normal. Postmortem examination after 47.5 hours of exposure showed foci of bronchopneumonia, bronchitis, and nephritis in several of the animals of each experimental group. There were no pathological findings in the controls on air.

These results are puzzling. It is hard to imagine that 5 percent or 10 percent helium in

a nitrogen-oxygen mixture would affect respiratory dynamics enough to give the above results. The even milder response to the 80-percent neon mixture is also puzzling. Contamination of the neon gas mixtures by toxic materials may be the answer. The lesions seen on postmortem examination of the guinea pigs need explanation. These equivocal findings require confirmation before acceptance of the conclusion that neon may be a good agent for stimulating respiration.

Argon.—Studies of the metabolic effects of argon are summarized in table 31. As discussed above, the findings of Cook¹¹¹ indicated that argon behaved like helium, although with less intensity, in modifying the growth and respiration of several insects, reptiles, and mice. The many interesting changes in insects seen in table 31 appear to be dependent on the stage of the life cycle of the experimental animal. Since there is little to be gained regarding the mechanism of action, details of these studies will not be covered. The review of Rinfret and Doebbler should be consulted for specific data.³⁶⁴

Metabolic changes indicating increased oxygen consumption and decreased carbon dioxide production in the several *in vitro* preparations were in the same direction but far less marked than those noted with helium or xenon. Details of these studies were covered in the discussion of helium.⁴⁰⁷ Argon was also inactive in the inhibition of nitrogen fixation.³¹⁵

Krypton.—Metabolic effects of krypton have received little attention. Comparative narcotic effects *in vivo* and *in vitro* fall in line with prediction from lipid solubility and its determinants. The metabolic manifestations of these phenomena have not been studied.

Xenon.—The metabolic effects of xenon have been compared with those of helium, nitrogen, and argon by Cook and his coworkers.¹¹³ The more pertinent findings are recorded in table 32. The augmentation of oxidation and suppression of anaerobic glycolysis were in the same direction as noted with helium and had an intensity between that of helium and argon. For example, in 95-percent xenon and 5-percent carbon dioxide atmospheres, anaerobic glycolysis was reduced 79 to 92 percent below the 95-percent nitrogen and 5-percent carbon dioxide values in

TABLE 31.—*Physiological Effects of Argon*[AFTER RINFRET AND DOEBBLER³⁶⁴]

Biological system	Partial pressure, atm	Effect
Man.....	10.0	Slight narcosis
Man.....	.8	None
Mouse.....	.8	None
Frog.....	41.0	Inhibition of encephalographic pattern
<i>Drosophila</i> (fruit fly).....	.8	No effect on O ₂ consumption, slight acceleration of development
<i>Tenebrio</i> (meal worm).....	.8	Slightly increased O ₂ consumption; decreased or increased CO ₂ production depending on stage of life cycle and nutritional state; accelerated development or no effect on development
<i>Tenebrio</i>	5.0	Delayed development
<i>Tenebrio</i>	10.0	Delayed development
<i>Mormoniella</i> (wasp).....	.8	None
<i>Mormoniella</i>	5.0	Delayed development
<i>Mormoniella</i>	10.0	Delayed development
<i>Cnemidophorus</i> (lizard).....	.8	Decreased CO ₂ production
<i>Coleonyx</i> (lizard).....	.8	Decreased CO ₂ production
<i>Sitophilus</i> (granary weevil).....	< 92.0	Narcosis; death at 92 atm
Yeast.....	.8	None
Frog spinal cord preparation.....	10.0	Reversible block of reflex action
Frog peripheral nerve.....	> 96.0	None
Mouse brain, liver, and sarcoma slices.....	.8	Slightly increased O ₂ consumption; slightly decreased anaerobic glycolysis
<i>Allium cepa</i> (onion) root.....	.95	
Rat nerve.....	75.0	Prod. c-pairs; inhibition mitosis
Rat nerve.....	12.6	Response to electric shock blocked
Rat nerve.....	310 to 340	Fiber conduction blocked

the different tissues studied. Yet, in spite of the severe narcotic effect of xenon, there was no change in oxidation or uncoupling of phosphorylation in brain tissue studied *in vitro*.²⁸³

Recent studies on unicellular and microbial organisms have added a new facet to the inert-gas effects on metabolism. Sears and Gittleson³⁹⁹ found that 1000 psi of argon, nitrogen, or helium have little effect on the movement of paramecia. However, less than 250 psi of xenon produces a decrease in movement leading to "narcosis" of the creatures. Apparent expansion of the cell borders of these organisms lends some credence to the hypothesis that decrease in surface tensions of films and membranes with subsequent expansion is a key factor in the action of these gases.

Schreiner and his associates^{385, 387, 388, 391} studied the longitudinal growth of *Neurospora crassa* hyphae as a model system for quantitative inert gas effects. The findings, summarized in figure 31, indicate that a linear relationship

exists between growth rate and the square root of the molecular weight of the inert component of the gaseous environment. It was speculated that the square root of the molecular weight represents a diffusion characteristic of the gas as controlling the growth rate. That other than diffusion properties were involved is indicated by the fact that sulfur hexafluoride, a metabolically inert gas of molecular weight 146.1 (Xe = 131.3), had no more effect on the growth rate than nitrogen.

Schreiner³⁸⁶ has reported that in preliminary studies with HeLa cells the growth is altered under 70 atmospheres of inert gases. The results are quantitatively similar to those given by *Neurospora crassa* where growth inhibition increased in the order: He < Ne < A < Kr < Xe.

Schreiner is inclined to feel that interference with oxygenation may be one of the key factors. He cites the work of Ebert and Howard,¹⁵⁴ indicating that in the p_{O_2} range from 0 to 100 mm Hg, cellular radiosensitivity increases nearly three-

TABLE 32. — *Biological Effects of Xenon*
[AFTER RINFRET AND DOEBBLER ³⁶⁴]

Biological system	Partial pressure, atm	Effect
Man.....	0.8	Anesthesia
Mouse.....	0.6-0.8	Partial narcosis
Dog.....	0.8	Partial narcosis
Cockroach.....	3.1	Partial narcosis
<i>Drosophila</i> (fruit fly)....	0.8	Decreased O ₂ consumption
Mouse liver, brain slices.	^a 0.8-0.95	Increased O ₂ consumption; decreased anaerobic glycolysis
Mouse — sarcoma slices.	^a 0.8-0.95	Increased O ₂ consumption; slightly decreased anaerobic glycolysis
Guinea-pig brain homogenate and mitochondria.	0.8-0.95	No effect on O ₂ uptake or on oxidative phosphorylation
Rat nerve.....	12.0	Decreased respiration; blockage of impulse transmission

^a Glycolysis measured anaerobically in 95 percent xenon and 5 percent carbon dioxide.

fold with most of the increase occurring between 0 and 20 mm Hg. This investigator showed that the radiosensitivity of several types of living cells, including plant tissue, ascites cells, and bacteria, exposed to an environmental p_{O_2} of

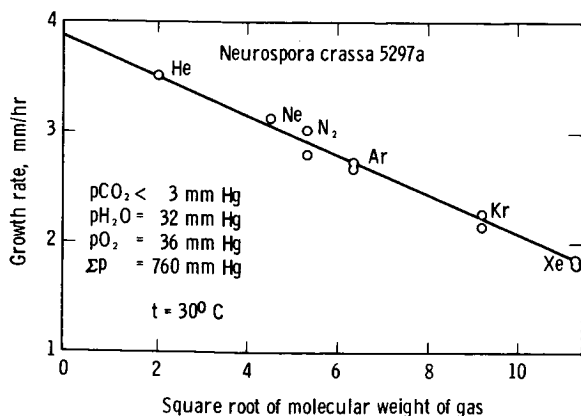


FIGURE 31.—*Growth response of Neurospora crassa 5297a in the presence of gases of the helium group. The computed standard deviation of regression is ±0.0651 mm/hr. Differences in growth rates due to the nature of the gas present (p < 0.01). (AFTER SCHREINER ET AL.³⁹¹)*

160 mm Hg is significantly reduced in the presence of metabolically inert gases. The concentrations of these gases needed to reduce the oxygen-dependent radiosensitivity of the bean (*Vicia faba*) root are listed in table 33. Since no change was made in the p_{O_2} of the gas mixture surrounding the tissues during irradiation, the conclusion drawn by these authors, admittedly tentative in nature, is that these gases may be capable of displacing oxygen from subcellular sites. Because these effects correlate with lipid solubility (table 2), Ebert and Howard feel that these sites are probably lipid in nature and possibly nuclear in location.

Schreiner indicates that the cellular growth of molds is likewise an oxygen-dependent phenomenon in that no growth occurs in the absence of oxygen and nearly normal growth is usually seen at a p_{O_2} of 40 mm Hg. He borrowed Ebert's concept and postulated states of "subcellular hypoxia" created by the physical displacement of oxygen by metabolically inert gases from subcellular sites for which they have a great affinity. He visualized these gases as occupying physically selected cellular or subcellular sites, thereby denying oxygen molecules access to centers of oxidative metabolic activity. The extent to which a gas could exercise such a blocking action would depend fundamentally on its polarizability which determines the degree of its interaction with the cellular environment as expressed by such parameters as solubility or distribution coefficients. It so happens that in the inert-gas group, polarizability increases with increasing molecular weight.

TABLE 33.—*Radioprotective Effect of "Metabolically Inert" Gases*
[AFTER EBERT AND HOWARD ¹⁵⁴]

Gas	Pressure for 50 percent effect, ^a atm
Helium.....	55
Hydrogen.....	55
Nitrogen.....	12.5
Argon.....	2
Xenon.....	1
Krypton.....	2

^a Pressure of metabolically inert gases added to 1 atmosphere of air to reduce the oxygen-dependent radiosensitivity of *Vicia faba* roots by 50 percent.

