VOLUME 34
NUMBER 4
APRIL 1963

Aerospace Medicine

FORMERLY THE JOURNAL OF AVIATION MEDICINE
FOUNDED BY LOUIS H. BAUER, M.D.
Official Publication of the Aerospace Medical Association

The Philosophy of Extremes for the Gaseous Environment of Manned, Closed Ecological Systems

C. J. LAMBERTSEN, M.D.

IT IS REGRETTABLE that physiologists concerned with the limits of human tolerance to environmental stress cannot routinely, promptly, and specifically answer the questions of the engineers responsible for advanced flight programs; it is also understandable. All men are not created physiologically equal in their ability to tolerate various stresses. Moreover, actual knowledge of human tolerance to particular environmental factors can be derived only from studies performed over the expected duration of flight. It must also be considered that many independently innocuous stresses may, when experienced together, interact to product harm.[21, 22] Thus, while a single advance in propulsion technology can predictably advance the duration of vehicle flight, the complexity of man and our relative ignorance concerning his physiology means we cannot depend entirely upon extrapolation from acute experiments in determining human tolerance to interacting stresses of long duration. Nevertheless, intelligent prediction is as necessary for the physiologist as for the engineer, at least in determining profitable directions for research.

Faced with a chronic shortage of vital physiological information and the consequent difficulty in predicting limits of tolerance, there has been a tendency for both physiologist and engineer to ignore the adaptability of the human organism. This tendency has contributed heavily to delays in obtaining answers to a number of key questions involved in choosing optimal gaseous environments for various projected forms of closed system existence.

Advanced flight is now in the stage of orbiting the earth for one to several days, using the one-man capsules of the US and USSR space programs. Existing physiological information and technical skills should be adequate to assure the continued success of this effort. However, as the duration of manned flight increases from the single day of Project Mercury to the two weeks of Projects Gemini and Apollo, and then to the eventual flights involving many months of detachment from earth, economy of mass and human tolerance to environmental stresses become more and more critically interrelated. Compromises will be required to make proper choice of conditions and more than usual attention must be given now to the design of studies aimed at making use of man's inherent adaptability to environmental extremes.[21] As in engineering, physiological research involves a lengthy lead time.

This presentation will concern itself with the range of gas pressure gradients which earthbound man experiences in the normal exchange of gases with his environment. On the basis of existing information, estimates will be made regarding possible environmental extremes and their application to closed system existence.

THE NATURAL EXTERNAL GASEOUS ENVIRONMENT OF MAN ON EARTH

Man may intentionally vary the composition of his respired gas in diving or in aviation to minimize certain of the stresses of altered total gas pressure. While both diving and airborne flight can now be considered normal human pursuits, it is also pertinent to consider the

From the Laboratories of Pharmacology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

This paper is based upon a presentation before the Manned Space Station Symposium, Institute of Aeronautical Sciences, April 20-22, 1960 and appeared in the program proceedings of the symposium.

extremes of gaseous environment experienced by earth-bound humans who neither fly nor dive, but encounter these extremes as conditions in their natural habitat.

Gaseous Composition of the Natural Atmosphere for Man on Earth:—Requiring precise regulation of intracapsular gaseous environment may be an unnecessary restriction in prolonged flight since the natural gaseous environment of man on earth is constant only in its composition. Table I shows the well known percentages of O_2, CO_2, N_2 and rare gases in earth's atmosphere. While the percentage composition of dry air is constant at all altitudes, pressure varies, as does the amount of gaseous water present.

TABLE I. PERCENTAGE COMPOSITION OF DRY ATMOSPHERIC AIR

Gas	Percent
Nitrogen (N_2)	78.096
Oxygen (O_2)	20.940
Carbon Dioxide (CO_2)	.030
Other (A, Ne, He, Kr, Xe)	.934

Table II shows the range of ambient pressure at which air is breathed by men living normal lives on earth; it varies from about 760 mm. Hg near sea level to as low as 400 mm. Hg at the highest altitude where permanent human habitations have been established. Man lives at about 18,000 feet in both the Andes and the Himalayan Mountains.[19] It is evident from the two tables that the natural gaseous environment of man on earth is not constant for all men, or even for one man from time to time in his travels over the earth's surface. Variations in total pressure result in gross alteration of the partial pressure of inspired nitrogen and oxygen. However, because of its extremely low concentration in atmospheric air, the inspired carbon dioxide pressure to which man is naturally exposed is negligible at all altitudes. Water vapor pressure, dependent upon both temperature and the availability of atmospheric water also varies, but is not directly determined by atmospheric pressure.

TABLE II. RANGE OF TOTAL AND PARTIAL PRESSURES OF NORMAL GASEOUS ENVIRONMENT (INSPIRED GAS)

Altitude	Total Ambient Pressure (mm. Hg)	P_{H2O} (mm. Hg)	P_{CO2} (mm. Hg)	P_{O2} (mm. Hg)	P_{N2} (mm. Hg)
Sea Level	760	6	0.2	158	589
18,000 ft.	400	6	0.1	83	308
Range	360	*	0	75	281

* P_{H2O} varies with temperature and available water. An arbitrary 6 mm. Hg is employed in this example.

The Range of Normal Environment:—Partly as a reaction against the tendency to consider only air breathing at sea level as providing a normal gaseous environment for man, attention will be given here to the range of oxygen and nitrogen pressures which have proven capable of supporting human life on earth. This entire range of pressures should be considered carefully in choosing the gaseous environments which will be suitable for truly prolonged human existence beyond the earth's atmosphere. Man has adapted to these extremes and to the intermediate conditions. By considering the major physiological barriers and the aids to gas exchange at the extremes of man's natural environment, it is probable that a variety of external milieu can be devised which not only will adequately meet the needs of man, but *by making effective use of his physiological characteristics,* will also present *minimal* demands upon engineering skill in designing a particular extra-atmospheric vehicle or station for human occupancy.

