PHYSIOLOGY IN THE SPACE ENVIRONMENT

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VOLUME II
Respiration

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SPACE SCIENCE BOARD
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NATIONAL RESEARCH COUNCIL
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FOREWORD

At the request of the Office of Advanced Research and Technology of the National Aeronautics and Space Administration, studies were undertaken in two areas of biomedical research germane to the space program: respiratory physiology and cardiovascular physiology. The two study groups were charged with determination of the current state of knowledge in their field, the assessment of problem areas related to space travel, and the course of future research to implement space travel. The products of these two studies are presented in separate volumes.

Other reports, such as the Space Medicine Advisory Group Study of 1966* and the Space Science Board Summer Study of 1965,† deal with general problems in the biomedical area. Also, there have been a large number of specific studies in the biomedical area, and these are referenced where pertinent in the papers in this volume. In addition, the U.S. Air Force, in support of its Manned Orbiting Laboratory (MOL) Program, has undertaken a study of the specific problems and possible applications of remedial measures in pertinent biomedical areas. By delineating specific areas, it is intended that the two volumes

*Medical Aspects of an Orbiting Research Laboratory, NASA Special Publ. 86, 1966. (Available from Superintendent of Documents, U.S. Government Printing Office, Washington, D.C., price $1.00.)

†Space Research: Directions for the Future, NAS - NRC Publ. 1403, 1966. (Available from Printing and Publishing Office, National Academy of Sciences, 2101 Constitution Avenue, Washington, D.C., price $7.50.)

from the 1966 conference be more comprehensive and suggest longer-range research with approaches that require extensive planning to assure the long-range result.

The selection of participants for the summer conference was guided by the need to cover areas of specific interest to the space program and to involve a number of scientists who are not directly concerned with space biomedical research, as well as many who have, or have had, contact with the program.

This volume deals with the respiratory physiology and relevant medical problems. Present and applied problems, including medical questions such as infection and toxicology, are discussed. In addition to the rather specific discussion and recommendations concerning the practical and applied problems, this report also suggests a number of basic experiments, such as experiments to validate the predicted changes in pulmonary function, especially the ventilation-to-perfusion ratio, in different regions of the lung.

The report indicates that no striking effects have been noted in respiratory function in space flight to date, nor is there expectation of any debilitating effect from prolonged space flight. There are problems introduced by the artificial environment and other supportive mechanisms that are necessary for maintenance of man in space.

I am especially indebted to all those who participated in the summer study, particularly to Dr. Robert E. Forster who was Chairman of the group in Respiratory Physiology, to Dr. Frank G. Favorite who was the National Academy of Sciences' Space Science Board Secretariat Representative in the Respiratory Group, and to the National Aeronautics and Space Administration and U.S. Air Force participants who contributed greatly to the effort.

It is hoped that this report will carry the challenge of space physiology to scientists in the discipline areas related to physiological investigation of the respiratory system.

Loren D. Carlson
Conference Chairman

SPACE SCIENCE BOARD

CONTENTS

PART I

INTRODUCTION, SUMMARY AND RECOMMENDATIONS

ROBERT E. FORSTER*

1

INTRODUCTION

Respiratory physiological considerations of manned space flight have been under review by various working groups of the National Academy of Sciences' Space Science Board from time to time since 1961. A working group of the Board's Man in Space Committee held meetings on the subject in 1961 and 1962. In April 1963, under the sponsorship of the American Physiological Society, a symposium, Respiratory Physiology in Manned Spacecraft, was held in Atlantic City, and the symposium papers were published by the Federation of American Societies for Experimental Biology in August 1963. Respiratory physiology was also the subject of a study by the Board's Working Group on Gaseous Environment for Manned Spacecraft in 1964.

Late in 1965 the National Aeronautics and Space Administration (NASA) asked the Space Science Board to look into the problems of respiratory physiology associated with long-duration manned space flights, that is, flights of 30 to 60 days and even of a year or more. The Board, drawing upon academic institutions for the membership of its study group, held the initial sessions in Washington on May 23 and 24, 1966; working sessions were held at Woods Hole, Mass., for the two-week period from June 24 to July 8, 1966; and between that time and January 1967 reviews of the study were under way.

With the development of space exploration, man's role in space flight is becoming increasingly complex and of longer duration. While his participation has never been entirely passive,

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the future will demand of him even more physical and mental involvement in the performance of the flight and its exploratory objectives. At this point in time, he has experienced a maximum of 14 continuous days in space flight, orbiting the Earth at a distance of several hundred miles. Nevertheless he has been able, if the need arose, to return to Earth within an hour or two of the decision to do so. He has spent up to 56 days in Earth-based experimental chambers where almost all conditions of space flight, except weightlessness, can be simulated.

Within a few years man will be orbiting the Earth for extended periods and will have made an initial two-week voyage to the Moon, a distance of approximately a quarter of a million miles from Earth. It is anticipated that within this decade man will be orbiting the Earth for periods of 60 to 90 days, and within two decades he may be orbiting or landing on the nearer planets—voyages lasting one to two years.

To realize these objectives, man must be placed in an artificial environment and furnished with all the necessities of life such as a breathing gas, adequate pressure, nutrition, hygienic facilities, and psychological satisfaction. In principle, these requirements for space travel vary little from those for prolonged submarine voyages, manned exploration of the ocean depths in diving bells, and stratospheric balloon and aircraft flights; in practice, long-duration space missions require significantly higher equipment reliability and confront man with psychological stresses that cannot be simulated at or near the Earth.