The polarizability of other gases cannot be related directly to their molecular weight; sulfur hexafluoride shows low polarizability, and, as one would expect, low solubility in water. The absence of a striking effect of this gas on *Neurospora crassa* growth is, therefore, not surprising. Nitrous oxide, on the other hand, is a permanent dipole with a high degree of polarizability, and one would expect a pronounced growth effect. Schreiner found that this gas completely inhibits the growth of *Neurospora crassa* at a p_{N_2O} of 0.95 atmosphere.^{383, 81}

The oxygen displacement hypothesis has been studied further.³⁸⁸ Experiments conducted with helium and nitrogen at pressures ranging up to 1775 psia indicate that the growth retardation of *Neurospora crassa* by krypton and xenon cannot be related to a critical intracellular concentration of metabolically inert gases. In the presence of an initial p_{O_2} of 3 psia, nitrogen at a partial pressure of 1772 psia reduces the linear mycelial growth rate of the mold by 27 ± 6 percent (range: 21 to 33 percent). Helium at a partial pressure of 1760 psia inhibits this parameter by 42 ± 2 percent (range: 41 to 44 percent). The difference in the growth effects produced by helium and nitrogen under pressure is statistically significant ($p=0.05$). Respiratory measurements indicate a shift in respiratory quotient as the gaseous environment is changed from air (RQ=0.75) to 1772-psia nitrogen and 3-psia oxygen (RQ=1.42), and then to 1760-psia helium and 15-psia air (RQ=2.05), indicating the association of metabolic changes with the observed growth effects. It is not clear at this time why helium, contrary to its behavior at ambient pressure, should under increased pressure have a biological effectiveness surpassing that of nitrogen. It is still not clear whether the polarizability factor is involved in displacement of oxygen from critical site or in the distortion of hydrate films about enzymes and their supporting membranous structures. The effect of the gases on tyrosinase must also be accounted for.³⁹⁰

Schreiner^{388, 394, 389} has continued these studies with the observation that 80 percent krypton and 80 percent xenon mixtures with oxygen decrease the protoplasmic streaming within the hyphae of *Neurospora crassa* while growth is being inhibited. There also appears

to be an adaptation to the gas in that after a time the mold seems to gradually resume mycelial growth, albeit at a much reduced rate. Transient alteration of the sol-gel relationship within a cell with resultant changes in cytoplasmic streaming is another effect of inert gases that must be accounted for by any overall theory of action.

It is still not clear whether or not the metabolic changes brought about by the inert gases are all caused by the same molecular mechanism. Interspecies differences, intertissue differences, and subtle differences in physical apparatus used in the experiments are no doubt confusing the issue. It would appear that solution of the molecular mechanism will open a new era in our understanding of gaseous anesthesia, diving narcosis, and effects of chronic exposure to space-cabin environments utilizing unusual inert gases.

CHRONIC EXPOSURE TO INERT GASES

In the preceding sections, the scene was set for the many possible toxic effects that may be expected from unusual inert gas environments in a space cabin. How many of these narcotic or subtle metabolic changes have actually been found in long-duration exposures of men and animals? In light of the discussion in chapter 2, it would appear that only helium and neon are likely candidates as substitutes for nitrogen in space cabins. These will, therefore, be the prime focus of this discussion.

In 1928 Hershey^{228, 229} reported that mice breathing 80 percent helium and 20 percent oxygen could survive on this mixture as well as in air. Barach repeated these studies for as long as 40 days and found no gross changes in the growth or oxygen consumption of mice. These studies led to the use of therapeutic helium-oxygen mixtures in bronchoconstrictive disorders. The studies of Cook and associates were covered in great detail in the second section of this chapter.^{113, 115, 474} Mice kept in various helium-oxygen environments showed no changes other than those accounted for by excessive heat loss due to high thermal conductivity of the atmosphere. Appropriate thermal control relieved the hypermetabolic state.

More recently, Schreiner³⁸⁸ has kept mice at sea level on mixtures of 80 percent helium and

20 percent oxygen (less than 1 percent nitrogen) for several generations. Initial findings show no gross biochemical differences between these mice and those on air with the exception of minor changes in albumin-globulin ratio of serum and abnormality in the electrophoretic pattern of heart-muscle protein. There has been no change in fertility, and animals have bred normally and given birth to litters as large as those of control mice on air. However, starting at an age of 65 days a significant loss in weight was noted.³⁹⁰ The serum and heart-muscle changes are being followed up with further study.

The helium-oxygen atmospheres at higher pressures also appear to be relatively free of side effects in animals. As discussed in chapter 2, Workman et al.⁴⁶⁵ exposed colonies of rats, guinea pigs, and squirrel monkeys at 200 feet of water pressure to mixtures of 97 percent helium and 3 percent oxygen for periods of 2 weeks. All animals survived and were free of physiological and pathological lesions in excess of endemic findings in controls. No narcosis was seen in any of these animals even after 14 days.

Subacute exposures to neon have been limited to the study of Young et al.⁴⁷⁵ reviewed above. The preliminary aspect of this study and the equivocal results preclude a definitive discussion of this gas.

Human studies of chronic exposure have, for the most part, been performed in support of "underwater living" projects. In 1963, as part of the Conshelf II Project, Cousteau and his coworkers studied two subjects at a depth of 90 feet for 1 week. A helium-oxygen mixture was used. In spite of the 100-percent humidity, there appeared to be no symptoms or major complaints. The change in voice frequency (see below) appeared to be the most disturbing aspect of the study. Working dives at 165 feet and maximum-effort dives to 360 feet on helium-oxygen were well tolerated during this 2-week period. Plans for Conshelf III will take five men on helium-oxygen to 165 feet for 2 weeks. Conshelf IV will be at 330 feet for 2 weeks with penetrations to 525 feet.

In the Man-in-the-Sea Project, two divers remained at 432 feet of water on a 3.6-percent oxygen and 96.4-percent helium mixture for 2 days without gross physiological difficulty.^{288, 304, 138}

The divers' speech was unintelligible at depth.

In phase A of Project Genesis I, 79 percent helium and 21 percent oxygen was breathed for 6 days. Voice changes were the only major difficulty encountered.³⁷⁶ In Sealab I studies, four men lived in a 9-foot-diameter by 40-foot cylinder for 11 days at an underwater depth of 193 feet in a mixture of 79 percent helium, 17 percent nitrogen, and 4 percent oxygen.³³² There were few significant medical findings. As noted in previous chamber runs and in Cousteau's studies, subjects showed an initial decrease in pace of activity and a sense of increased fatigability early in the study. These symptoms are reported to have diminished day by day. There appeared to be an increase in sensitivity to subsequent nitrogen narcosis after living in a helium-oxygen environment. No hematological defects were found. The absence of hemolytic disorders previously reported by Cousteau is attributed to the better control of oxygen at a level less than 210 mm Hg.

Finally, recent laboratory studies were performed upon two men exposed for 2 days to 3 percent oxygen in helium at a depth of 650 feet of sea water followed by 6 days of decompression.²¹² Results were as predicted for subjects breathing gas 3.8 times as dense as air at sea level. Maximum voluntary ventilation was reduced 59 percent and timed vital capacity also was reduced to a lesser extent. No reduction was seen in forced vital capacity; volume-flow loops were changed in shape, but returned to normal with reduction in density. No signs of narcosis were noted.

Long-duration exposures to helium atmospheres at altitude began with the use of a helium-nitrogen-oxygen mixture in Project Man-High.^{6, 403} A mixture of 170 mm Hg oxygen, 79 mm Hg helium, and 20 mm Hg nitrogen with a total pressure of 269 mm Hg was breathed for 10 hours with no obvious difficulty resulting from the mixture.

In 1964, the Russians reported two studies of 22 and 33 days' duration in cabins, containing at one point 22.5-percent oxygen, 76 percent helium, and 1.5-percent nitrogen.^{137, 270} Two subjects remained in this helium atmosphere for totals of 10 and 25 hours. The concentration of carbon dioxide in this atmosphere did

not exceed 0.7 percent and humidity was held at 30 to 60 percent. Subjects wore cotton jersey underwear and sweatsuits.

It was demonstrated that at temperatures of 18° to 24° C (65° to 75° F) the usual comfort in air was replaced by a chilly sensation. At a cabin temperature of 25° C (77° F), the average skin temperature was 2° C lower in these subjects than in air at the equivalent temperature. The zone of thermal comfort in periods of wakefulness was 24.5° to 27.5° C (76° to 82° F), while at night, during sleep, it ranged from 26° to 29° C (79° to 84° F). These findings represented a reduction in zone of thermal comfort of about 3° C below that usually found in air environments. Body temperatures remained in the 36.2° to 37° C (97.2° to 98.6° F) range. It was reported that the test subjects detected atmospheric temperature changes more rapidly than in air. Exercise at a comfortable temperature produced a sensation of warmth more readily in the helium-oxygen environment than in air, but return to comfort after exercise was also more rapid.

Numerous studies of nervous, cardiovascular, and respiratory function were performed. Whatever changes occurred could be attributed to the hypodynamic environment and isolation rather than to the helium and oxygen.^{281, 184} There was a significant change in speech expressed by a shift in spectrum to the high frequencies by an order of 0.7 octave. Intelligibility of speech decreased but was not intolerable. No change in auditory function was noted.

Subsequent studies of this group related to effects of helium-oxygen environments in space-suit cooling. Two subjects remained in space suits for 8 and 24 hours on the same helium-oxygen-nitrogen mixtures as those used in the cabin. The same subjects also breathed air. During the course of the thermal balance experiments in the air medium, the temperature in the airtight cabin was maintained at a level of 27° to 30° C (81° to 86° F) and the ventilation of the space pressure suit was kept at a level of 160 to 180 l/min. The temperature of the air at the inlet to the space pressure suit fluctuated around 22° C (72° F). Under these conditions, the bodies of the test subjects experienced overheating. Their reaction to heat was one of "dis-

comforture," abundant perspiration was noted, and body temperature rose to 37.2° to 37.4° C (99.0° to 99.4° F). In the calculation of the heat balance, an accumulation of heat of up to 2 kcal/hr was noted in the test subjects. During the 24-hour experiment conducted in a helium-oxygen medium at the same values for the ambient temperature and the ventilation of the space pressure suit, the subjects experienced no discomfort due to heat, although the temperature of the gaseous mixture at the inlet to the space pressure suit was 3° C higher (25° C or 77° F) than in the analogous experiment in an air medium. When the temperature of the gaseous medium at the inlet to the space pressure suit dropped to 22° C (72° F), the test subject evaluated his reaction as "cool." During the 8-hour experiment in a helium-oxygen medium, the reaction to heat on the part of the test subject was one of comfort, despite the fact that the ventilation of the space suit was lower by a margin of 60 to 80 l/min, while the temperature of the gaseous mixture at the inlet to the space pressure suit was higher by a margin of 4° to 6° C than in the analogous experiment in an air environment.