BARRIERS AND AIDS TO GAS EXCHANGE AT EXTREMES OF EXTERNAL ENVIRONMENT

Few of the cells of human vital organs could survive prolonged, direct exposure to the gas pressures characterizing the normal atmosphere on earth. Carbon dioxide pressure in atmospheric air is so low that extreme intracellular alkalosis would result, altering the conditions of cellular metabolic processes. Enzyme systems in organs such as the brain and heart would be inhibited by even the normal 158 mm. Hg of oxygen partial pressure in air at sea level.[4, 12] Thus, while simple, poikilothermic, animal forms such as amoebae can withstand direct exposure to the partial pressures of gases in our ambient atmosphere, man and other warm blooded animals are protected from excessive cellular P_{O_2} by a sequence of anatomo-physiological barriers. Because of these barriers the oxygen and carbon dioxide environment of our internal cells differs grossly from the gas we inhale. The effects of these barriers upon gas exchange at sea level are illustrated elsewhere.[19]

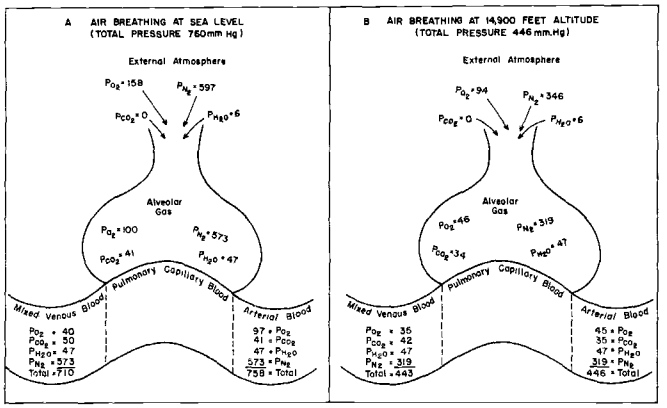

Fig. 1A and B. Gas exchange between atmosphere and alveoli, and alveoli and blood extremes of natural gaseous environment.

A. *Breathing air at sea level.* The partial pressures of each of the major gaseous constituents of the normal external atmosphere are shown as different from the tensions of the same gases in the pulmonary alveoli. In the gas exchange between alveoli and blood only P_{H2O} and P_{N2} fail to undergo substantial change. Even during air breathing at sea level, a prominent fall in P_{O_2} occurs during the passage of blood through the tissue capillaries, resulting in a reduction of total gas tension below atmospheric pressure (Data from Barker, et al.[2]).

B. *Breathing air at 14,900 feet altitude.* The difference in total tension between alveolar gas and the mixed venous blood is small, since the fall in P_{O_2} from alveoli to mixed venous blood is only a few mm. Hg larger than the rise in P_{CO_2} (Data from Hurtado, et al.[16]).

The Pulmonary Barrier to Gas Exchange in the Natural Environment:—At sea level as at high altitude the composition of the alveolar gas during air breathing is established largely by a dynamic balance between the rate of metabolism (oxygen consumption and carbon dioxide production) and the rate of alveolar ventilation (pulmonary oxygen uptake and carbon dioxide elimination).[20, 29] Water vapor pressure is a function of deep body temperature, and the levels of carbon dioxide and oxygen pressures are intimately related to their function in respiratory control. For these reasons, only nitrogen pressures can be considered as passively following changes in total ambient pressure. The inert gas nitrogen, not being metabolically consumed, is in essential equilibrium with body fluids and, in individuals not given to deviation from sea level existence, remains at a nearly constant pressure from pre-natal existence through post-mortem decomposition. Of the four normal respiratory gases, only oxygen must be supplied from the external atmosphere.

Figure 1 indicates the usual relationships among the partial pressures of inspired and alveolar gases in resting men breathing air at sea level (A) and in men acclimatized to an altitude of 14,900 feet above sea level (B). The former values are derived from measurements upon residents of Philadelphia,[2] the latter are values obtained from the extensive data provided by the work of Hurtado, et al.,[16] at Morococha, Peru. It is evident that at each of these two near-extremes of natural, earth-bound existence the metabolism-ventilation equilibrium attained by the normal respiratory regulatory mechanisms results in the establishment deep in the lungs of a portable gaseous environment (the alveolar gas mass) much different in composition and in partial pressures from the ambient atmosphere. This is the true gaseous environment to which man presents the pulmonary capillary blood as an interface for gas exchange.

Barriers to Exchange of Gases Between Alveoli and Arterial Blood:—As shown above, the partial pressures of respiratory gases change considerably between the external atmosphere and the alveoli. However, the partial pressures of gases in arterial blood normally approach very closely those of alveolar air. Figures 1A and 1B illustrate the results of this extremely efficient gas exchange at man's air-blood interface. In a single, well ventilated alveolus the blood flowing through the alveolar capillary should approach equilibrium with the oxygen and carbon dioxide tensions of the alveolar gas. Failure of the peripheral arterial blood to match within a fraction of a millimeter of mercury the oxygen pressure of the mean alveolar gas results from the passage of some blood through portions of the lungs in which effective exposure to alveolar gas does not occur,[29] rather than from interference with diffusion across any alveolar membrane. This small inefficiency of gas exchange between alveoli and blood, termed a "shunt," averages only about one to three per cent of the blood flow across the lungs[3] and normally accounts for a difference of only about 5-6 mm. Hg P_{O_2} between mean alveolar gas and the peripheral arterial blood.[2]

Barriers to Exchange of Gases Between Blood and Tissues:—There do exist significant barriers to gas exchange between arterial blood and the metabolizing tissue cell. Relatively few cells of the body, perhaps only those lining the pulmonary veins, the chambers of the left side of the heart, and the systemic arterial tree, are actually exposed to the gas pressures of the arterialized blood as it comes from the lungs. Loss of oxygen to the metabolizing tissues and the concurrent diffusion of metabolically produced carbon dioxide from the tissues into the flowing stream of capillary blood result in changing levels of P_{O_2} and P_{CO_2} as the blood passes through the tissue capillaries. As a result, the partial pressures of gases in the blood as it leaves a tissue by way of the veins are quite different from the gas pressures in the blood as it enters a tissue by way of the arteries. These partial pressure changes are largest for oxygen, considerable for carbon dioxide, very small for water vapor, and essentially nil for nitrogen. The change in gas pressure between arterial and venous blood varies considerably from one tissue, capillary or cell to another, the variation being due to differences in the rate of local metabolism and blood flow.