The absence of the Earth's gravity is, however, unique to space travel, and there has been much speculation on how its absence will affect the functioning of the human organism. Some have considered that it may be necessary to provide artificial gravity, by centrifugal force for instance, for long-term space flights. While this may yet prove to be necessary, it is very unlikely that the requirement will be dictated on the grounds of respiratory physiology. In many respects pulmonary function will be optimal in the weightless state. The only serious effect of weightlessness on the respiratory system that is anticipated is the increased possibility of aspiration of particulate matter; this problem can be handled better, however, by reducing the particulate matter in the ambient air than by producing artificial gravity. Nevertheless, the possible role of the volume changes in thoracic structures, affecting the capacitance and blood volume of the systemic circulation, has to be considered within the general area of deconditioning.

Acceleration and deceleration forces are significant constraints to man's exploration of space. His lungs cannot tolerate more than 10 G—ten times the force of gravity on earth—and that level only within the time limits of breath holding,

unless there is some deliberate alteration of the lungs' normal state. Above this level, at about 12 to 14 G, tissue of the normal lung tears and blood vessels rupture.

The conferees defined 16 major topics related to respiratory physiology in manned space flight for review. Summaries of the conference deliberations, recommendations, and needs in bioinstrumentation are presented in Part I, Chapter 2. Parts II, III, and IV consist of papers treating in some detail each of the 16 chosen topics. Conference participants are listed in the Appendix.

2

SUMMARY AND RECOMMENDATIONS

This chapter presents a summary of the deliberations on each of the major topics considered at the conference. Each summary concludes with a series of recommendations. The recommendations vary from specific objectives to general observations on research problems.

Special needs occur in the area of bioinstrumentation for manned space flight. At the end of this chapter some of the more urgent needs are listed.

SUMMARY OF CHAPTERS

Structural Changes in Lung and Thorax (Chapter 3)

While there is no apparent reason to expect prolonged space flight to cause changes in primary lung structure, general deconditioning of the body could extend to the thoracic cage and muscles, altering the mechanics of ventilation. Such factors as radiation, inhalation of particulates and contaminants, and possible tissue damage resulting from higher than normal P_{O_2} could lead to cellular changes in the lungs.

Recommendations

1. Quantitative histological techniques should be applied to the lung to determine changes of its cellular structure.

2. The effects of acceleration deformation and damage should be studied, with the use of rapid freezing techniques, and should include such problems as airway trapping, atelectasis, fluid transudation, hemorrhage, and tissue rupture.

3. Functional, structural, and chemical analyses of the lungs should be made on animals exposed to various patterns of simulated space radiation.

Respiratory Mechanics (Chapter 4)

Sufficient acceleration will limit or prevent lung movements during launch, but such periods will probably not exceed the limits of breath holding. The mechanical strength of the lung may place a limit on the accelerative forces to which the human body can safely be subjected. Probably the pulmonary blood vessels would rupture before the parenchyma tore. During zero G, changes in lung mechanics would be minimal. One would predict a decrease of about 20 percent in end-expiratory lung volume and a resulting small decrease in airway conductance. Inspiration of particulate matter might be more common, in which case the cough mechanism is more important. On theoretical grounds, the air velocity with a cough would probably be greater, but the decreased density of the gas might make the cough less effective.

Recommendations

1. Vital capacity and lung volume should be measured under flight conditions. A method of measuring expired gas volumes will be needed, possibly a waterless spirometer.

2. The mechanism of coughing should be examined under conditions of low ambient pressure.

3. The mechanical strength (tear strength) of the lungs should be investigated under acceleration stress. This might be done in cadavers.

4. The variation in individual susceptibility to and rate of recovery from atelectasis under acceleration while breathing atmospheres containing low concentrations of inert gases and complicating infections should be studied.

Pulmonary Gaseous Diffusion (Chapter 5)

There is no reason to suppose that gaseous-diffusion processes will be affected by zero G, unless the lung parenchyma sustains chronic or acute damage secondary to accelerations at launch or re-entry.

Recommendations

The pulmonary diffusion capacity should be investigated as a general test of lung function in space flight. It should give a convenient estimate of changes in the lung that might make reentry dangerous, such as those secondary to toxic contaminants in the cabin atmosphere, parenchymal changes due to increased oxygen tension, and changes in the pulmonary vasculature secondary to weightlessness.

Pulmonary Circulation and the Distribution of Blood and Gas in the Lungs (Chapter 6)

Prolonged space travel appears to offer no significant problems in this respect. On the contrary, the relations between blood flow and ventilation are likely to be optimal in the weightless state. Acceleration may produce adverse effects, however, and it is important to be able to evaluate risks and the physiological tolerances involved. Basic knowledge is needed concerning the effect of acceleration on the blood volume and capacitance of the systemic circulation, and of changes of volume in the vascular structures of the thorax presumably caused by reflex and hormonal mechanisms. The effects of gravity are so profound in altering the distribution of blood and gas within the lungs that many problems in basic pulmonary physiology can be studied more effectively under weightlessness than in a normal gravitational field. One of the dividends of space flight will be the opportunity to carry out experiments on the lungs that are impossible on Earth.

Recommendations

1. Distribution of intrapleural pressures and pressures on the surface of the heart and great vessels should be studied during weightlessness.
2. Studies should be made, as a function of gravity, of forces across and within the heart chambers, heart function, and the distribution of blood volume in the thorax and lungs, particularly in the pulmonary artery, lung capillaries, and pulmonary veins.
3. Distribution of blood volume between systemic and pulmonary circuits as a function of gravity should be studied.
4. Reflex and hormonal control of systemic blood volume and pulmonary venous pressure as a function of blood volume in the lung should be investigated.
5. Starling resistor effects upon lung capillaries as they affect filtering, transudation, and the passage of blood-formed elements through the lung capillaries should be studied.