In these experiments with the helium-oxygen medium, the temperature of the body and the skin of the test subjects exhibited no significant change, while the losses of moisture were lower by a factor of 40 percent. There was no accumulation of heat in the bodies of the test subjects and a negligible heat deficit was actually noted. From consideration of the thermal factors in space-suit design³⁶⁷ it would appear that the 40-percent reduction in moisture loss resulting from the helium-oxygen mixture may indicate a design where thermal conductivity at the skin-gas interface is somewhat restricted. Dr. Wortz of the AiResearch Manufacturing Co. agrees with this opinion. However, the rate of evaporation of water has been shown to increase with increasing molecular weight of the gas phase and may be a factor in this case.^{254, 255, 299}

Studies of helium-oxygen environments are currently underway at the U.S. Air Force School of Aerospace Medicine, Brooks Air Force Base,⁴⁴⁸ at the Douglas Aircraft Co.,²³⁹ and at the AiResearch Manufacturing Co.⁴³⁹ These are being conducted in the range of 7 psi with a

mixture of 50 percent oxygen and 50 percent helium. In all of these studies there has been an inward leak of nitrogen amounting to several percent of this gas in the final mixture. In the longest of these studies at the School of Aerospace Medicine, subjects were exposed for 15 days at 7.3 psi to a mixture of 51 percent helium and 46 percent oxygen, with from 3 to 10 percent nitrogen. There appears to be no gross physiological change evident. Slightly discernible voice changes have been noted. Studies of 56 days on 70 percent oxygen and 30 percent helium at 5 psia are being planned.⁴⁴⁸ Results of all these current studies will be covered in part IV of this series.

A final question to be answered is the specific requirement for at least trace amounts of nitrogen gas for long-range survival of organisms. The studies, of Allen,⁸ Boriskin et al.,⁷⁰ Hiatt,^{231, 232} and Wright⁴⁶⁷ indicate that survival and development are possible with helium as the only inert gas if the atmosphere is contaminated with the same trace amounts of nitrogen as present in these experiments. Helium and neon gas are available with nitrogen impurities as low as 50 ppm by volume.²⁸⁷ Oxygen is available with less than 0.01 percent total impurities. Use of such gases in future studies may help to answer this question regarding the requirement of trace amounts of nitrogen.

One must keep in mind, however, the related problem of oxygen toxicity. This subject has been covered in detail in the first report of this series on the "Selection of Space-Cabin Atmospheres."³⁶⁹ The role of inert gases in atelectasis in both normogravic and hypergravic environments was reviewed. The role of inert gases in radiosensitivity was also covered. Therefore, these subjects are not discussed in any detail in this report.

As was pointed out in part I of this series, the choice between helium, neon, and nitrogen does not depend in any significant way on the radioprotective aspects of these gases at the partial pressures anticipated for space vehicles. In fact, 100 percent oxygen at 5 psi has been recently shown in mice to be no more hazardous than air during exposure to 250-kvp X-rays.²⁵⁶ The following references are a supplementary list of papers which amplify the radioprotective aspects of inert gases at very high pressure.^{153, 154, 161, 334, 361} The significance of this concept to the theory of inert-gas narcosis has already been covered in this chapter.

In conclusion, it can be stated that the most marked effect of helium and possibly neon on the metabolism of intact homoiothermic organisms is the stimulation of oxidative processes by increasing the rate of heat loss. This thermal conductivity factor will be discussed in greater detail in chapter 4. There is, however, a direct effect on the oxidative metabolism of tissues which can be separated from the heat-loss factor in studies of isolated tissues. This more direct metabolic factor may be related in some as yet undefined way to inert-gas narcosis. In the space-cabin environment, it would appear that neither the heat-loss nor "narcotic" factors are serious enough to preclude the use of helium in the atmosphere for periods of at least 15 to 30 days. Because a potential metabolic distortion does exist, it would be well to substantiate more prolonged use of this gas with adequate experiments on humans.

The use of neon gas on humans for prolonged periods of time is definitely not justified without more animal studies. The single study by Young et al.⁴⁷⁵ indicated presence of a toxic factor which may or may not be related to the neon per se. Extension of these studies is most desirable.

Engineering Implications of the Use of Inert Gases in Space Cabins

THE PRIME CONSIDERATIONS of inert-gas physiology in the engineering of space cabins were covered in the first three chapters. They are decompression sickness, explosive decompression, ebullism, blast, and metabolic changes in long-range missions. This chapter discusses the secondary biophysical properties of the inert gases which may play a role in engineering decisions on cabin design and atmosphere selection. These effects include some which have already been mentioned in chapter 3. They are thermal control, voice changes, sound transmission, and leak rate.

THERMAL CONTROL

As indicated in chapter 3, the major difficulty observed with helium in long-duration exposure to the gas is thermal control. Homoiothermic animals tend to lose heat to a helium-oxygen environment at a faster rate than to an air environment and to compensate by increasing metabolic rate and oxygen uptake. The physical data on thermal conductivity of the inert gases were presented in chapter 1. From table 1 and the appropriate kinetic theory equations cited, the thermal conductivity of any mixture of any inert gas and oxygen may be determined. Figure 1 of this report is the result of such a calculation for the monatomic inert gases and oxygen. It can be seen that at the same pressure, the thermal conductivity of a 50-percent helium and 50-percent oxygen mixture would be 1.7 times that of a mixture of 50 percent neon and 50 percent oxygen, and from molecular-weight considerations, about twice the thermal conductivity of a mixture of 50 percent nitrogen and 50 percent oxygen. The presence of oxygen with about the

same thermal conductivity as nitrogen tends to damp out the thermal conductivity differences between the inert gases in these oxygen-enriched mixtures.

The Russian data presented in chapter 3¹³⁷ indicated that the comfort zone in an environment of 80 percent helium and 20 percent oxygen at 1 atmosphere was about 3° C less than that found in air at sea level. In a cabin with a pressure of 7 psi and an atmosphere of 50 percent helium and 50 percent oxygen, this effect should be markedly decreased. Reduction of skin temperatures in cool environments also should not be as great as the Russians found.

The thermal studies of Epperson¹⁵⁸ at the U.S. Air Force School of Aerospace Medicine, during the 15-day experiments, with an atmosphere of 51 percent helium, 46 percent oxygen, and 3 percent nitrogen agree with this prediction.⁴⁴⁸ Epperson is preparing a definitive report on these differences for future publication and was kind enough to permit the presentation of his results. The subjects expressed no specific feeling about changes in comfort zone during these studies at altitude. At rest, the difference between skin temperature and air temperature was 6.75° F in a mixture of 79 percent helium and 20 percent oxygen at altitude, and 5.5° F in 79 percent helium and 20 percent oxygen at ground level. With exercise, differences in temperature between the two gas mixtures disappeared. The skin-temperature differences at altitude in a mixture of helium and oxygen were essentially the same as those for equivalent composition of nitrogen and oxygen. Cabin temperatures selected by subjects as comfortable tended to be about 75° F as compared to 73° F for equivalent oxygen and nitrogen mixtures.

Therefore, it would appear that thermostatic control of the cabin would require a temperature setting of a few degrees higher and possibly a narrower deadband width in cabins with a 50–50 mixture of helium and oxygen compared with the nitrogen-oxygen environment. In cabins at sea level a slightly higher temperature and even narrower deadband width would be required. Because of the differences in thermal conductivity, however, the blower requirements of the air-conditioning system will be altered. The power, volume, and weight tradeoffs involving this factor will be covered in part IV of this series, supported by a complete thermodynamic analysis of man in these unusual gaseous environments.

VOICE AND SOUND TRANSMISSION

The "Donald Duck" characteristics of the voice while breathing helium in diving operations have always been a problem.⁴¹ Several studies of voice changes in helium-oxygen atmospheres at or below sea level have been presented.^{43, 144, 148, 375, 376} One can summarize these studies by indicating that speech quality is determined by the oscillatory frequency of the cavities of the mouth, nose, throat, and larynx. The laryngeal muscles controlling tension on the vocal cords are trained from childhood to produce different tones in the resonating systems. The output of these systems is fed back to the speaker via the ear, and speech is modified to attain the learned pattern for each individual. Modification of either the cords or resonating cavities can alter the quality of this sound.

As a first approach to the problem, the air passages may be considered as a simple tube. The wavelength of a resonating air column depends on the volume and length of the column. The dimensions of the resonating passages of the upper respiratory tract can be little altered voluntarily. The frequency of the sound produced by a vibrating air column is proportional to the velocity of gas/wavelength of sound. The velocity of sound, in any "perfect" gas mixture, can be obtained by the equation⁴²⁵

$$V_{\text{sound}} = \sqrt{\frac{\gamma p}{d}} = \sqrt{\frac{\gamma RT}{M}}$$

where

T	absolute temperature
γ	ratios of specific heat
p	equilibrium pressure
γp	adiabatic bulk modulus
d	equilibrium density
R	universal gas constant
M	molecular weight

These values for individual inert gases may be obtained from table 1. The value of γ for oxygen is 1.41, and the density at 1 atmosphere is 0.001429 g/cm³. The sound velocities for the inert gases are also recorded in table 1. From table 1 it can be seen that for any given wavelength, the frequency for pure helium should be three times greater than for pure nitrogen. When 20 percent oxygen is added at sea level, this theoretical ratio reduces to 1.8 to 1. Experimentally, the ratio turns out to be 1.5:1.³⁷⁵ This difference can be partially explained by the fact that the audiovocal feedback system may alter the frequency of the vocal cords in response to the higher audible frequency and bring about the altered frequency. The resonant systems of the human are probably not ideal and may also alter the ratio from the theoretical values. Dilution of helium by nitrogen in the alveoli may have also been involved.⁴³

Several detailed reviews of the mechanics of phonation are available.⁹⁶ Wathen-Dunn has recently reviewed the physical effects of the simultaneous alteration of pressure and density of gas on the formant frequency of vowels.⁴⁴⁴ He points out that the relationship between the formant frequencies of the different sounds, not their absolute values, is probably important in determining intelligibility. Intelligibility fails when the relative formant frequencies are shifted beyond a given bound. Wathen-Dunn suggests that the above equation is not adequate for explaining the effect of pressure on speech. This equation indicates that the sound velocity in a gas depends on the product of γ and the ratio of pressure to density. Since density is a function of pressure, any variation in velocity should be caused only by variations in γ . Because γ for air changes little with pressure¹⁶² and assuming this is also true for helium-oxygen mixtures, the formant frequencies would be expected to

be independent of pressure. Speech in compressed air belies this prediction. By treating the vocal tracts as Helmholtz resonators where the impedance of the wall of the vocal tract provides a fixed mass reactance in parallel with the mass reactance of air in the oral cavity or neck of the resonator, it was shown that the minimum formant frequency at a given pressure is equal to the frequency at 1 atmosphere times the square root of the ambient pressure in atmospheres. This would account for the pressure effect at depth.

Altitude would, therefore, be expected to reduce only slightly the minimum formant frequency for a gas mixture of given percent composition. The physical factors determining intelligibility of speech are so complicated that no quantitative predictions can be made of intelligibility from first principles. Since the velocity of sound in 50-50-percent mixtures of oxygen and helium at 380 mm Hg is increased by only 35 percent above that at sea-level conditions in air, little change in voice is expected.