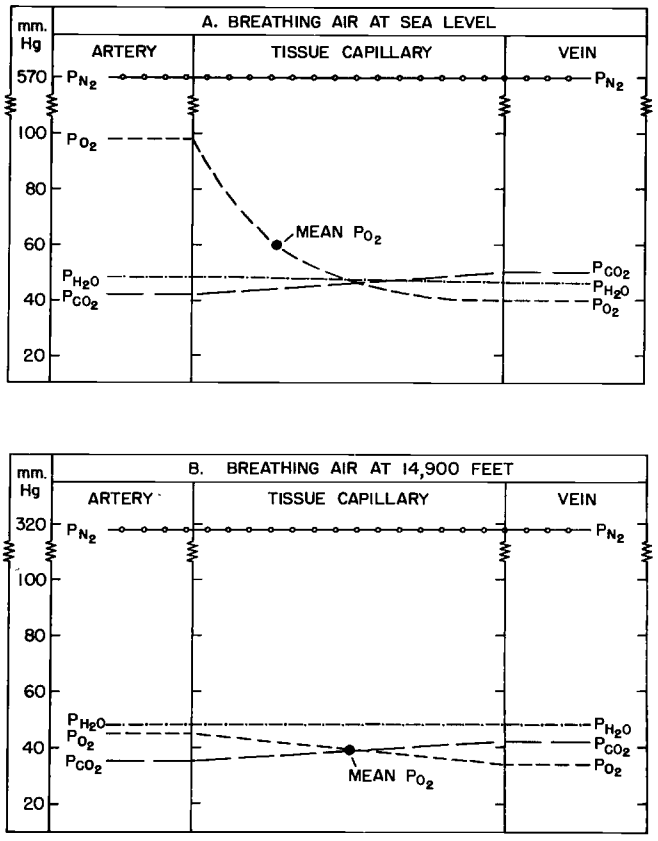

Fig. 2A and B. Gas exchange between blood and tissues at extremes of natural environment.

A. *Breathing air at sea level.* The diagram shows the fall in P_{O_2} during the passage of blood through the tissue capillary,[1, 15, 28] from the nearly 100 mm. Hg of arterial blood to the approximately 40 mm. Hg in mixed venous blood. Mean capillary P_{O_2} represents the average P_{O_2} presented to the total body tissue (Data from Barker, et al.[2]).

B. *Breathing air at 14,900 feet.* The P_{O_2} of arterial blood entering the tissues is less than the mean capillary P_{O_2} estimated for air breathing at sea level. Nevertheless, the P_{O_2} of the mixed venous blood of these less well oxygenated, but acclimatized individuals is not grossly lower than the mixed venous blood P_{O_2} of subjects at sea level (Data from Hurtado, et al.[16]).

The relative magnitudes of changes in blood gas tensions across the total vascular bed of the body are shown in Figure 2A for men at rest breathing air at sea level[2, 19] and Figure 2B for residents of Morococha, Peru.[16] The average tensions of water and nitrogen are seen to be similar for arterial, capillary and venous blood, and also are representative of the cellular tensions of these gases. Unfortunately it is not feasible to determine experimentally the average tension of either oxygen or carbon dioxide in the metabolizing cells and tissues of vital organs. It is possible to approximate the mean tensions of oxygen and carbon dioxide in the blood of the tissue capillaries by an integration procedure.[1, 6, 15, 23] The values given for capillary blood in Figure 2 represent the averages of individual gas tensions existing at the interface between man's tissues and their own local environment in the two situations selected to represent the normal extremes for continued life on earth.

SUBSTITUTION OF OXYGEN FOR AIR

Pulmonary Oxygen Toxicity:—While the engineering advantages of a system utilizing a single gas have been evident from the beginning of manned space flight, the specter of pulmonary oxygen toxicity demonstrated in men breathing high concentrations of oxygen at sea level[4, 5, 7] focused attention on the use of O_2-inert gas mixtures and even delayed the experimental exposure of men to pure oxygen for many days at low ambient pressures. Rather than stressing the occurrence of pulmonary irritation during oxygen breathing at sea level, it should be re-emphasized that this chemical effect is related to the partial pressure of oxygen, rather than to the absence of inert gas; no pulmonary irritation was demonstrated during 24 hours of pure oxygen breathing at an altitude equivalent to 17,000 feet in an early, well controlled study of pulmonary tolerance to pure oxygen in man.[7] In view of the clear relation to Po_2 it is almost inconceivable that chemical, pulmonary oxygen toxicity could be produced at ambient pressures no greater than 158 mm. Hg, even during long periods of breathing pure oxygen, since at this inspired oxygen pressure the alveolar oxygen pressure is less than the normal level during air breathing at sea level.[21] The fact that chemical oxygen toxicity does not occur during pure oxygen breathing at low inspired Po_2 appears now to have been substantiated by important, recent experiments in man.[10, 13, 14, 26] Previously it had been demonstrated that rats and mice can tolerate exposures to pure oxygen at reduced pressures for periods of seven days to many weeks.[25] It remains of great importance to determine the maximum level of Po_2 which will not produce pulmonary oxygen toxicity in man during exposures of extreme duration.