6. Distribution of blood in the lungs should be investigated during transient weightlessness. Injections of labeled macroaggregated albumin might be used for this purpose.

7. Astronauts should be trained to use observations of the veins of the neck in association with respiratory maneuvers as an index of left atrial pressure.

8. Measurements of diffusing capacity, particularly as a function of lung volume, could be used to give an index of overall lung performance and of the distribution of blood in the pulmonary capillaries.

Regulation of Breathing (Chapter 7)

The slight alterations in pulmonary mechanics to be expected under zero G and possible deviations in inspired oxygen and carbon dioxide, depending on the composition of the cabin atmosphere, could affect the level of ventilation through well-known mechanisms. Current knowledge indicates that these effects would be too small to be physiologically significant. Minute volume tends to decrease during acceleration even to the point of apnea, but as long as its duration is brief no more serious stress than that of ordinary breath holding would exist. Hyperventilation can occur under stress, but it is not a problem unique to space flight.

Recommendations

1. Minute ventilation during increased G at launch and reentry and during weightlessness should be monitored both during exercise and at rest.

2. The ventilatory response to exercise and to hyperoxia, particularly in the capsule and in the space suit, should be monitored under chronic conditions.

Exchange of Fluids in Lungs (Chapter 8)

Fluid may enter the lungs through aspiration of secretions or by transudation from the lung capillaries. Such fluids would normally be removed by the various lung-clearing mechanisms, which should operate sufficiently well in space flight. Intentional filling of the lungs or pleural space with liquid to support the pulmonary blood vessels and lung parenchymal tissues during accelerations greater than 15 G may be tried experimentally in anticipation of life-support systems for flights far in the future and for the re-entry phase of the flight.

Recommendations

1. Measurements should be made of those pressures related to filtration of fluid in the lungs, including vascular pressure (pulmonary artery and pulmonary vein), intrapleural and alveolar-gas pressures, and osmotic pressure of the blood as a function of gravitational force.

2. Arterial oxygen saturation and the pressure-volume curve of the lungs should be investigated as indicators of filtration into the tissue.

3. Long-term studies should be carried out to determine the feasibility of liquid ventilation of the lungs or collapsing of the lungs in order to permit surviving high G.

4. Possible changes in the lung surfactant should be studied.

Respiratory Tract Clearance Mechanisms for Nongaseous Materials (Chapter 9)

Three physiological mechanisms keep epithelial surfaces of the respiratory tract relatively free of contaminants: (1) ciliary mucous transport, (2) endocytosis, and (3) lymphatic drainage. Ciliary mucous transport may be affected, probably slightly, by gravity and may also be influenced by the high concentration of ions presumed to exist in space capsules. In vitro and in vivo preparations exist for study of mucous transport and should be employed to test responses under appropriate conditions. There is no evidence that endocytosis is influenced by gravity, but on the other hand there is insufficient data on endocytosis in mammals. Little is known about the role and mechanism of pulmonary lymphatic drainage even under normal gravity conditions.

Recommendations

1. Mucous clearance and sinus drainage as a function of posture, humidity, and drugs at 1 G, zero G, and increased G should be studied.

2. Ciliary preparations (animal trachea) should be used as one means of studying the toxicology of contaminants.

Diffusion of Gases in Peripheral Tissues (Chapter 10)

If translocation of O_2 within tissues is, as most of the evidence suggests, caused purely by diffusion driven by gradients in P_{O_2}, the gravitational field or lack of it should not have any important effect on the diffusion coefficient or on diffusion itself. To insure adequate delivery of O_2 to the tissues, arterial capillary P_{O_2} should be maintained at the normal value at sea level.

Given this condition, adequate oxygenation of tissues will depend on functional capillary blood flow, which determines the volume of tissue supplied by each capillary. The distribution of functional capillary blood flow conceivably can be affected by variations in and lack of gravity.

Recommendations

1. Methods should be applied to assess tissue hypoxia in intact man, including measurement of chemicals in the blood, such as creatine phosphokinase, myoglobin, and growth hormone.
2. Methods for monitoring tissue oxygen tension directly should be investigated.
3. Distribution of peripheral capillary blood flow under flight conditions should be investigated.

Temperature Regulation (Chapter 11)

It is not anticipated that the role of the respiratory system as a heat exchanger will be significantly altered during space travel. If the space cabin atmosphere has a lower total pressure or uses helium as an inert gas, the decreased air density will cause a slight and physiologically insignificant decrease in body heat lost to the inspired air. Except for the possibility of heat hyperpnea under unusual or emergency situations, heat loads encountered in space travel should have minor influence on the level of minute ventilation. The possibility of untoward temperature regulation resulting from altered circulation in the weightless state is conceivable but on the basis of present knowledge is unlikely.

Recommendations

1. The rate of evaporation from the respiratory tract at zero G should be studied.
2. The nature of heat hyperpnea should be elucidated to determine whether it is adaptive to heat exposure.
3. Studies should be made of the redistribution of blood between the periphery and the lungs under heat stress.
4. Circadian periodicity of respiration, diffusing capacity, and other physiological variables should be studied.
5. The desirability of periodically altering the environmental conditions (at least those of temperature and oxygen) should be investigated. It is suggested that measurement on submariners after a long trip could provide such information.

Oxygen Toxicity at Near-Normal Partial Pressures (Chapter 12)

The basic metabolic defect (or defects) associated with the physiological changes caused by O_2 toxicity are still unknown. The literature fails to demonstrate that increased inspired P_{O_2} (at least to 5 psi) is safe for prolonged use by man. Further testing for long periods with human subjects is essential before such a conclusion can be drawn. Normal (sea level) partial pressures of inspired O_2 are known to be acceptable. Reduced partial pressures may also be acceptable, and sometimes unavoidable, but the conditions and limits have yet to be pinpointed.