Divers actually learn to alter their voices to lower the frequency and modify the nasal quality. Expert divers take great pride in this ability.³⁷ After several periods in a mixture of 80 percent helium and 20 percent oxygen at sea level, even novice divers learn to improve the intelligibility of speech,³⁷⁶ but supplementary means are often required for higher pressures of helium.

Experience with helium-oxygen at altitude has been limited. In practical diving at depths great enough to make speech unintelligible with helium-oxygen alone, speech of the divers is improved by adding a small fraction of nitrogen to the gas. For situations in which continuous administration of nitrogen is undesirable, Lambertsen devised a speech-improving procedure involving partial washout of pulmonary helium by a nitrogen-containing mixture. This procedure, used for periods of critical speech, was employed in the Man-in-the-Sea Project.¹³⁸ A further gain has been accomplished by substituting periods of neon-oxygen breathing to improve speech without risk of severe narcosis. This has been utilized at 650 feet²¹² and at 300 feet in Cousteau's Conshelf III studies. Electronic modification of helium speech is also under study.¹⁹³

The recent studies of Cooke and his coworkers have clarified the problem somewhat.^{117, 118, 119} Subjects exposed in a small decompression chamber to an atmosphere of 50 percent oxygen and 50 percent helium at a total pressure of 395 mm Hg were given test digits over earphone sets. There were no errors and no reported reduction in subjective intensity. Slight modification of tone was noted. Conversation at a distance of 73 cm (2 ft) was also normal. No significant degradation of intelligibility was noted.¹¹⁹

Voice studies at altitudes while breathing 50 percent helium and 50 percent oxygen were performed during the recent 15-day experiments at the U.S. Air Force School of Aerospace Medicine, by Welch and coworkers.⁴⁴⁸ Dr. Nickson of the Acoustic Laboratory at Wright-Patterson Air Force Base is currently reviewing the data. A general analysis of the mechanics of phonation is available.⁹⁶

Sound transmission can be affected by temperature, pressure, gas composition, and many other changes in an atmosphere. The acoustic impedance of a gas was defined in chapter 1, and comparative values for several inert gases are given in table 1. Calculations of mixtures of gases under specific atmospheric conditions can be made, but they are beyond the scope of the present discussion.²⁴⁰ The degradation of sound by absorption or attenuation occurs by conversion of organized systematic motions of the particles of a medium into random thermal agitation. Viscosity, heat conduction, diffusion, radiation, and many other factors play a role. Theoretical formulation requires that 12 absorption factors describing the classical absorption coefficient be combined with 6 or more factors describing intramolecular interactions to give a total absorption coefficient. Needless to say, such an exercise can be avoided by restricting the data to several well-defined variables in a fixed environment.

Cooke^{117, 118} studied the attenuation in a small chamber (2-foot transmission path) using a white noise generator of 3.13-watt output. The atmospheres were all mixtures of 50 percent inert gas and 50 percent oxygen. Barometric pressures and sound pressure levels at the sound meter pickup are recorded in figure 32.

Figure 33 indicates the attenuation of sound

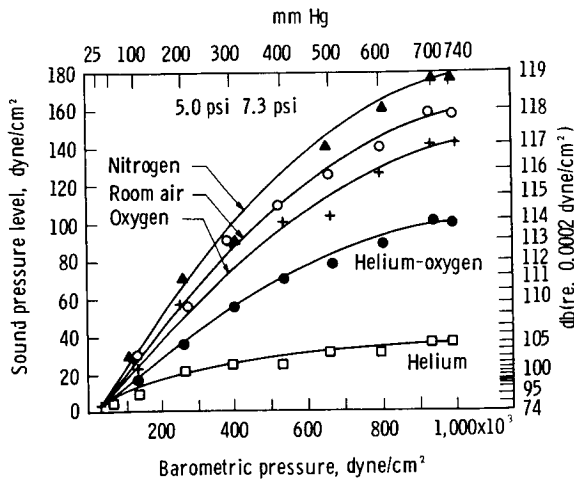


FIGURE 32.—Sound pressure levels (random noise) in different gases at reduced barometric pressures (74 dB=1 dyne/cm² above 0.0002 dyne/cm²). (AFTER COOKE.¹¹⁸)

generated from two speakers of different impedances (8 ohms and 16 ohms) at similar power outputs (1.0 and 1.1 watts) in 50 percent helium and 50 percent oxygen and in 50 percent nitrogen and 50 percent oxygen. It is seen that for each gas mixture there was very little difference in the pressure coefficient of attenuation. Helium attenuates the sound most severely. These decibel values are for a 2-foot transmission path: longer paths cause greater attenuation of sound.

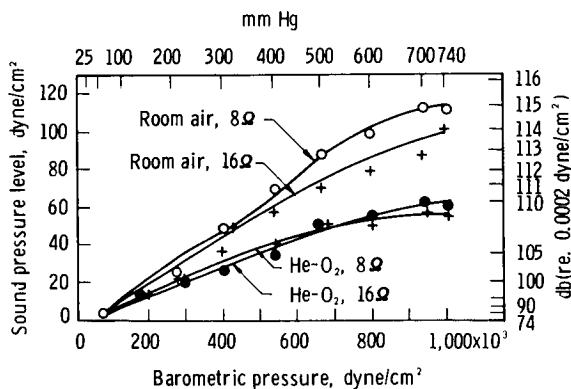


FIGURE 33.—Comparative sound levels produced by an 8-ohm speaker at 1.1 watts and a 16-ohm speaker at 1.0 watts in two gas mixtures at reduced barometric pressures. (74 dB=1 dyne/cm² above 0.0002 dyne/cm²). (AFTER COOKE.¹¹⁸)

For intense noise of booster firing, there may be some practical value in having helium-oxygen atmospheres present in a cabin. On the other hand, for speech levels of intensity there will be little impairment over relatively short distances. There may even be a reduction of background noise which will more than compensate for the slight decrease in sound intensity at the ear of the listener.

In summary, significant problems would not be expected in intelligibility of the spoken voice in space-cabin atmospheres of 50 percent helium and 50 percent oxygen mixtures and even fewer in 70 percent oxygen and 30 percent helium mixtures. Less distortion would be expected with neon-oxygen mixtures. For higher sound intensities, there may actually be some advantage to the helium-oxygen mixture in cabins from increased sound absorption.

LEAK RATES OF GAS

One of the limiting factors in the survival of astronaut crews after penetration of cabins by meteoroids is the leak rate of gas from the cabin. Adequacy of gas supply may determine time available for return to Earth. The engineering tradeoffs for each gas mixture also depend on the minimal leak rate of gas around seals and penetrations as determined by the state of the art of sealing techniques. How does the inert-gas factor play a role in determination of this leak rate?

There has been some disagreement as to the appropriate equations for describing the effect of cabin composition and pressure on leak rates. There is a choice between the sonic orifice equation for larger holes and pure diffusion equation for the smaller holes. It appears appropriate to review the development of an equation that can express the difference in mass leak rate of any mixed gas system.

Dryden et al.¹⁴³ attempted to calculate the leak rate of any cabin atmosphere by using a sonic orifice equation for steady flow. In this calculation the molal rate of leak of dry gas per hour L is defined by the equation for an ideal gas:

$$L = 3600 \rho \left(\frac{A}{144} \right) \mu = 25 P_c A \mu / RT_c \quad (34)$$

where

- ρ density, moles/cu ft
- A effective leak area, in.²
- μ velocity of flow, ft/sec
- P_c cabin pressure, atm
- R gas constant, atm = ft³/lb-mole·°R
- T_c temperature of cabin, °R

By rearranging the variables in terms of Mach number, M

$$P_c A \mu / RT_c = 46.2 (\gamma g / m RT)^{0.5} (P_c A M) \quad (35)$$

where

- γ ratio of specific heats
- g gravitational constant, 32 lb/slug
- m average molecular weight of gas

For critical isentropic flow, the Mach number is unity

$$P_c = P_d (2/\gamma + 1)^{\gamma(\gamma-1)} \quad (36)$$

where P_d is dry cabin pressure,

and

$$T = T_c (2/\gamma + 1) \quad (37)$$

Substituting equations (35), (36), and (37) into (34) yields

$$L = 1160 (\gamma g / m RT)^{0.5} (P_d A) (2/\gamma + 1)^{(\gamma+1)/2(\gamma-1)} \quad (38)$$

The total pressure and temperature may be considered equal to the cabin pressure and temperature. The cabin pressure used is the corrected pressure (P_d) and temperature is equal to 540° R. The coefficient of discharge for sharp-edged orifices handling compressible fluids at pressure ratios in excess of 5 is assumed to be nearly constant at 0.85. Equation (38) may, therefore, be written as

$$L/\delta_c A = 279 (\gamma/m)^{0.52} (\gamma + 1)^{[(\gamma+1)/2(\gamma-1)]} \quad (39)$$

where δ_c is the ratio of absolute pressure to standard value of 1 atmosphere.

From table 1, the value of γ for the inert gases is 1.66; for nitrogen and oxygen, 1.4. Therefore, for any nitrogen-oxygen mixture, equation (39) reduces to

$$(L/\delta_c A)_{N_2-O_2} = 191/(m_{av})^{0.5}$$

where

- m_{av} 28 + 4z
- z the mole fraction of oxygen

In dealing with helium, the average γ of the mixture (γ_{av}) is determined by

$$\gamma_{av} = 1.4[1 - 0.288(1 - z)]/[1 - 0.399(1 - z)]$$

and

$$m_{av} = 4 + 28z$$

It is obvious from the m_{av} factors that for nitrogen-oxygen atmospheres, the percent composition will not change the leak rate significantly on a weight or molar basis. The percent composition of helium, on the other hand, will affect the flow rate and there will be a distinct difference between mass and molar flow. Figure 34 gives the flow rate on a weight as well as a molar basis for helium-oxygen and nitrogen-oxygen mixtures of varying composition.

A leak parameter for a 0.1-in.² hole, $L/(A/0.1)(\delta_c)$, is used to eliminate the factors of hole size

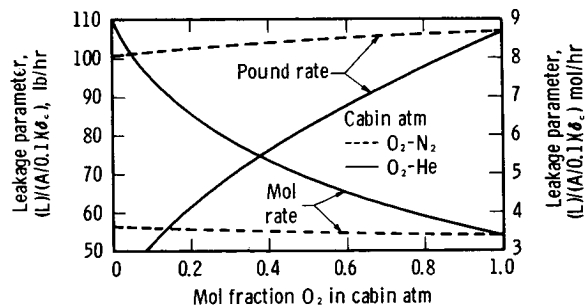


FIGURE 34.—Variation in cabin leakage parameter with cabin oxygen concentration for oxygen-nitrogen and oxygen-helium atmosphere. (AFTER DRYDEN ET AL.¹⁴³)

and pressure ratio. For a mixture of 50 percent oxygen and 50 percent inert gas, the molar leak rate for helium-oxygen is $4.5/3.5 = 1.3$ times greater than for the nitrogen-oxygen mixture. The pound leak rate is $8.4/6.3 = 1.3$ times greater for the nitrogen-oxygen mixture than for the helium-oxygen mixture. These differences will be much smaller for neon than for nitrogen.