Physical Factors in Oxygen Breathing:—Even if the chemical form of pulmonary oxygen toxicity can be completely prevented by simple reduction of inspired Po_2, physical problems associated with pure oxygen breathing may remain. Such problems, related to alteration of the total gas tension gradient from ambient atmosphere to tissue capillary, may limit the ultimate utility of oxygen as the sole inspired gas. To illustrate these potential forms of physical intolerance to oxygen, two examples will be used (Figure 3A and 3B). One, Figure 3A, describes alterations of total gas tension

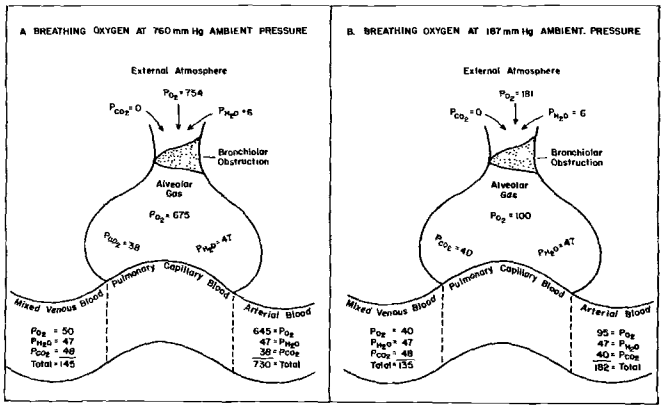

Fig. 3A and B. Problems of gas exchange during prolonged oxygen breathing at sea level and at low ambient pressure.

A. *Bronchiolar obstruction at one atmosphere.* The figure illustrates a bronchiolar obstruction. In the absence of inert gas, oxygen occupies the greatest proportion of the alveolar space. Since total gas tension in the mixed venous blood is more than 600 mm. Hg lower than in the alveolus, a large alveolar-pulmonary capillary gradient for oxygen exists (see text).

B. *Bronchiolar obstruction at reduced inspired Po_2.* Lowering of inspired Po_2 to 187 mm. Hg or less should result in an alveolar Po_2 of about 100 mm. Hg, preventing development of the chemical form of oxygen toxicity. At the lower arterial Po_2, hemoglobin limits the fall in Po_2 of blood passing through tissues. The Po_2 gradient from alveoli to mixed venous blood is smaller than when oxygen is breathed at sea level, as is the difference between total gas pressure in alveolar gas and mixed venous blood (see text).

such as occur in the lungs during oxygen breathing at one atmosphere, even though it is clearly not to be expected that men will breathe oxygen at 760 mm. Hg for missions of many days. In the second situation, Figure 3B, oxygen breathing at 187 mm. Hg ambient pressure, a normal alveolar P_{H2O} of 47 mm. Hg and Pco_2 of 40 mm. Hg will result in an alveolar Po_2 of 100 mm. Hg; this is approximately the alveolar Po_2 associated with air breathing at sea level.

Oxygen Breathing at One Atmosphere:—During prolonged oxygen breathing, the elimination of gaseous nitrogen from the body leaves only water, carbon dioxide and oxygen to exert gas pressure in the lungs and body fluids. Figure 3A shows that, at an ambient pressure equal to that at sea level, the 760 mm. Hg tension of dry, inspired oxygen results in a very high alveolar Po_2, approximately 675 mm. Hg. The sum of the partial pressures of oxygen, water vapor and carbon dioxide in the alveoli is essentially the same as the total pressure of the gas surrounding the body. However, from the alveoli onward in the gas exchange, total gas pressure falls; the decrease being brought about by several different mechanisms, as follows:

(a) In the lung capillaries, the blood of normal human subjects comes into nearly perfect equilibrium with the oxygen pressure in the alveoli. However, a small degree of "shunting" of poorly oxygenated, mixed venous blood across the lungs without exposure to

alveolar gas normally occurs.[3, 19, 29] The mixing of this shunted fraction of venous blood with the oxygenated blood from the pulmonary capillaries, results in a peripheral arterial blood Po_2 which is approximately 30 mm. Hg lower than the 675 mm. Hg in the alveolar gas.[8]

(b) The second basis for a fall in total gas pressure

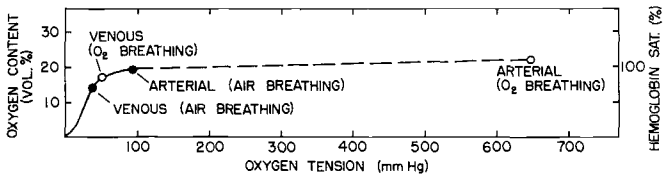

Fig. 4. Uptake and release of oxygen by blood during air breathing and oxygen breathing at sea level.

The diagram indicates the oxygenation of arterial and mixed venous blood in the transition from air to oxygen breathing at sea level. When hemoglobin is saturated, a further rise in oxygen tension causes an increase in oxygen content only by increasing the oxygen in physical solution in the water of blood. Utilization of this additional oxygen by the tissues results in a large fall in oxygen tension. Mixed venous oxygen tension during oxygen breathing at sea level is thus only slightly higher than when air is breathed (after Lambertsen, C. J.[19] (Fig. 228).

is illustrated in Figure 4 which diagrams characteristics of oxygen uptake and release by blood. The figure shows that above approximately 100 mm. Hg an increase in blood Po_2 adds oxygen primarily in physical solution; the amounts added per mm. Hg increase in Po_2 are small compared with the amount of oxygen taken up by chemical combination of oxygen with hemoglobin between 0 and 100 mm. Hg. As blood with a total gas pressure of about 730 mm. Hg enters the tissue capillaries and into gas exchange with the metabolizing tissues, carbon dioxide is added and oxygen removed in amounts determined by the metabolism and blood flow of the tissue. A great fall in the Po_2 of blood in the tissue capillary results; efficient buffers in blood prevent more than a small rise in Pco_2; water vapor pressure is increased an insignificant amount by a minute warming of blood in the tissue capillaries. As a result the *sum* of the oxygen, carbon dioxide and water vapor pressures in the venous blood of an actively metabolizing organ such as the brain during oxygen breathing at sea level is only about 145 mm. Hg.[23] The average total gas pressure of the capillary blood throughout the body should be about 160 mm. Hg, close to 600 mm. Hg lower than the ambient and alveolar total gas pressure of 760 mm. Hg. This is the state of the blood flowing back to the alveoli from the tissues.