Recommendations

1. A normal inspired oxygen tension, as contrasted with an elevated inspired oxygen tension, is recommended.
2. The advantages and disadvantages of an inspired P_{O_2} less than normal sea level should be investigated for times adequate to demonstrate a steady-state response. Low inspired P_{O_2} should also be investigated as an emergency mode of operation in the event that the cabin develops leaks or the oxygen supply runs short.
3. The advantages and disadvantages of an inspired P_{O_2} greater than normal sea level should continue to be investigated for times adequate to demonstrate a steady-state response. This does not imply that an elevated inspired P_{O_2} is recommended, but this information should be extremely useful.
4. Cabin P_{O_2} and total pressure should be monitored for a mixed gas environment.
5. The influence of cabin P_{O_2} on the radiation hazard, particularly proton radiation at lower than normal P_{O_2}, should be investigated. The effects of chronic radiation at low levels on the aging of proteins and tissues, such as the lungs, should be studied.

Considerations of Carbon Dioxide Concentration (Chapter 13)

Ideally, from the physiological point of view, it would be best to keep inspired P_{CO_2} close to zero, as it is under normal sea-level conditions. In the manned space flights to date the circulating atmospheric P_{CO_2} has apparently been kept to less than 7.6 torr, although this may be because of engineering (thermal exchange) rather than physiological considerations. A maximum limit of 7.6 torr was chosen because chronic exposure to CO_2 concentrations just above that limit has demonstrated adaptive changes. The effect of chronic exposure to low inspired concentrations of CO_2 should be explored. Furthermore,

a time-concentration-response curve to CO_2 exposure should be obtained to guide procedure in the event that the CO_2-removing equipment fails.

Recommendations

1. The physiological limits of tolerable ambient CO_2 tension, such as would exist if there were a breakdown in the carbon dioxide absorbing system, should be determined. This would be of the nature of a time-concentration-response curve.

2. The inspired (as contrasted to suit or cabin values) and alveolar P_{CO_2} should be measured under flight conditions, both awake and asleep.

3. The effects of inspiring low concentrations of P_{CO_2} (such as 7.6 torr P_{CO_2}) for prolonged periods should be investigated.

Inert Gases (Chapter 14)

Advantages of adding an inert gas or gases to the space cabin atmosphere are that (1) fire danger is reduced; (2) aural and pulmonary atelectasis is inhibited; (3) there is a possible, but unproved, long-term physiological need for at least low pressures of nitrogen; and (4) ventilation and heat dissipation within the cabin may require a total gas pressure greater than the ceiling recommended for cabin P_{O_2}. The only physiological disadvantage is the risk of the gas's producing the bends. There may be engineering disadvantages in that a double monitoring system is required and, depending on cabin leakage, there will be the extra cost of carrying a supply of inert gas. With a possible exception if absolute lack of nitrogen for long periods proves deleterious, a deficit not overcome by helium, there is little to choose between nitrogen and helium. It was concluded that some inert gas should be added, at least until an effective method of controlling fires in 100 percent oxygen becomes available. A pressure of 2 or 3 psia (assuming total pressure remains at 5 psia) is suggested as a reasonable concentration.

Recommendations

1. A two-gas atmosphere is recommended. Given present knowledge, nitrogen would be the first choice as the inert gas's and helium would be the second. However, other inert gases such as neon should be investigated.

2. The desirability of using different concentrations of gas for different circumstances such as pre-launch, in-flight, reentry, and post-flight should be studied.

3. The fire hazard is an important consideration in deter-

mining the presence and concentration of the inert gas in the atmosphere. The detection of fire, or increased temperature in the vehicle, as well as measures for its extinguishment, should be investigated. All considerations should include fires within the space suit. The possibility of rapidly introducing a high concentration of inert gas into the space containing the fire should be considered.

4. The long-term effects of varying concentrations of inert gases should be investigated with the use of animals. Nitrogen concentrations of from 0.5 to 80 percent atm should be included, as well as replacement of nitrogen with helium.

5. Detailed studies of production of the bends, starting from 7 and 5 psi and normal oxygen tensions, should be carried out to delineate the probability of the bends' being produced in going from the cabin atmosphere to a suit at lower pressure.

Trace Contaminants (Chapter 15)

Because the capsule gas is recycled, contaminants that are normally present in only negligible amounts may increase to toxic levels and may concentrate on airborne particulate matter, which in turn will be increased in the absence of the sedimentation process. All the existing and possible atmospheric contaminants in the space capsule, including gases, particles, and infectious agents, have not been identified, nor have their effective concentrations been determined. These contaminants should be monitored and regulated, pre-flight and in-flight (manned), with particular attention to contaminants produced by fire or unusual heat in the vehicle. The threshold limit value (TLV) of tolerance to various contaminants should be determined for continuous exposure, as contrasted with the more usual intermittent exposure, and the possibly additive effect of stress and infection should be included.

Recommendations

1. Trace contaminants, infectious agents, and particles in the cabin atmosphere should be monitored, under both weightless and 1-G conditions, manned and unmanned. These studies should include periods of pre-flight and in-flight after fires, high temperatures, or the use of fire extinguishers.

2. Studies should be carried out on individual hypersensitivity reactions to various trace contaminants in space vehicle environments.

3. The development of a system for more effective removal of contaminants should be continued.

4. Studies with primates or other large animals should be

made on the toxicity of contaminants when in combination or when in conjunction with space flight stresses, or both.

5. The TLV for many of the common trace contaminants should be determined on the basis of a 24-hour-day 7-day-week exposure in small and large animals for extrapolation to man. These studies should include various atmospheric pressures and oxygen tensions as well as various physical stresses and infections.