Several other calculations of cabin leak rates have made use of the sonic orifice equation. Cullins¹²⁷ used essentially the same equation as did Dryden et al. (eq. (38)) in calculating the mass flow of gas through meteorite punctures, assuming compressible flow through a nozzle with infinite pressure ratio. Joule-Thompson throttling with constant internal orifice was used in a constant pressure equation to give the leak rate for constant mass flow.

These equations cover the case of flow through an orifice in a wall of negligible thickness. It is still not clear whether wall thickness can be neglected for small puncture holes. Where wall thickness becomes a factor, Poiseuille flow must be assumed.

A question now arises regarding the type of leak that occurs through joints and seals in space cabins. Is the leak of sonic orifice type or is it diffusive in nature? The first attempt to answer this question is the report by Greenspan and Curtis.²⁰⁶ These authors reviewed the type of diffusive leak through solid materials such as plastics, rubbers, and metals used in space vehicles. Data on many materials studied are presented and may be consulted for details. It was the conclusion of this group, however, that the actual permeation rates of the gas-metal

systems were all less than the sensitivity of the test method and that it was not possible to compare metals by their permeation rates alone. They also concluded that if welding and joining techniques are sound, the cabin wall itself should present a negligible leak path compared with those paths attributable to hatches, cables, and shafts. The total leakage expected due to permeation of skin and joints should be less than 1 percent of the structure's original volume for a mission of 1 year's duration. No allowance was made in this calculation for "pinhole" leaks after micrometeoroid penetration or initial flaws in metal surface or joints.

The Douglas Aircraft Co. has presented a review of diffusivity factors to be expected for various spacecraft materials.³⁷⁴ Tables 34 and 35 indicate the data available to this group. These authors indicate that solute diffusivity of a given gas varies with temperature, pressure, and crystal structure in such a complex, unpredictable way that reliable values of leak rates through metals can be obtained only by experimentation with operational simulation. For nonporous, nonmetallic membranes and walls, the prediction of solute diffusivities is even more unreliable due to their more complex organic structure and the possibility of the gas or vapor physically combining with or re-forming the nonmetallic barrier.

The crux of the problem lies in the type of hole expected to cause the leak. Metallurgically, the confining walls may consist of a multitude of minute holes which could be treated as orifices or capillaries, depending on the thickness of the wall. Once the nature of the holes is established,

TABLE 34.—*Solute Diffusivity of Gases Through Metallic Membranes*

[AFTER RUTZ AND CULLINS³⁷⁴]

Gas	Solid matrix	Temperature, °F	Diffusivity $\times 10^{10}$, ft ² /sec
H ₂	Palladium.....	338	768
H ₂	Iron.....	77	.16
H ₂	Nickel.....	77	1.23×10^{-3}
H ₂	Copper.....	77	1.15×10^{-6}
H ₂	Molybdenum.....	77	1.15×10^{-8}
CO.....	Iron.....	77	2.29×10^{-8}
O ₂	Silver.....	77	7.69×10^{-10}
N ₂	Iron.....	77	1.23×10^{-11}
H ₂	Aluminum.....	77	9.00×10^{-24}
N ₂	Molybdenum.....	77	6.62×10^{-26}

TABLE 35.—*Solute Diffusivity of Gases Through Nonmetallic Membranes*
 [AFTER RUTZ AND CULLINS³⁷⁴]

Gas	Solid matrix	Temperature, °F	Diffusivity $\times 10^{10}$, ft ² /sec
He.....	Vycor.....	77	9.51×10^3
CO ₂	Vycor.....	77	5.57×10^3
N ₂	Vycor.....	77	4.17×10^3
O ₂	Vycor.....	77	3.93×10^3
H ₂ O.....	Rubber (vulc.).....	77	204
O ₂	Silicone.....	77	48.1
CO ₂	Polyethylene.....	77	1.31
N ₂	Neoprene.....	80	1.06
He.....	Neoprene (vulc.).....	68	.704
Air.....	Rubber.....	77	.343
O ₂	Polyethylene.....	77	.246
He.....	Pyrex.....	68	5.23×10^{-4}

the ratio of the mean free path of the gas molecules to the diameter of the pore will determine whether the diffusivity of the gas should be evaluated by the laws of orifice flow, or effusion (radiation of mass) through pores of zero length. The diffusivity of any fluid through long pores can, in turn, be determined by the laws of Poiseuille or Knudsen. Formulas for transfer of gas through microporous media have been used in many applications.^{22, 150, 250, 373} It is not clear which ones are of significance in space-cabin leaks.

The nearest approach to the problem is the recent study of Mason at AiResearch Manufac-

turing Co., who was kind to permit presentation of this preliminary work.^{308, 309} Mason agreed with Dryden et al.¹⁴³ and Cullins¹²⁷ that for larger holes, a sonic orifice equation with isentropic expansion (similar to eq. (38)) would be applicable. The only difference was the choice of orifice coefficient. Dryden chose a coefficient of 0.85 for sharp-edged orifices handling compressible fluids at pressure ratios in excess of 5. Mason chose 0.6 as his orifice coefficient. The study of Busemann⁸⁸ indicates that the orifice coefficient can vary from 0.6 to 1.0, depending on the Mach number of flow that is chosen. This relationship for round, sharp orifices is seen in figure 35.

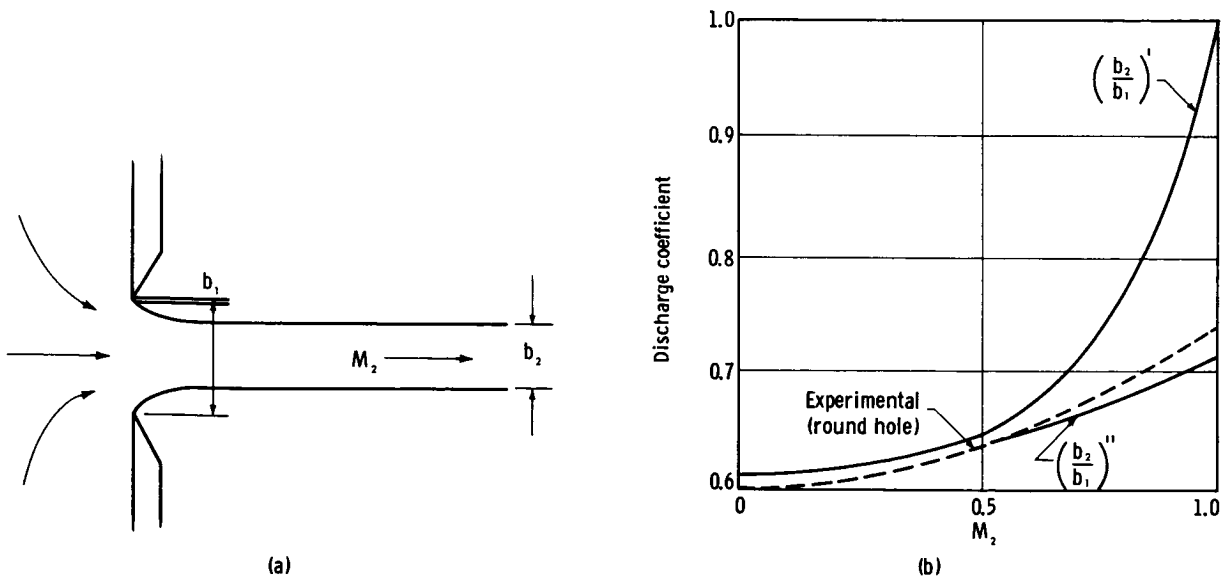


FIGURE 35.—*Theoretical coefficient of contraction for jet escaping from sharp-edged slit.* (AFTER BUSEMANN.⁸⁸)

The $(b_2/b_1)'$ value is for the "tangent gas approximation," and $(b_2/b_1)''$ is for the exact isentropic relationship. It would appear that the empirical value of 0.73 may be a good compromise. The orifice coefficient does vary from gas to gas because of the variation in specific heat ratios, but this is almost negligible in this situation.⁸⁸

For "small holes," Mason feels that a capillary-flow equation would be a better approximation of reality. Mason defines a large hole as one having a diameter of 25 to 50 percent of wall thickness. Any hole with a smaller diameter-to-thickness ratio is considered small. By this definition, meteoroid penetrations would probably all be "large hole types."

In "capillary flow," each capillary is assumed to be a long, straight cylinder with cabin pressure upstream and zero pressure downstream. Intake flow is of laminar-continuum type, with a transition to the free-molecular flow at the zero-pressure end. Mason³⁰⁸ used as the formula for this type of a flow a semiempirical equation which was originally derived by Knudsen. The equation was obtained from two sources.^{209, 344} Mason felt that the equation was erroneously quoted in both sources, and so he rederived the capillary-flow equation to a workable form. This lengthy derivation which is available from Mason³⁰⁸ or from the author, is not within the scope of this report. The final form of the equation is:

$$QL = \frac{5.22 D^4 p'^2}{\mu'} + \frac{7.42 D^3 P}{\sqrt{M'}} + \frac{0.0744 D^2 \mu'}{M'} \ln(1 + 23.9 DP \sqrt{M'})$$

where

P pressure, dynes/cm²
 Q leak rate, micron-liters/sec
 L length of capillary, cm
 D diameter of capillary, microns
 μ' $\frac{\text{viscosity}}{\mu_{\text{air}}} = \frac{\mu}{1.81 \times 10^{-4} \text{ poise}}$
 M' $\frac{\text{molecular wt}}{M_{\text{air}}} = \frac{M}{28.97}$
 p' $\frac{\text{pressure}}{p_{\text{atm}}} = \frac{p}{760 \text{ mm}}$

It is obvious from this equation that the assumed capillary diameter is crucial. This point is so crucial that it appears worthwhile quoting Mason's discussion verbatim. Mason assumed that the smallest conceivable diameter would be no less than 0.01 μ . The above equation indicated that for this diameter or less, some oxygen-helium atmospheres will have 7.3 times the molar leak rate of some oxygen-nitrogen atmospheres.