(c) From its already low value in capillary blood, total gas pressure falls to its minimal value at the cellular level. Most of this final fall, as in (a) and (b), is due to a drop in oxygen partial pressure, here related largely to the rate of tissue oxygen metabolism, the distance over which diffusion of oxygen must occur from the capillary to the cell, and the diffusion coefficient of the tissue through which oxygen must pass.[34] The fall in Po_2 outside the capillary is certainly not uniform in all regions of an organ or even within a single cell.[23, 34]

Possible Effects on Gas-Containing Body Spaces:— The low venous and tissue total gas pressures resulting from absence of inert gas in a closed life support system should cause no difficulties unless certain gas-containing spaces of the body such as the middle ear cavities, the paranasal sinuses and the pulmonary alveoli lose their normal, free connection with the ambient atmosphere. If this occurs the partial pressure gradients and the low total gas pressure of the venous blood and tissue fluids should result in absorption of the gases trapped in these body chambers. Since the hydrostatic pressure of the tissue fluids is determined largely by the pressure of the atmosphere upon the body surface, the absorption of gas from blocked cavities not freely collapsible, such as sinuses or the middle ear, will reduce the total intracavity gas pressure below the hydrostatic pressure of the blood and the tissues. This pressure difference can cause painful distortion of adjacent tissue structures, exudation of fluid into the cavity, and even rupture of small blood vessels lining the gas space. While uncommon, these phenomonena have been observed during or following oxygen breathing at sea level, in diving, and in flight. They have important bearing upon comfort, performance, communication, and susceptibility to infection of the sinuses and middle ear.

An additional possibility of physical alteration during prolonged oxygen breathing is now receiving deserved attention. In the absence of inert gas a diffuse pulmonary atelectasis may occur due to complete absorption of oxygen, carbon dioxide and water vapor from alveoli. During air breathing at sea level or at high altitude the random obstruction of bronchioles by normal secretions probably occurs frequently. However, this should be transient and easily overcome by breathing or coughing. The presence of nitrogen in air is a considerable asset in preventing the progression of this process since the inert gas in the alveolar spaces beyond the obstruction is essentially in equilibrium with the inert gas of mixed venous blood. Nitrogen is only slowly absorbed from the alveolus and tends to hold with it the alveolar oxygen, carbon dioxide and water vapor. Time is thus available for the eventual relief of the obstruction and re-establishment of ventilation of the alveolus.

When pure oxygen is breathed at sea level, even for periods too short for development of chemical pulmonary toxicity, the occurrence of diffuse atelectasis should be much more rapid than when inert gas-oxygen mixtures are breathed. The high gradient of oxygen tension from the alveolus (Po_2 about 675 mm. Hg) to the flowing mixed venous blood results in ready absorption of oxygen and with it the associated carbon dioxide and water. In studies on isolated lungs the rate of collapse of obstructed lungs containing oxygen without inert gas is much greater than that of lungs obstructed following ventilation with air.[30] This being the case, the questions most pertinent to the prolonged use of pure oxygen by man relate to the development of diffuse atelectasis during spontaneous normal breathing and to the ease of reversing any alveolar atelectasis which may, in fact, occur. Should obstruction of bronchioles prove to be not readily reversible in normal in-

dividuals breathing pure oxygen at one atmosphere, a progressive atelectasis would be induced by effects of chemical oxygen toxicity and also by the complicating physical consequences of a low total gas pressure in mixed venous blood. Should irreversible, diffuse atelectasis occur, the end result would be arterial anoxemia due to excessive shunting of blood across the lungs via those pulmonary capillaries supplying collapsed alveoli.

Oxygen Breathing at Reduced Pressure:—It is quite possible that the physical problems concerned with absorption of gases from sinuses, middle ear and alveoli will differ at low and high ambient pressures. At low pressures and in the absence of irritative factors leading to bronchospasm or hypersecretion, the physical basis for atelectasis may be grossly altered in importance. As stated above, this condition could be satisfied while breathing pure oxygen at ambient pressures no greater than 187 mm. Hg.[21, 28] For this reason, one of the most critical experiments concerned with selection of the gaseous atmosphere for prolonged, closed-system existence is that involving extended exposure of many normal men to pure oxygen at 187 mm. Hg ambient pressure (about 34,000 feet altitude equivalent) or less to determine whether lack of inert gas in the breathing medium results in the physical problems described and, if they occur, to further determine the factors which either exaggerate or aid in their reversal.

Figure 3B illustrates a prediction of the gas exchange in normal men breathing humidified oxygen at 187 mm. Hg ambient pressure. Insofar as inert gas is absent in alveoli and body fluids, the situation resembles that of pure oxygen breathing at 760 mm. Hg. However, because of the level of reduced ambient pressure selected, alveolar P_{O_2} is now only 100 mm. Hg, and the alveolus contains less than one fifth the mass of oxygen it contains during the breathing of oxygen at one atmosphere. Due to the previously mentioned, small, transpulmonary shunting of blood, total gas pressure in the arterial blood, approximately 182 mm. Hg, is a few mm. Hg less than the total ambient pressure. In the present example most of the oxygen released by the blood to the tissues is derived from the relatively large amounts of oxygen combined with hemoglobin, with little oxygen being provided from that in physical solution. Hence a relatively small drop in P_{O_2} (and therefore in total gas pressure of blood) occurs in the transit of blood from the arterial to the venous end of a tissue capillary. In the particular situation illustrated by Figure 3B the predicted value for total gas pressure in venous blood is close to 135 mm. Hg, or only about 50 mm. Hg lower than the pressure of the ambient atmosphere and alveolar gas. The smaller number of molecules of oxygen contained in an alveolus at reduced pressure should tend to shorten the time required for complete collapse of an alveolus even with a smaller P_{O_2} gradient from alveolus to pulmonary capillary.[30] An additional consideration, with even greater bearing upon tolerance to pure oxygen, is the influence of total ambient pressure upon the reopening of collapsed alveoli. The gas pressure within a completely closed alveolus can be considered to be, not zero, but a gas pressure potentially equal to the sum of the partial pressures of the gases in the adjacent fluids. Thus in oxygen breathing at 760 mm. Hg and at 187 mm. Hg the "potential" gas pressures within collapsed alveoli are 145 and 135 mm. Hg, respectively (see Figure 3A and B). The collapsed and *blocked* alveolus, held closed in part by forces of surface tension, is also prevented from opening by the difference in absolute pressure between the ambient total gas pressure transmitted to the alveolus via body fluids and the "potential" gas pressure of these body fluids. At the low ambient pressure selected this absolute pressure difference is still a considerable 50 mm. Hg, but it is less than one tenth of the approximately 600 mm. Hg total pressure difference expected during oxygen breathing at sea level. It may not be too great to be overcome temporarily by the muscular effort of inhalation; negative intrathoracic pressures of such magnitude may be expected to acompany the inspiratory phase of coughing.[31]

There also exists serious uncertainty regarding the behavior of the bronchopulmonary system when altered by development of bacterial or viral infection.[33] Experimentation under such conditions will be required to determine the ultimate tolerance of man to the breathing of pure oxygen.