6. The increase in toxicity of various contaminants because of concentration on the surface of particulate matter should be investigated.

Particulate Matter (Aerosols) (Chapter 16)

In zero G at hypobaric pressure, airborne stability of dusts will be affected by inertial impaction (large particles), by diffusion or deposition by Brownian motion (smallest particles), but not by sedimentation. Interception of fibers (small diameter, great length) may increase in the bronchial tree. A different distribution of aerosol deposition in the respiratory tract is thus anticipated with respect both to particle size and to site. This has important implications for production of pulmonary disability. It is recommended that studies of aerosol composition (size and association of contaminants with various particle sizes) be instituted. Moreover, tests should be made in simulated respiratory tracts to determine the size and site of deposition of aerosols under flight conditions. Additional studies of aerosol-removal methods are also indicated.

Recommendations

1. Additional information should be obtained, under weightless conditions, on the aerosols in the space capsule, particularly the composition of the aerosols and their relation to the atmospheric contaminants present. Special attention should be paid to the particles of the sizes most likely to enter the lungs.

2. Selective samplers should be employed to simulate the deposition characteristics of the upper and lower respiratory tracts under weightless conditions.

3. To remove alkaline carbon dioxide absorbents from the air, filters that remove particles less than 5 μ in size, such as deep-bed filters or an acid scrubber, should be used in the air conditioning system.

4. The deposition of monodispersed particles during weightlessness in a parabolic flight could be studied by single inhalation and exhalation of a suitable suspension.

5. The frequency of aspiration of solid material at zero G and effective measures available for the removal of a foreign body from the respiratory tract should be investigated.

6. The effect of a completely dust-free atmosphere on humans and animals would be of interest.

Infection (Chapter 17)

The likelihood of microbial infections increases with (1) the size of the space crew; (2) less than ideal facilities for personal hygiene over long periods; (3) possibly altered viability of microorganisms, autoflora, and mechanisms of challenge; and (4) individual susceptibility associated with the space cabin environment. It is recommended that the microbial content of the space vehicle be controlled, that consideration be given to selection of space crews on the basis of similar immunological patterns (including cross matching for blood types), and that crews be isolated as a group before the flight both to prevent exposure to infection and to allow cross-immunity to develop.

Recommendations

1. In selecting the crew, consideration should be given to immunological characteristics, including, for example, consideration of tuberculin tests and blood groups.

2. Consideration should be given to extensive pre-flight isolation.

3. Droplet formation and the flora in the vehicle at zero G should be investigated.

4. The routes of infection and susceptibility to infection as a function of cabin environment should be studied at zero G in the space cabin atmosphere.

5. Viability and pathogenicity of organisms in the space cabin environment should be studied.

6. The microbial contents and resistance to infection should be determined in flight.

7. The efficiency of removal of flora from the atmosphere and of disinfecting procedures in the vehicle under in-flight conditions should be investigated.

Respiratory Drugs and Manned Space Flight (Chapter 18)

Space flight conditions may lead to nasal congestion, obstructed sinuses, and the like, and to the increased possibility of inhaling food and large particles. Decongestants and dilators would

probably be needed in such instances. Pulmonary infection would require a battery of therapeutic agents similar to those used at sea level. Otherwise, there appear to be no specific considerations peculiar to space flight. A critical review of possible problems and of the methods by which drugs have been selected, tested, and dispensed, indicates that the subject needs thorough study and, possibly, continuing evaluation by an advisory board.

Recommendations

1. Many types of drugs, particularly those that affect respiration and respiratory structures, and the closely allied cardiovascular responses should be investigated in primates during the condition of weightlessness.
2. A panel of experts should be established to study space flight data and the use of drugs by astronauts. This or another group should advise in the establishment of the basic medical training needed for certain types of missions and those missions on which a properly qualified physician must be carried. The study of isolated small groups in which self-medication problems are experienced should be initiated.

SUMMARY OF NEEDS IN BIOINSTRUMENTATION

During the conference deliberations there were frequent instances where the need for a measurement was recognized but no suitable method or instrument capable of making the measurement was known to exist. Bioinstrumentation requirements of greatest need include:

1. An instrument to measure inspired and expired gas volumes such as a waterless spirometer to be connected to the airway. This should be usable for the breath-holding measurement of pulmonary diffusing capacity.
2. A method for measuring lung volume changes while performing work (1) free in the cabin, and (2) when in the pressure suit, without obstructing the mouth. An instrument that measures movements of the chest wall might fulfill the purpose, or an instrument that records minute pressure changes in the cabin atmosphere, sensitive to a few hundredths of a torr, might also be used. (There is an increase in volume and therefore in total pressure in a closed space if gas is inhaled, because it is both warmed and wetted.)
3. An instrument to measure the number and size of particles suspended in the air, including the full range of sizes that

might be deposited in the lung, and similarly to monitor the particles in the inspired and expired breath. This same instrument or a separate one should monitor organisms in the air.

4. An instrument to analyze a wide range of possible contaminants in the cabin atmosphere. This instrument should also be able to analyze the gases needed for the diffusing capacity. An instrument to monitor cabin-inspired P_{CO_2} and P_{O_2} might or might not be done by the same apparatus.

5. A method of estimating capillary blood flow in the periphery, such as the use of reactive hyperemia, external counting of radioisotopes, or other techniques.

6. A method for estimation of peripheral oxygen tension.

7. A method of fighting fires in a 100-percent-oxygen atmosphere.

PART II
THE LUNGS

NORMAN C. STAUB

3

STRUCTURAL CHANGES IN LUNG AND THORAX

THORAX AND DIAPHRAGM

General deconditioning of the body, especially of the musculoskeletal system, could extend to the thoracic-cage bony structures and to the muscles of breathing under conditions of prolonged space flight with its potential weightlessness, decreased work of breathing, and resulting decalcification.