The leakage through such a small capillary is so small that an extremely large number of capillaries (of the order of 10^{12}) would be required to result in leakage at an appreciable rate, such as 1 lb/day of gas. The only readily imaginable way such a large number of paths could occur in a spacecraft is as an integral part of the wall metal structure, such as between the grain boundaries, or through defects in the crystal structure. Thus, such leakage would have to take place literally through the walls of the spacecraft. It is well known that metal walls only a few thousandths of an inch thick can be made quite leaktight against helium. Thus, extremely small capillaries can be discarded as a significant mode of leakage.

Mason then assumed for subsequent calculations that the smallest capillary diameter is 0.3 micron (12 microinches).

We assert that 0.3 micron is an unrealistically small capillary size because of the larger number of such capillaries required to account for the specified leakage rate of 1 lb/day. Specifically, 3.9 billion of these capillaries in parallel would be required to give 1 lb/day leakage from a 5-psi pure oxygen atmosphere. If the spacecraft is a cylinder 10 feet in diameter and 20 feet long, it would take 34 000 capillaries per square inch of spacecraft surface to give the 3.9 billion capillaries necessary for 1 lb/day.

Even this probably unrealistically small diameter (0.3 micron) does not lead to excessive helium leakage, when the helium is a constituent of a two-gas atmosphere. Thus, if we select a small enough capillary diameter for our model (of the order of 0.01 micron), we can obtain unfavorable high leak rates for helium, or for helium-oxygen atmospheres. But capillary diameters expected to be significant in spacecraft leakage—larger than 0.3 microns—do not show helium at any disadvantage.

Mason actually calculated the leakage rate for 5 capillary diameters from 0.3 to 30 microns. The number of equal-sized capillaries were chosen so as to give, for each diameter, a leak rate of 1 lb/day with 5-psi 100 percent oxygen. For this normalization, the capillary length was chosen as typical of a pressure wall in a space cabin ($L = 1 \text{ mm} \approx 0.04 \text{ in.}$). Seven individual atmospheres were used; table 36 is the result of these calculations. The variable sensitivity of the relative leakage rate to capillary diameter

TABLE 36. — Leakage of 7 Spacecraft Cabin Atmospheres: Capillary Flow
[AFTER MASON³⁰⁹]

Capillary diameter, <i>D</i> , microns	Capillary ratio, $\frac{\text{number}}{\text{length}}$	Leakage, <i>W</i> , lb/day, for —						
		Pure O ₂ <i>P</i> = 259 mm Hg 5 psia	<i>p</i> _{O₂} = 180 mm Hg <i>p</i> _{N₂} = 200 mm Hg <i>P</i> = 380 mm Hg 7.35 psia	<i>p</i> _{O₂} = 180 mm Hg <i>p</i> _{N₂} = 338 mm Hg <i>P</i> = 518 mm Hg 10.00 psia	<i>p</i> _{O₂} = 180 mm Hg <i>p</i> _{N₂} = 580 mm Hg <i>P</i> = 760 mm Hg 14.70 psia	<i>p</i> _{O₂} = 180 mm Hg <i>p</i> _{He} = 200 mm Hg <i>P</i> = 380 mm Hg 7.35 psia	<i>p</i> _{O₂} = 180 mm Hg <i>p</i> _{He} = 338 mm Hg <i>P</i> = 518 mm Hg 10.00 psia	<i>p</i> _{O₂} = 180 mm Hg <i>p</i> _{He} = 580 mm Hg <i>P</i> = 760 mm Hg 14.70 psia
0.3	3.9×10^9	$\left\{ \begin{array}{l} W_{O_2} = 1.00 \\ W_{N_2} = 0.0 \\ W = 1.00 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 0.73 \\ W_{N_2} = 0.71 \\ W = 1.44 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 0.72 \\ W_{N_2} = 1.24 \\ W = 1.96 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 0.78 \\ W_{N_2} = 2.21 \\ W = 2.99 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 0.95 \\ W_{He} = 0.132 \\ W = 1.08 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.07 \\ W_{He} = 0.250 \\ W = 1.32 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.22 \\ W_{He} = 0.495 \\ W = 1.72 \end{array} \right\}$
1.0	9.7×10^7	$\left\{ \begin{array}{l} W_{O_2} = 1.00 \\ W_{N_2} = 0.0 \\ W = 1.00 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 0.78 \\ W_{N_2} = 0.75 \\ W = 1.53 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 0.85 \\ W_{N_2} = 1.39 \\ W = 2.24 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 0.98 \\ W_{N_2} = 2.77 \\ W = 3.75 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 0.96 \\ W_{He} = 0.133 \\ W = 1.09 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.12 \\ W_{He} = 0.261 \\ W = 1.38 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.34 \\ W_{He} = 0.538 \\ W = 1.88 \end{array} \right\}$
3.0	2.7×10^6	$\left\{ \begin{array}{l} W_{O_2} = 1.00 \\ W_{N_2} = 0.0 \\ W = 1.00 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 0.87 \\ W_{N_2} = 0.85 \\ W = 1.72 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.04 \\ W_{N_2} = 1.71 \\ W = 2.75 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.34 \\ W_{N_2} = 3.79 \\ W = 5.13 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 0.98 \\ W_{He} = 0.137 \\ W = 1.12 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.20 \\ W_{He} = 0.281 \\ W = 1.48 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.54 \\ W_{He} = 0.62 \\ W = 2.16 \end{array} \right\}$
10.0	3.8×10^4	$\left\{ \begin{array}{l} W_{O_2} = 1.00 \\ W_{N_2} = 0.0 \\ W = 1.00 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 0.99 \\ W_{N_2} = 0.96 \\ W = 1.95 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.28 \\ W_{N_2} = 2.10 \\ W = 3.38 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.80 \\ W_{N_2} = 5.10 \\ W = 6.90 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.00 \\ W_{He} = 0.139 \\ W = 1.14 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.30 \\ W_{He} = 0.305 \\ W = 1.60 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.79 \\ W_{He} = 0.723 \\ W = 2.51 \end{array} \right\}$
30.0	6.0×10^2	$\left\{ \begin{array}{l} W_{O_2} = 1.00 \\ W_{N_2} = 0.0 \\ W = 1.00 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.06 \\ W_{N_2} = 1.03 \\ W = 2.09 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.43 \\ W_{N_2} = 2.34 \\ W = 3.77 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 2.10 \\ W_{N_2} = 5.91 \\ W = 8.01 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.02 \\ W_{He} = 0.142 \\ W = 1.17 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.37 \\ W_{He} = 0.321 \\ W = 1.69 \end{array} \right\}$	$\left\{ \begin{array}{l} W_{O_2} = 1.97 \\ W_{He} = 0.79 \\ W = 2.76 \end{array} \right\}$

can be readily seen for different mixtures. Several facts can be noted from the flow equation and table 36.

(1) The leakage rate for capillary flow is strongly pressure dependent. At $D=0.3 \mu$, the mass leak rate W is proportional to the pressure, while at $D=30 \mu$, $W \approx P^2$.

(2) For normalized values, the leakage of a mixture of 50 percent helium and 50 percent oxygen at 7.35 psi is remarkably insensitive to hole diameter.

(3) As the hole diameter increases, the weight rate leaks of the oxygen-helium mixture become smaller than oxygen-nitrogen mixture rates.

(4) Since the larger holes are more realistic, the mass-flow rate of 50 percent oxygen and 50 percent nitrogen mixtures may be as much as twice that of 50 percent oxygen and 50 percent helium mixtures at 7.35 psi.

It is of interest to note that in the review of the calculations of Dryden et al.,¹⁴³ it was indicated that for sonic orifice flow, mixtures of 50 percent

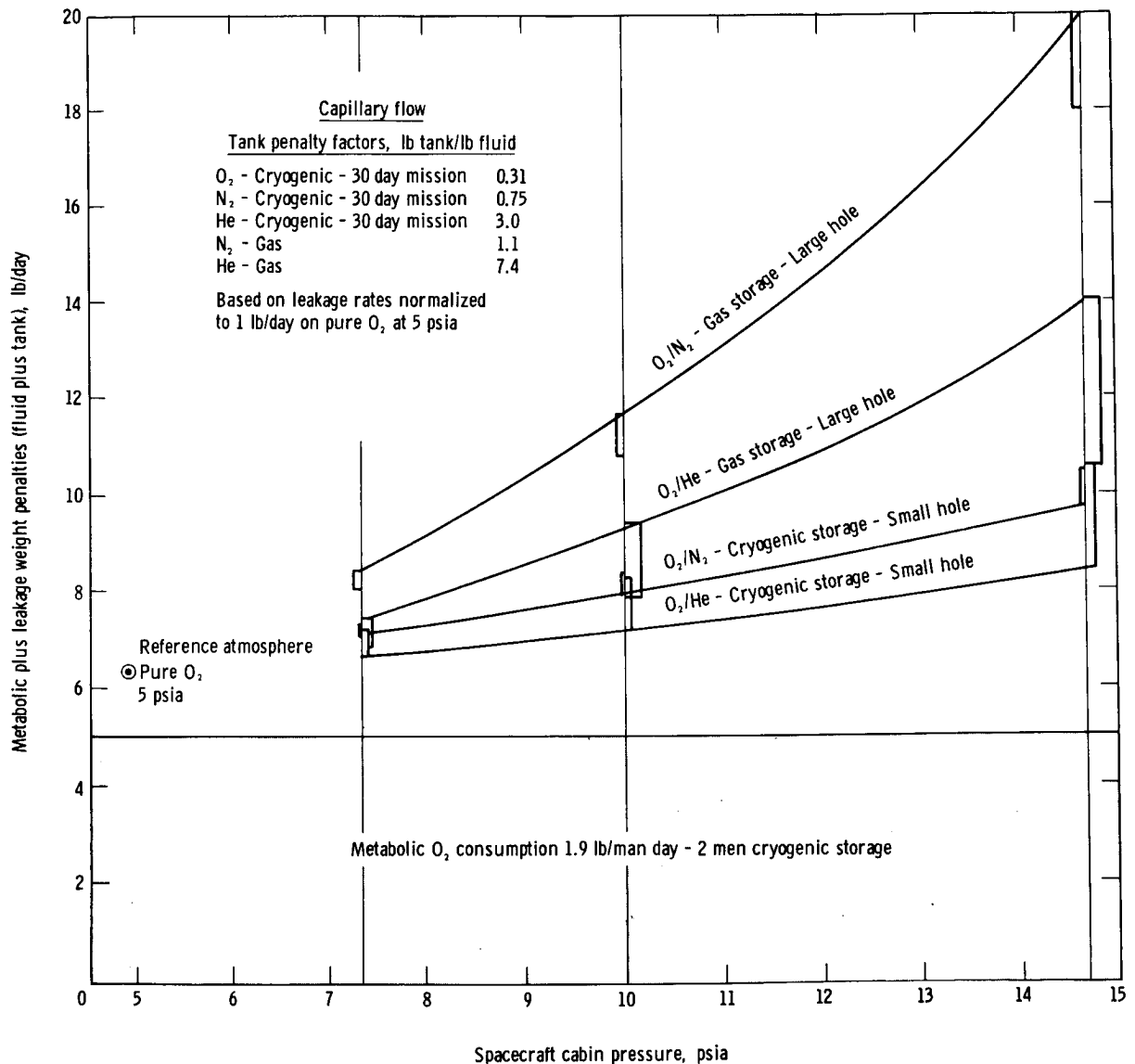


FIGURE 36.—Total gas systems weight penalty calculated for capillary flow. (AFTER MASON.³⁰⁹)

oxygen and 50 percent nitrogen would have a mass flow rate 1.3 times that of helium-oxygen mixtures. Mason's calculation for mixtures of 53 percent inert gas and 47 percent oxygen with orifice flow gave nitrogen-oxygen mixtures a greater mass flow rate by a factor of 1.28.