It must continue to be asked, "Will incapacitating alveolar atelectasis or sinus and otic barotrauma occur and be sustained during pure oxygen breathing when ambient pressure is low?" and, if alveolar collapse does occur, "Will simple measures such as occasional deep inspiration prevent or even overcome any physical atelectasis brought about through absence of inert gas in the respired medium?" Until recently the occurrence of such alveolar atelectasis at any ambient pressure had been only postulated. It is now known that atelectasis, reversible on return to air breathing, is induced in normal man by the combination of pure oxygen breathing and acceleration.[24] To determine whether such atelectasis will progress or be reversed when oxygen breathing is continued without interruption at reduced ambient pressure after acceleration requires studies in man such as are now in progress.[13, 14, 26, 32] The possible advantages of extreme reduction of ambient pressure as a means of avoiding the necessity for inert gas as a component of his breathing medium in normal man and in the presence of infection can also be evaluated only by experimentation in man himself.

EXTREME REDUCTION OF AMBIENT PRESSURES

The intent of this presentation has been to emphasize not only extreme alteration of gaseous composition, but limits of tolerance to reduction of ambient pressure. A close estimate of the minimal intra-station pressure which can be tolerated by humans can be derived by re-examining the physiological data obtained upon residents of Morococha[16] (Figure 1B). These individuals, chronically acclimatized to air at a pressure averaging 446 mm. Hg, have an inspired P_{O_2} of about 94 mm. Hg. Under these "normal," but extreme, earthbound conditions the acclimatized residents were shown to have arterial P_{O_2} and P_{CO_2} levels averaging 45 and 35 mm. Hg, respectively.[16] An atmosphere of pure

oxygen at a pressure of 127 mm. Hg should provide arterial P_{O_2} and P_{CO_2} values comparable to those measured in these people during air breathing at their natural altitude. Thus, 127 mm. Hg, equivalent to an altitude of about 42,000 feet, could be considered the near minimum intra-capsular pressure for man, even with prolonged periods of acclimatization and the use of pure oxygen.

Problems Associated with Low Total Gas Pressure:—Use of minimal ambient pressures, either with oxygen breathing or with mixtures containing an inert gas, requires that attention be given to factors such as "bends," duration of consciousness on damage to the compartment or controls, tolerance to acceleration, and need for acclimatization to low inspired P_{O_2}. With adequate removal of inert gas from the tissues prior to or during initial decompression, "bends" should not interfere with attaining minimal pressures compatible with adequate oxygenation. However, to function effectively at the minimal ambient pressure cited, man would require acclimatization to low inspired P_{O_2}, again either prior to or in the course of intra-station residence. While such measures may be unnecessary for flights of only a few weeks duration, the eventual extension of manned space flight to many months may require means whereby man can be temporarily altered to aid in accomplishing the mission.[21]

METHODS OF ACCLIMATIZATION

Prolonged Exposure to Low Inspired P_{O_2}:—It is usually considered that full acclimatization to low ambient P_{O_2} can be accomplished only by prolonged sojourn in an atmosphere low in oxygen pressure, as by residence at high altitude.[16] However, many of the physiological changes responsible for acclimatization can result from exposure to reduced pressure in an altitude chamber. The latter form of induced acclimatization was experimentally accomplished by Houston and Riley. In an exhaustive study four subjects were exposed to gradually decreasing air pressure in a decompression chamber reaching the altitude of twenty thousand feet in about three weeks where the subjects remained for an additional ten days.[15] The data of this study should be of considerable value in predicting physiological trends during pre-flight or intra-station acclimatization.

Acute Acclimatization:—It now also appears possible to bring about the immediate acclimatization of normal men to certain effects of low inspired P_{O_2}. This has been carried out both during administration of gas mixtures low in oxygen concentration[20] and during oxygen inhalation at 39,000 feet simulated altitude (147 mm. Hg)[28] without pressure breathing. On the basis that acclimatization involves not only primary responses to diminished oxygen tension but secondary alterations in acid-base balance, 30 per cent carbon dioxide has been added to the inspired oxygen at low ambient pressure to prevent the hypocapnia normally associated with arterial anoxemia and thus the respiratory alkalosis which often prominently contributes to the symptoms of mountain sickness. By preventing hypocapneic cerebral vasoconstriction, brain oxygenation was maintained at a higher level than existed without the addition of carbon dioxide to the inspired gas.[20, 28] Together with previous indications that tolerance to high altitude is improved when carbon dioxide is added to the oxygen inspired,[11, 18] such studies of acute "acclimatization" to anoxia emphasize the desirability of additional studies aimed at eliminating the need for a prolonged period of adjustment to low inspired P_{O_2}. By such means it may become possible to increase the rate at which man can reach the lower limit of tolerable ambient pressure.

UTILIZATION OF GASEOUS WASTES OF METABOLISM

It appears from examples such as the foregoing that metabolically produced carbon dioxide, normally considered only a troublesome waste product, may be useful in improving the habitability of or in solving certain engineering problems of manned, extra-atmospheric vehicles.[22] The uses of carbon dioxide, in addition to further lowering the limit of physiologically tolerable compartment gas pressure during air or oxygen breathing, could include: cycling of P_{CO_2} levels for purposes of periodic central nervous system arousal,[21, 22] maintaining high percentages of carbon dioxide to slow combustion rates in order to reduce the efficiency required by carbon dioxide removal systems, and accelerating of oxygen generation in photosynthetic systems. Although in some areas of a capsule carbon dioxide could be considered useful as an inert gas, in the human body its relation to acid-base balance and respiratory control obviates utilizing the molecular features of this gas.