While gravity is a factor in mechanical ventilation of the lung, it does not appear to be a major one. Estimates of changes in the work of breathing (see Chapter 4, p. 26) suggest only slight decreases. The magnitude of the problem of loss of thoracic musculoskeletal strength and power as a general manifestation of astronaut deconditioning in space flight is unknown. Studies of bone demineralization (Mack et al., 1966) in astronauts show measurable density changes (equated with calcium loss) within a few days. The current hope is to prevent such losses through proper attention to exercise and diet. In summary, current knowledge suggests that thoracic-cage structural changes will not be significant unless they are part of general body deconditioning. It would, of course, be desirable and relatively simple to examine chest wall structure and function immediately after successively longer space flights.

LUNG STRUCTURE

There is no known theoretical reason to expect any primary changes in lung structure as a result of prolonged space flight. Usual mechanical lung ventilation is not markedly gravity dependent except for the transient distortions during acceleration at launch and during re-entry. Data up to this time suggest that acceleration effects are reversible and not cumulative (Banchero et al., in press). A similar study by Korolev (1964), however, showed persistent changes in dogs exposed to + G_x (8 G × 3 min or 12 G × 1 min). He found focal hemorrhagic edema up to 24 hours, patchy bronchopneumonia after 3 to 7 days, and focal scarring at 1 to 2 months.

Several secondary factors that might affect lung cellular structure are listed below. (See pertinent chapters in this volume for more detailed discussions.)

O_2 Toxicity

Changes in lung structure due to breathing 100 percent O_2 at 760 mm Hg are well described in animals (Schulz, 1959; Kistler et al., 1965). Physiological studies indicate that similar events probably occur in man. Whether the changes result from direct actions of O_2 on lung tissue or indirect actions via autonomic reflexes is uncertain. P_{O_2} of lung-tissue slices is relatively insensitive to high-pressure O_2 in short-duration experiments.

There are few data on the effects of the slightly hyperoxic levels currently used in space cabin atmospheres (258 mm Hg P_{O_2}). Hagebusch (1966) reported some increased bronchitis and pneumonitis in dogs after continuous exposure for 235 days. In the same report, however, he stated that monkeys showed no evidence of toxic effects. Kistler et al. (1966) found no electron microscopic evidence for oxygen toxicity in rats after 1, 5, and 14 days of breathing an inspired (P_{O_2}) equal to the ambient pressure (P_b) of 258 mm Hg. They did infer an O_2 effect on lung growth and development, but were careful to dissociate it from evidence of toxicity. Felig (1965) found liver and kidney mitochondrial changes in rats at $P_{IO_2} = P_b = 258$ Hg for 1 week but no pulmonary pathology.

Pollutants

With the multitude of known and unknown trace contaminants in space cabin air, any variety of lung reactivity, from acute

inflammation to neoplasia to degeneration, is possible. Severe pulmonary hypersensitivity reactions to inhaled agents and immunochemical changes have recently been recognized. Such effects could develop during long flights or years afterward, thus decreasing life expectancy.

It would be a nearly endless task to test every identifiable pollutant. Proper cleansing and testing of the total atmosphere on animals and humans for successively longer periods seem to be the reasonable approach.

Infection

The pulmonary response to infection should be the same as on Earth, although some distributional alterations might be expected.

Radiation

Early deaths (under 60 days) from acute massive exposures to ionizing radiation are mainly due to the destruction of bone marrow and gastrointestinal epithelial tissues. Direct damage to the lungs, while it may occur, has never been implicated.

Late effects on man of continuous low-level radiation are not known, but extrapolations from animals suggest a linear decrease in life expectancy with total accumulated dose (Langham et al., 1965). The lungs, however, have not been mentioned as playing a significant role. Whether the radiation-aging effect (Curtis, 1963) involves the lungs is unknown.

Other

Clearance of pulmonary microemboli, a normal lung function, is not completely understood. It is possible that such embolizations would be more frequent in long-term space flight. The possibility of loss of alveolar nutrition with consequent depression of metabolism, even focal necrosis, should be kept in mind.

Interactions

The combined effects on the lungs of space flight factors cannot be predicted. The problem should probably be approached pragmatically, by total system testing during progressively longer space flights by both animals and humans.

RESEARCH PROBLEMS

Considering the advances in pulmonary pathological technique within the past 10 years, it should be easy to perform very sophisticated lung structural studies on animals. There are several methods for quantitative histology that can be used instead of 1 to 4+ subjective grading. In addition, investigators should use animals that have lung structure reasonably similar to humans', and these animals should be free of endemic lung disease.

Study of acceleration deformation and damage to lung structure during and after centrifuge runs, with the use of rapid freezing in the centrifuge to prevent posttest tissue changes, would help to clarify such problems as airway trapping, atelectasis, fluid transudation, hemorrhage, and lung tissue rupture.

In animals exposed to various patterns of simulated space radiation, functional, structural, and chemical analyses of the lungs should be made.

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JERE MEAD

4

RESPIRATORY MECHANICS

Aspects of respiratory mechanics of interest to prolonged space flight include lung volume, airway conductance, coughing, atelectasis, and lung tearing at high-G forces. Apart from those alterations produced by transients of increased G, the effects of space flight factors on respiratory mechanics should be minor and comparatively innocuous. Atelectasis may prove to be a problem, but because its occurrence should not be much influenced by the weightless state, ground-based investigations should be sufficient to determine the likelihood and long-term effects of this condition.