To determine the overall weight penalty for the different atmospheres, Mason again assumed a weight leak of 1 lb/day normalized to 5 psi with 100 percent oxygen and a total oxygen-system weight penalty of 5 lb/day to cover breathing oxygen for two men. The weight penalties

include tankage for supercritical cryogenic storage or gas phase storage which are at the present stage of the art. Using the mass leak rates of table 36, the total gas systems weight penalty (wall thickness is constant) was calculated. Figure 36 gives the results of these calculations for capillary flow. Figure 37 gives the results of orifice flow. Both figures indicate the total pressure effects and the inert gas factors.

Mason concluded from these computations that—

(1) Oxygen-helium mixtures show consistently

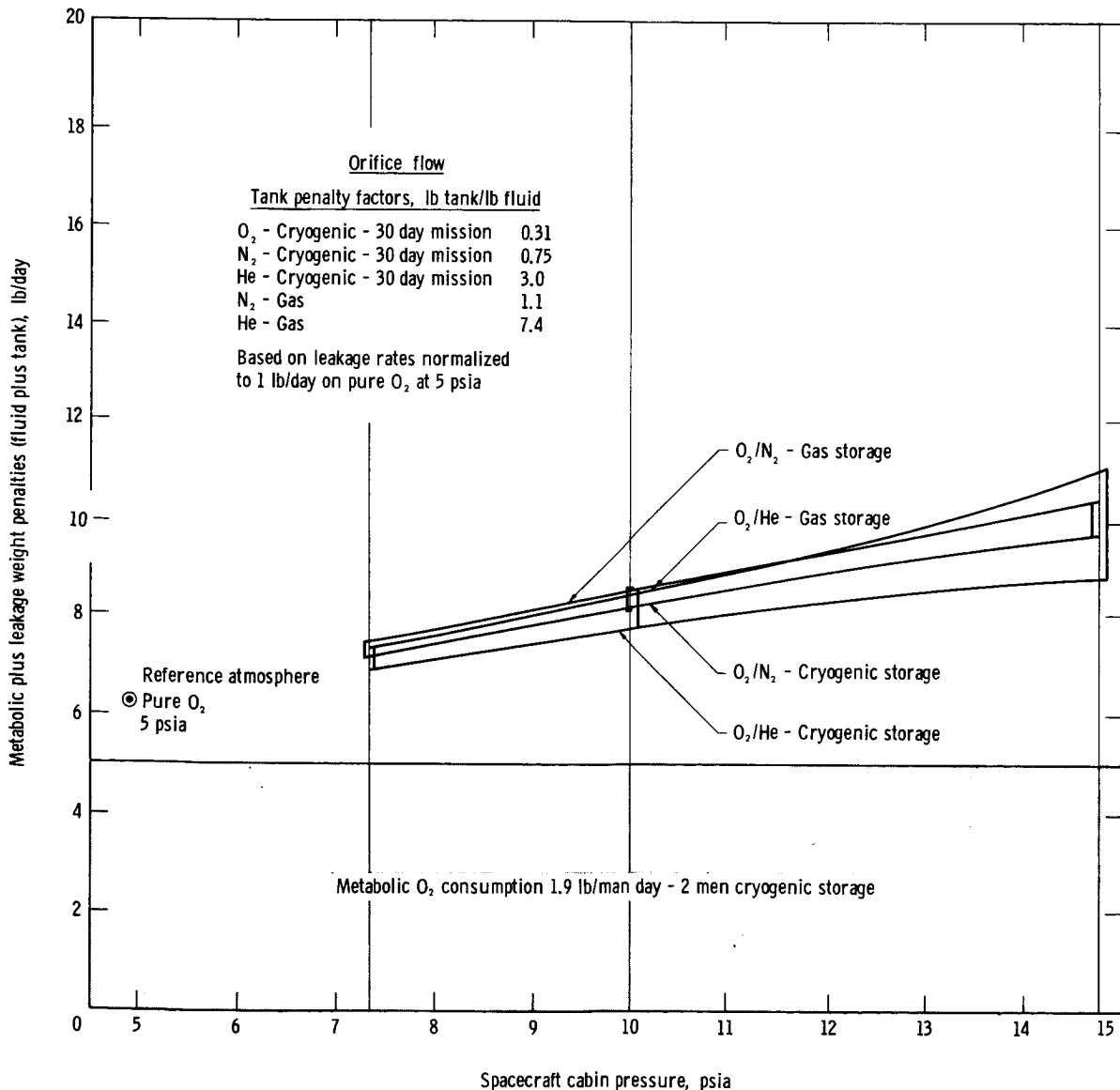


FIGURE 37.—Total gas systems weight penalty calculated for orifice flow. (AFTER MASON.³⁰⁹)

lower leakage penalties than oxygen-nitrogen mixtures for gaseous or cryogenic storage at all pressures, except in orifice flow for those above 12 psi with gaseous storage where oxygen-nitrogen penalties become less.

(2) Oxygen-helium total gas system leakage weight penalties are only slightly less than oxygen-nitrogen penalties under orifice flow or capillary flow ($D < 0.03 \mu$).

(3) Oxygen-helium total gas system leakage weight penalties are considerably less than those

for oxygen-nitrogen if flow through large capillary holes (30μ) is concerned.

It must be remembered that these figures give only rough systems estimates. Other mission-dependent factors could, for instance, alter the cryogenic storage weight penalties considerably. A factor which was not considered is the leakage of gas through the gas-phase storage cylinders. An example of this factor is seen in table 37.

It would appear from the leakage ratios noted in the discussion of Mason's study that the leak-

TABLE 37.—*Fiber-Glass Bottle Leakage Rate Experiments*

[AFTER BENDIX AVIATION ⁴⁵]

Fiber-glass bottle (3000 psig)			Leakage rate	
Volume, cu in.	Weight (empty), lb	Outside diameter, in.	Air, lb/wk	Helium, lb/wk
870	16	13	0.05	0.10
1300	25	15	.064	.128
1770	30	16.38	.10	.20
2570	48	18.5	.15	.30

age through the bottles is of the smallest capillary type. This is what one would intuitively expect. Mason reports ³⁰⁸ that he is currently studying this gas-bottle leakage problem for several different gas mixtures.

It is still not clear what type of leakage is found at the sealing surfaces in space vehicles. Mason's study suggests that large capillary or small sonic orifice flows are the most probable. In an operational study of this question, Mason ³⁰⁸ has attempted to compare the actual leak rates of helium-oxygen and nitrogen-oxygen in a cabin simulator at the AiResearch Manufacturing Co. The cabin was sealed, filled with the appropriate mixture several psi above sea-level pressure, and allowed to leak gas slowly. The rate of pressure drop was the only recorded parameter. There appeared to be no significant difference in pressure drop between gas mixtures. These results indicate that the molar flow rates out of the cabin seals are the same. This may be true with pressure ratios of an operational cabin. Such would be consistent with a total effective sonic orifice flow of small diameter or a capillary flow of large diameter. The results, no doubt, represent a compromise between flow through a small number of sonic orifices and a large number

of larger capillary orifices which overall favors helium-oxygen on a mass flow rate criterion.

In conclusion, it can be stated that helium-oxygen mixtures cannot be excluded and are probably to be favored over nitrogen-oxygen mixtures as far as a gas systems weight penalty for leakage is concerned. Previous fears of excessive leakage penalties appear to be unjustified.

The comparative leakage of neon-oxygen mixtures is not quite as clear. There is little experimental work, but one can make several predictions from sonic-flow theory. Equation (38) is derived from the same basic consideration as equation (33). The reciprocal of the square root of the average molecular weight of the mixture appears to determine the molar flow rate out of the trachea as well as out of the sonic orifice of the cabin. The molar leak rates of the different 50-50 gas mixtures through a sonic orifice would, therefore, be proportional to the reciprocal of the explosive decompression hazard of table 25. The molar leak rate of neon-oxygen mixtures would, therefore, approximately equal those of nitrogen-oxygen mixtures. From the above discussions, it appears that the mass leak rates of neon-oxygen would lie between those of helium-oxygen and nitrogen-oxygen in a real

space-cabin leak experiment. From the critical properties (table 1) it appears that the cryogenic storage of neon would be a relatively efficient process as far as weight penalty is concerned. The overall gas system weight penalty for neon-oxygen mixtures may be more favorable than even the helium-oxygen mixtures.

In summary, the overall gas-system weight penalty for leakage of inert gas in enriched oxygen

mixtures does not appear to favor markedly any one of the three inert diluents: nitrogen, helium, or neon. If cryogenic storage is contemplated, neon may have a slight advantage over helium, and helium, a slight advantage over nitrogen. A more quantitative systems weight analysis is required. In part IV of this series a more detailed tradeoff study will be presented.

Role of Inert Gas Physiology in Selection of Space-Cabin Atmospheres

IN PART I of this series on the selection of space-cabin atmospheres, it was pointed out that oxygen toxicity was a major factor limiting the use of 100 percent oxygen atmospheres in space cabins.³⁶⁹ Minimal data indicated that 100 percent oxygen at 5 psi appeared to be validated for missions of 14 days or less. It was suggested that variations in subject response to this condition required that simulator studies be at least twice as long as the projected space mission for validation experiments with the limited number of subjects usually employed.