Other gaseous wastes of metabolism, including carbon monoxide, hydrogen sulfide, ammonia, hydrogen, and methane, are less adaptable to useful purposes in closed systems than are carbon dioxide and water vapor. CO, H_2S, and NH_3 are physiologically reactive and toxic in low concentrations. While both hydrogen and methane are inflammable, neither reacts chemically with body fluids and, if it should become necessary to employ an inert gas in the breathing medium for flights of more than a few months duration, the use of one of these wastes at a controlled, low non-explosive concentration may have to be considered. The possible advantages of the inert gases of our natural atmosphere are also under consideration.

CYCLIC ALTERNATION OF GASEOUS ENVIRONMENTS

Along with pulmonary intolerance to oxygen, one of the prominent difficulties that will be encountered in the closed system existence of prolonged flight or space station residence is loss of valuable gas by leakage. Here the interests of physiology and engineering blend completely and the concept of "extremes of gaseous environment" takes on broader meaning. If an inert gas is necessary to prevent pulmonary pathology and sustain life, the progressive loss of a non-regeneratable inert gas from a closed system may be the limiting factor in manned space flight. Without the inert gas, systemic anoxia due to pulmonary changes may terminate flight even in the presence of high, intracapsular P_{O_2} and

abundant oxygen stores. It is in this area that gains may be accomplished by planned and purposeful, but possibly irregular, alternation from one extreme of gaseous environment to another.

Controlled fluctuation of carbon dioxide tension has been mentioned. However, changing the oxygen and any inert gas composition of a spacecraft may offer more generally useful physiological gains for several important reasons. Both the chemical form of oxygen toxicity and the physical collapse of alveoli have finite latent periods; each also has a finite recovery rate on resumption of exposure to an atmosphere containing an inert gas and having a low or normal oxygen tension. When sufficient information has been obtained regarding these latent periods and recovery rates, alternation of oxygen with inert gas-oxygen mixtures should reduce the loss of inert gas while most effectively utilizing its desirable physical and physiological properties. Studies should be made to determine the best sequence for cycling gaseous composition and pressure to (a) prevent bends in the event of explosive decompression on take-off (pre-flight oxygen breathing), (b) prevent pulmonary atelectasis on take-off or re-entry (brief period on inert gas-oxygen mixture), (c) minimize inert gas loss and prevent bends on explosive decompression in flight (maximum period on extreme upper limit of oxygen concentration), (d) prevent or reverse pulmonary atelectasis or even chemical oxygen toxicity (recovery during minimal period of exposure to inert gas-oxygen mixture at low ambient pressure). The advantages of alternating oxygen and an inert gas-oxygen mixture to prevent oxygen toxicity and bends in animals during exposure to *increased* ambient pressures have been described.[17, 27]

SUMMARY

When an engineer asks a physiologist "What is the gaseous environment required by man?", clearly the answer will depend upon the expected duration of exposure to the environment and man's tolerance to the stresses involved. Even on earth man lives and functions in natural environments varying widely in pressure, temperature, humidity, P_{N_2} and P_{O_2}. Certain extremes are tolerated only by virtue of specific physiological adjustments which can be considered normal for the particular environment. Thus, there is a broad range of natural environments to which man has been able to adapt. In addition, man is extending his areas of operation by use of artificial atmospheres which support his existence in aviation and early spaceflight, in direct exposure to the pressure of 1000 feet of sea water and in prolonged periods of residence under the sea.[35]

Where it is desirable, from an engineering standpoint, advantage should be taken of the intrinsic adaptability of man which permits him to experience gross alterations of his external environment while sustaining an internal environment adequate for the effective functioning of his cells. As interest in extending the duration of extra-atmospheric existence increases, attention will have to be given not only to the extremes of total pressure, to the partial pressure and percentage of oxygen, and to the physiological problems associated with absence of an inert gas in respired mixtures, but also to further limits made tolerable as a result of slow or rapid alteration of man and to the consequent desirability of utilizing these different environmental extremes in purposeful sequence.

The potential interactions of physiological factors in attaining these extremes are beyond simple deduction; much new knowledge will have to be obtained.