LUNG VOLUME

In the upright posture at 1 G, the weight of the abdominal contents pulls the diaphragm downward and tends to increase lung volume, while in the supine posture at 1 G the abdominal contents press against the diaphragm and tend to decrease lung volume. The effect of weightlessness on the influence of the

abdominal contents was simulated by Agostoni and Rahn (1960) by having subjects immersed in water to the top of the abdomen. As would be expected, lung volumes at resting end-expiration were found to be intermediate between those in the upright and supine postures at 1 G.

In relation to total lung capacity (TLC), that is, lung volume

at the peak of a maximally deep inspiration, lungs at 1 G are about one half inflated during quiet breathing in the upright posture and about one third inflated in the supine posture. End-expiratory volumes in the weightless state should be in the neighborhood of 40 percent of TLC. Accordingly, the difference in lung volume between the upright posture at 1 G and the weightless state may be expected to be modest.

AIRWAY CONDUCTANCE

A decrease in lung volume from 50 to 40 percent (TLC) would result in about a 20-percent decrease in airway conductance (Briscoe and DuBois, 1958). When the influence of gas density is added, it may be estimated that airway conductance in the weightless state at a total gas pressure of oxygen of 5 psi should be approximately 2.5 times that in the upright posture at 1 G. This estimate is derived as follows: The specific gravity of oxygen in relation to air being 1.1, the relative density of oxygen at 5 psi to air at 15 psi is approximately 0.36. Over the range of the total pressures that have been studied experimentally, airway conductance varies approximately inversely with gas density (Mead, unpublished observations; Marshall et al., 1956). This approximation assumes no change in gas viscosity. Since gas viscosity is essentially independent of total pressure, and since the viscosity of oxygen is only 10 percent greater than that of air, this approximation should hold for breathing 100 percent oxygen at 5 psi. Accordingly, airway conductance should be increased approximately 180 percent at the same lung volume. Combining the influences of lung volume and gas density, it may be expected that airway conductance would be increased by about 150 percent. This change is probably not of functional significance. It is comparable to changes in airway conductance experienced in everyday living. For example, greater changes in airway conductance due to changes in the nasal passages are readily tolerated; merely switching from nose to mouth breathing increases airway conductance nearly 100 percent. The implications of the increase in airway conductance to the control of breathing are discussed in Chapter 7.

COUGHING

One possible harmful effect of reduced gas density might be a diminished effectiveness of the cough. Flow during coughing

equals the maximal expiratory flow rate at the given lung volume. Driving pressure during coughing can be assumed to be the same at different total ambient pressures. Under these circumstances,

$$\text{driving pressure} = \text{constant} \times \text{density} \times (\text{flow rate})^2. \quad (1)$$

Solving for flow rate,

$$\text{flow rate} = [\text{driving pressure}/(\text{constant} \times \text{density})]^{1/2}. \quad (2)$$

Because the gas density is less at 5 psi by 0.36 as compared with 15 psi, the flow rate should increase by the factor

$$1/(0.36)^{1/2} = 1.67. \quad (3)$$

Therefore, at 5 psi, gas flow during coughing should increase by about two thirds, and, for the same degree of airway compression, linear velocities should be increased by the same amount. The kinetic energy of the flowing gas, which is directly proportional to gas density and to the square of linear velocity, would in such a case be unchanged. But in all likelihood, factors other than the kinetic energy of the gas stream are important, in particular the distribution of airway compression. In fact, very little is known about the cough mechanism. It should be possible to study the influence of gas density on the effectiveness of coughing by simulating coughs in excised lungs at different total gas pressures.

ATELECTASIS

It is well known that subjects breathing 100 percent oxygen for periods as short as a few hours may have reductions in vital capacity (the deepest breath possible), which may be reversed by repeated deep breaths. It is likely that these changes reflect atelectasis It is of practical importance to determine the long-term physiological significance of such atelectasis and the optimum regimen of deep breathing that may be required to obviate any deleterious effects. Two matters, in particular, needing further study are (1) the extent of, and mechanisms responsible for, the marked individual variations in susceptibility to these changes (DuBois et al., 1966); and (2) the basis and significance of the observations that, whereas in some instances (and perhaps individuals) vital capacity is easily restored to normal after deep breathing, in other instances it remains subnormal despite repeated deep breaths (DuBois et al., 1966).

The influence of weightlessness on atelectasis should be small and, if anything, favorable. The slight reduction in lung volume would in itself predispose to atelectasis, but the removal of the gradient of stress within the lungs from top to bottom (because of their weight) would result in increased volume of the previously dependent regions, with a resulting decrease in their tendency to become atelectatic. Because one would expect weightlessness to have little influence on atelectasis, the problems mentioned above can be studied at 1 G in chamber experiments and the results applied to zero G conditions.

The problem of atelectasis is discussed further by Permutt in Chapter 6 (p. 38).

LUNG TEARING AT HIGH G

Lung tearing at high G is the single most important problem in respiratory mechanics in relation to space flight (Coburn et al., 1964). The lungs may be likened to a spring stretched by its own weight. In effect, they hang from their uppermost surfaces and, just as in the case of the spring, there is a gradient of stress from top to bottom—the uppermost part supporting the greatest weight and undergoing the greatest stretch. At increased G the part of the lung farthest from the direction of the G vector comes under the greatest stretch. That this stretch may result in tearing of tissue has been demonstrated in centrifuge experiments, although the level of G stress at which human lungs tear is not known. Measurements made on human cadavers should be informative if it can first be established with other species that lung tearing in dead animals bears a consistent relation to lung tearing in living animals.

The tendency to tear should be less in lungs oriented with their shortest diameter in the direction of the acceleration, and it should be less in small lungs at low volumes than in large lungs at high volumes.

Of lesser practical importance, because of its reversibility, is the trapping, and any associated atelectasis, that occurs on the opposite side of the lung at high G.