The problem of atelectasis in the absence of inert gases was also discussed. In 100 percent oxygen atmospheres at 5 psi and 3.8 psi, experimental subjects have appeared to be in a borderline atelectatic state. The atelectatic tendency in a 3.8-psi 100-percent oxygen cabin was shown, theoretically, to be 370 times greater than that in air at sea level. The practical aspects of this hazard are still not clear. Temporary bronchial obstruction secondary to infection will no doubt be made more hazardous by the atelectatic tendency. High g-loads on takeoff and landing will also be more hazardous in 100 percent oxygen. Review of experimental work suggested, however, that for current missions, the g-level and duration of loading will not create sufficient operational hazards to preclude the use of pure oxygen in space vehicles.

Higher g-loads for longer durations may cause blood desaturation from ventilation/perfusion defects to become operationally hazardous. Atelectasis remaining after the high g-load could predispose to pulmonary infections. Quantification of the infectious hazard is also still lacking.

The following maneuvers, in the order of de-

creasing desirability, were suggested to alleviate the atelectatic tendency:

(1) Encourage intervals of deep inspiration, especially during high g-loads, but also during the zero-gravity phase of space missions.

(2) During periods of extreme acceleration, allow subjects to breathe with as much positive pressure as is physiologically tolerable.

(3) Just before and during high g-load maneuvers, let the subjects breathe mixtures of oxygen and inert gases. It was shown that the effectiveness of the inert gas in preventing atelectasis would be inversely proportional to its solubility in blood or water. Table 2 indicates that helium would be best, neon next, and nitrogen the least effective in reducing the atelectatic tendency during the unsteady state of incomplete inert-gas equilibration with the blood.

(4) Maintain in the cabin as high a percentage of inert gas as is compatible with proper oxygenation, structural limitations, and considerations of decompression sickness.

The radiation hazard does not seem to be significantly increased by 100 percent oxygen at 5 psi.²⁵⁶ Pertinent experiments were performed with 250-kvp X-rays. Analysis of the problem in part I of this series suggests the hazard arising from synergism between hyperoxia and particles of LET's expected from space radiation should be less than that arising from synergism between hyperoxia and these X-rays.

The blast hazard has very little effect on the consideration of 100 percent oxygen at 5 psi. During missions of high blast probability, 100 percent oxygen may be favorable from a purely physiological point of view. Gas emboli from a disrupted lung would be safer if they were com-

posed of 100 percent oxygen than of any inert-gas mixture. One-half hour after a blast, if there is no hypoxic episode requiring 100 percent oxygen, the presence of an inert gas may be of some help in minimizing pulmonary oxygen toxicity. In any event, the presence of inert gas does not appear to be a significant requirement even in the recovery period after blast injuries to the lung.

It was also pointed out in part I of this series that there is evidence that elevation of p_{O_2} above normal partial pressures tends to alleviate fatigue. The equivocal data on this point have as yet not been clarified. In long and complex missions, such a factor may assume some operational importance.

Part II of this series dealt with fire and blast hazards in space vehicles. The complexity of the problem was shown to preclude definitive conclusions. Evidence regarding all aspects of the problem suggested that for missions of the Gemini and Apollo type, where crew activity is restricted and optimum fire prevention and control can be attained, 100 percent oxygen at 5 psi is not precluded as a choice of atmosphere by the potential fire and blast hazard. For orbiting laboratories, military operations, and other missions where the probability of fire and blast accidents looms large, addition of inert diluents to the atmosphere appears to be the prudent course.

Selection of an inert diluent to minimize fire and blast hazard was shown to be difficult. In several types of ignition and burning conditions, helium appears safer than nitrogen. In other conditions, nitrogen is favored. In still other conditions, there is very little difference. Unfortunately, in fires starting from hot electrical insulation, the type of greatest probability, there are not enough data to distinguish between nitrogen and helium. Because of its greater thermal conductivity, helium may be the best for maintaining the insulation temperatures below the ignition point in potential overheat conditions. In zero gravity, helium may also diffuse more rapidly to the site of burning or degradation, and counter more readily the oxidative tendency of the atmosphere. More specific data are required on this point.

Because of its greater specific heat, nitrogen was indicated as the most effective overall diluent in preventing fires. This has been the

philosophy in industry where inert gases are often used in the manufacture of high-risk materials. Neon should be intermediate between the other two gases in most of these factors. There is, therefore, no overwhelming factor on which to base the selection of an inert gas for minimization of fire and blast hazards. The properties of neon may well present the best overall compromise. Adequate test should be made of this hypothesis.

Analysis of the physiological properties of inert gases presents very little overpowering evidence in favor of helium, neon, or nitrogen. Argon, krypton, and xenon can be eliminated quite clearly on the grounds that they increase the hazard of decompression sickness above the level for nitrogen.

Helium will not eliminate the occurrence of bends when used in an environment of 50 percent inert gas and 50 percent oxygen at 7 psi. Empirical and theoretical evidence has been presented that helium-oxygen mixtures probably will not reduce the symptom frequency of bends and may even increase it slightly above the expected frequency for nitrogen-oxygen mixtures of the same pressure and composition. Neon, although most inadequately studied, appears somewhat more favorable than helium or nitrogen in reducing the incidence of bends. Preliminary empirical evidence supports theoretical conclusions on this point.

There is theoretical evidence that the incidence of neurocirculatory collapse, and possibly chokes, may be considerably lower in neon than in helium or nitrogen. Helium is more favorable than nitrogen on theoretical grounds, but from diving experience, the evidence is not clear. There is not at present, nor is there likely to be available in the near future, empirical data to support the advantages of neon in relieving the hazard of these very rare events. Because of the extremely low probability of severe neurocirculatory collapse or chokes after equilibration with an environment of 50 percent inert gas and 50 percent oxygen at 7 psi, this factor should receive minimal weighting in the overall hazard analysis.

Prediction of bends incidence in space operations is based on inadequate extrapolation from indirect World War II data. Bends incidence

after decompression from 7-psi, 50 percent nitrogen and 50 percent oxygen environments, can be predicted only from the semiempirical Bateman equation supported by statistical analysis of denitrogenation factors and World War II chamber experience. It is suggested that for well-conditioned astronauts after equilibration with this environment, decompression to 35 000 feet (3.5 psi) at rest will lead to less than 1 percent bends symptoms of any grade. Exercise at the 35 000-foot (3.5 psi) altitude should result in a maximum of about 7 to 10 percent symptoms in this group, and up to 15 percent incidence in an unconditioned population of 20 to 40 years old. Grades 1 and 2 bends should predominate.

Equilibration with mixtures of 30 percent nitrogen and 70 percent oxygen at 5 psia should reduce the expected incidence considerably. Final suit pressures of 5 psi (27 000 ft) should reduce these predictions by a factor of 3. Equilibration in a 100-percent oxygen environment at 5 psi should almost completely eliminate bends symptoms occurring after exercise at an altitude of 35 000 feet (3.5 psi) and even possibly at an altitude of 38 000 feet (3.0 psi). There is a chance that predominantly carbon dioxide and oxygen bubbles or gas pockets may be formed in severely exercising subjects above these altitudes. No statistics on this point are available or can be predicted from theoretical grounds. Physical conditioning, by modifying the rate of denitrogenation of critical tissues, is a major factor in determining bends incidence and should be kept in mind in any analysis of hazards.

Adequate preoxygenation patterns for subjects in space cabins have been suggested. Age and physical conditioning again are important factors in predicting adequate preoxygenation time before ascent to different altitudes. A minimum of 2 and possibly 3 hours is recommended for the astronaut group and possibly 5 hours for poorly conditioned passengers in the older age groups to reach the denitrogenation level equivalent to equilibrium p_{N_2} conditions of 50 percent nitrogen and 50 percent oxygen at 7 psi.

In the case of explosive decompression, there is some advantage to helium over neon, and neon over nitrogen, as inert diluents. For mixtures

of 50 percent inert gas and 50 percent oxygen, the predicted hazard index can be seen in table 25. It has been indicated that the expected incidence of lung damage resulting from explosive decompression from 7-psi cabins to a vacuum is so low relative to the incidence of other traumatic factors that this parameter should receive very little weighting in the overall hazard analysis. The same holds true for the lung damage after blast exposure. Mission-specific factors must be considered in the evaluation.

It is also clear from theoretical and some empirical grounds that inert-gas factors do play a minor role in the ebullism syndrome. Exposures to space vacuum for up to 1.5 to 2 minutes may not be fatal to the astronaut population. Exposure to these conditions for periods greater than 60 seconds may lead to serious psychomotor aberrations for at least several hours following the event. The exact duration of exposure resulting in transient aberrations lasting several seconds to minutes is not known. In any event, this physiological phenomenon should not in any significant way influence the selection of an inert diluent gas unless dictated by mission-specific factors.

Inert-gas narcosis is a fascinating subject, but it will probably have little role in selection of space-cabin atmospheres. There are some indications that metabolic changes occur in cells exposed to helium-oxygen atmospheres. These do not appear to be significant in missions of less than 15 to 30 days' duration. Beyond this period of time, there is a rare possibility that chronic changes may affect the crew. Validation with animal and human subjects is required for longer missions.

The minor side effect of chronic exposure of humans to 50 percent helium and 50 percent oxygen environments is the elevated thermal conductivity of the environment. It has been shown, however, that at 7 psi in 50-50 percent mixtures there is minimal change in skin temperature or thermal comfort zone. The effect on power requirements of the air-conditioning system will be covered in part IV of this series.

Changes in voice and sound transmission are of minimal effect in space cabins at 7 psi with 50 percent inert gas and 50 percent oxygen mix-

tures. Decrease in transmission of background noise may even be a positive factor in the use of helium or neon as inert diluents.

In contrast to previous prediction, leakage of inert-gas mixtures from a cabin will not preclude the use of helium as an inert-gas diluent at 7 psi, 50 percent inert gas conditions. There is actually an overall storage weight advantage in favor of helium. Table 36 and figures 36 and 37 demonstrate this point. For cryogenic storage there is less difference between the mixtures than for gas storage. Theoretically, neon should offer a lower storage system weight penalty than the other two gases. These predictions should hold for meteorite penetrations and spontaneous leakage from seals.

In conclusion, neon appears to offer some advantages over helium and nitrogen as an inert gas diluent. The greatest advantage on theoretical grounds is in minimizing decompression sickness. In all other areas, neon appears to be as good as or slightly better than nitrogen or helium. The cost of pure neon is very great as compared to pure nitrogen or even pure helium. There is available a crude neon contaminated with up to 15 percent helium which is not much more expensive than pure helium.⁴⁶² Such a gas may well offer a practical solution to the problem of optimizing the inert-gas selection. From a physiological point of view, there is no overall mandate for the selection of helium versus nitrogen as the inert diluent in space cabins.

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