REFERENCES

1. Barcroft, J.: Architecture of Physiological Functions, Cambridge, Eng.: Cambridge Univ. Press, 1934.
2. Barker, E. S., Pontius, R. G., Aviado, D. M., Jr., and Lambertsen, C. J.: Comparative evaluation of several methods for determining alveolar gas tensions in man. *Federation Proc.*, 8:7, 1949.
3. Bartels, H., Beer, R., Fleischer, E., Hoffheinz, H. J., Krall, J., Rodewald, G., Wenner, J., and Witt, I.: Bestimmung von kurzschlussdurchblutung und diffusionskapazitat der lunge bei gesunden und lungenkranken. *Arch. ges. Physiol.*, 261:99, 1955.
4. Bean, J. W.: Effects of oxygen at increased pressure. *Physiol. Rev.*, 25:1, 1945.
5. Becker-Freyseng, H., and Clamann, H. G.: Die wirkung langdauernder sauerstoffatmung in verschiedenen hoehen auf den menchen. *Luftfahrtmed.*, 7:272, 1943.
6. Bohr, C.: Uber die spezifische tatigkeit der lungen bei der respiratorischem gassaufnahme und ihre verhalten zu der durch die alveolarwand stattfindenden gasdiffusion. *Scandinav. Arch. Physiol.*, 22:221, 1909.
7. Comroe, J. H., Jr., Dripps, R. D., Dumke, P. R., and Deming, M.: Oxygen toxicity; effects of inhalation of high concentrations of oxygen for 24 hours on normal men at sea level and at simulated altitude of 18,000 feet. *J.A.M.A.*, 128:710, 1945.
8. Fasciolo, J. C., and Chiodi, H.: Arterial oxygen pressure during pure O_2 breathing. *Am. J. Physiol.*, 147:54, 1946.
9. Fenn, W. O., Rahn, H., and Otis, A. B.: A theoretical study of the composition of the alveolar air at altitude. *Am. J. Physiol.*, 146:637, 1946.
10. Hall, A. L., and Martin, R. J.: Prolonged exposure in the Navy full pressure suit at "space equivalent" altitudes. *Aerospace Med.*, 31:116, 1960.
11. Hall, F. G., and Hall, K. D.: Effect of adding carbon dioxide to inspired air on consciousness time of man at altitude. *Proc. Soc. Exptl. Biol. Med.*, 76:140, 1951.
12. Haugaard, N., Hess, M. E., and Itskovitz, H.: The toxic action of oxygen on glucose and pyruvate oxidation in heart homogenates. *J. Biol. Chem.*, 227:605, 1957.
13. Helvey, W. M., et al.: Effects of Prolonged Exposure to Pure Oxygen on Human Performance. Final Report on NASA Contract NASr-92, Republic Aviation Corp., 1962.
14. Hendler, E., D'Amato, H., and Highly, F. M.: Rapid Decompression Hazards After Prolonged Exposure to a 50% O_2-50% N_2 Atmosphere. Final Report on NASA Order R-40, Air Crew Equipment Laboratory, US Navy Base, Philadelphia, Penna., 1962.
15. Houston, C. S., and Riley, R. L.: Respiratory and circulatory changes during acclimatization to high altitude. *Am. J. Physiol.*, 149:565, 1947.
16. Hurtado, A., Valasquez, T., Reynafarje, C., Lozano, R., Chavez, R., Aste-Salazar, H., Reynafarje, B., Sanchez, C., and Munoz, J.: Mechanisms of Natural Acclimatization. Studies on the Native Resident of Morococha, Peru, at an Altitude of 14,900 Feet, USAF, SAM Report 56-1, 1956. Also *in* Benson, O. O., and Strughold, H. (ed.): Physics and Medicine of the Atmosphere and Space, New York: Wiley, 1960.
17. Kaufman, B. D., Owen, S. G., and Lambertsen, C. J.: Effects of brief interruptions of pure oxygen breathing upon central nervous system tolerance to oxygen. *Federation Proc.*, 15:107, 1956.

18. KLINE, R. F.: Increased tolerance to severe anoxia on carbon dioxide administration. *Am. J. Physiol.*, 151:538, 1947.
19. LAMBERTSEN, C. J.: Respiration, *in* BARD, P. (ed.): Medical Physiology, 11th ed., St. Louis: C. V. Mosby, 1961.
20. LAMBERTSEN, C. J.: Oxygen, Carbon Dioxide and Helium, *in* DRILL, V. A. (ed.): Pharmacology in Medicine, 2nd ed., New York: McGraw-Hill, 1958.
21. LAMBERTSEN, C. J.: From submarines to satellites. *Circulation Research*, 6:405, 1958.
22. LAMBERTSEN, C. J.: Physiology and Pharmacology of Extra-atmospheric Flight. I. Environmental and Physiological Interactions in Sustained, Extra-atmospheric flight. II. Isolation and Weightlessness. National Academy of Sciences—Air Research and Development Command Special Study, 1958.
23. LAMBERTSEN, C. J.: EWING, J. H., KOUGH, R. H., GOULD, R., and STROUD, M. W., 3RD.: Oxygen toxicity. Arterial and internal jugular blood gas composition in man during inhalation of air, 100 per cent O_2 and 2 per cent CO_2 in O_2 at 3.5 atmospheres ambient pressure. *J. Appl. Physiol.*, 8:255, 1955.
24. LEVY, P. M., JAEGER, E. A., STONE, R. S., and DOUDNA, C. T.: Aeroatelectasis: A respiratory syndrome in aviators. *Aerospace Med.*, 33:988, 1962.
25. MACHATTIE, L., and RAHN, H.: Survival of mice in absence of inert gas. *Proc. Soc. Exptl. Biol. Med.*, 104:772, 1960.
26. MORGAN, T. E., ULVEDAL, F., and WELCH, B. E.: Observations in the SAM two-man space cabin simulator. II. Biomedical aspects. *Aerospace Med.*, 32:591, 1961.
27. PENROD, K. E.: Effect of intermittent nitrogen exposures on tolerance to oxygen at high pressures. *Am. J. Physiol.*, 186:149, 1956.
28. PIERCE, E. C., LAMBERTSEN, C. J., STRONG, M. J., ALEXANDER, S. C., and STEELE, D.: Blood Pco_2 and brain oxygenation at reduced ambient pressure. *J. Appl. Physiol.*, 17:899, 1962.
29. RILEY, R. L., and COURNAND, A.: "Ideal" alveolar air and the analysis of ventilation-perfusion relationships in the lungs. *J. Appl. Physiol.*, 1:825, 1948-49.
30. ROBERTSON, W. G., and FARHI, L. E.: Effects of ambient pressure on the rate of collapse of the rat's lung. *Physiologist*, 4 (Aug.):95, 1961.
31. ROSS, B. B., GRAMIAK, R., and RAHN, H.: Physical dynamics of the cough mechanism. *J. Appl. Physiol.*, 8:264, 1955.
32. WELCH, B. E., and CLAMANN, H. G.: Personal communication.
33. Gaseous Environment for Manned Spacecraft. A Report of the Study Group on Gaseous Environments. DUBOIS, A. B. (chairman): Man in Space Committee, Space Science Board, National Academy of Sciences, 1962.
34. SYMPOSIUM: Oxygen Tension, COMROE, J. H., JR. (chairman): *Federation Proc.*, 16:665, 1957.
35. WORKMAN, R. D., BOND, G. F., and MAZZONE, W. F.: Prolonged Exposure of Animals to Pressurized Normal and Synthetic Atmospheres, US Naval Medical Research Laboratory, US Naval Submarine Base, Groton, Conn., Report No. 374, 1962.