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NORMAN C. STAUB

5

PULMONARY GASEOUS DIFFUSION

DIFFUSION AND DIFFUSING CAPACITY

Diffusion is the process by which oxygen is passively transferred from the inspired fresh air that reaches the respiratory portion of the lung across the alveolar-capillary membrane to react chemically with the hemoglobin of the erythrocytes in the pulmonary capillaries. If the process is essentially complete within the time each red cell remains within the gas exchange vessels, then diffusion is adequate and not rate limiting under the existing conditions. Clearly, there is a series of processes, which are:

1. Gas-phase diffusion within the terminal respiratory units (respiratory bronchiole and distal alveolar ducts and alveoli; see Staub, 1963b)
2. Diffusion across the alveolar-capillary membrane and through the capillary plasma
3. Diffusion across the erythrocyte membrane followed by diffusion plus chemical reaction within the concentrated hemoglobin solution of the red cell interior

If fresh ventilation fails to reach the terminal units because of airway obstruction, atelectasis, or filling of the airspaces with foreign material, then the diffusion process is not involved; rather, this situation is considered a problem of imbalance of ventilation with respect to perfusion.

If plasma alone flows through the pulmonary capillaries, oxygen behaves like any inert gas and very rapidly (in several

milliseconds) equilibrates between the plasma and the surrounding alveolar gas. By the above criterion this constitutes adequacy of the diffusion process. But it is not very useful to the living mammal because of the low O_2 solubility of plasma. Thus, it is essential that we consider diffusion in terms of red cells; whether they are present in the pulmonary capillaries, whether they are moving or stagnant, and whether they reach equilibrium at the end of their transit through the gas exchange vessels.

In actual practice the test of the diffusion process in the intact lungs is called the diffusing capacity (D_L). The test cannot actually measure the end-capillary difference in P_{O_2} between alveolar gas and the red cell. Instead, it measures the rate of oxygen removal from the alveolar gas per unit of partial pressure difference per unit of time (ml/mm Hg x min). The measurement includes many factors other than diffusion, such as the distribution of gas volume within the lungs with respect to the distribution of red cells in the pulmonary capillaries, the lung volume, and the quantity and chemical state of the hemoglobin in the red cells. As an example of the lung volume effect, if one lung is removed, D_L may be half of normal although diffusion is complete. It is important to remember the distinction between diffusion and D_L. In this paper discussion will be based on the D_L test.

Although O_2 is the gas of most pertinent biological interest, D_L references involve carbon monoxide (CO) as the test gas. All D_L references in this paper are to CO unless otherwise specified.

By breathing gases with different partial pressures of O_2, the D_L measurement with CO can be subdivided into the alveolar-capillary membrane diffusing capacity (D_m) and the instantaneous pulmonary capillary blood volume (Vc) according to the method of Roughton and Forster (1957).

Within reasonable limits, CO diffusion data can be converted to O_2 diffusion data (Staub, 1963a).

DATA RELATING TO SPACE FLIGHT

There is no theoretical reason why diffusion processes in general should be affected by space flights of any duration. Under current cabin conditions there would actually be an increase in gas phase diffusion because of the decreased density of gas at about one third atm pressure. There would not be any noticeable effect on D_L in normals, however, because the gas phase diffusivities of O_2 and CO are about 300,000 times the values in the alveolar tissues.

Acceleration

The launch and re-entry accelerations for long-duration space flights will exceed those currently involved in low Earth-orbital flights. The total G x sec is given as 1,500 to 2,000 in comparison with the current 300. Acceleration effects on D_L have been studied in man (Power et al., 1965) where forward acceleration (+ G_x) of 8 G for 1 min (480 G x sec) decreased D_L an average of 35 percent. These events were readily reversible at the end of acceleration. They probably represent marked redistribution of Vc and loss of diffusion surface by compression atelectasis as might be inferred from macrosections of dog lungs after similar exposures (Wood et al., 1963). This is basically a problem in the distribution of ventilation volume to capillary blood volume.

One unknown factor relating acceleration to D_L is how a long period (1 to 3 years) of weightlessness with possible deconditioning might interact with deceleration during re-entry.

Weightlessness

Weightlessness should improve the measured D_L because of more even distribution of Vc with respect to alveolar volume. In the usual 1-G environment both the tendency to pool blood in the systemic low-pressure circuit and the hydrostatic gradient of blood within the thorax (upright posture) tend to make the distribution of Vc less than ideal.

On the other hand, we cannot predict for certain the pulmonary vascular pressures relative to alveolar pressure in weightlessness. This aspect is discussed in full by Permutt in Chapter 6 (p. 38). The intrathoracic pressure relations will determine the fullness of the pulmonary capillaries (Vc) on which D_L is dependent. I suspect that in normal breathing the capillary pressure will exceed alveolar pressure giving an increased D_L (well-filled capillaries).

Cabin Atmosphere

The effect of breathing O_2 at elevated partial pressures with reduced total barometric pressure on D_L needs to be considered carefully. A study by DuBois et al. (1963) before and after a two-week ground test of the Apollo atmosphere (P_{IO_2} = Pb = 258 mm Hg) showed normal values in single-breath D_L in three men within 1 day after return to normal atmosphere. A more extensive study by Robertson et al. (1964) on eight men for 30

days showed no changes in steady state D_L in four men using the Apollo atmosphere and no changes in four men breathing 33 percent O_2 (P_{AO_2} = 171 mm Hg: P_b = 700 mm Hg). The diffusion tests were done within 1 hour of leaving the artificial environment.

More recently, Robertson and McRae (1966) tested D_L immediately before and after a 56-day run, using a helium-oxygen atmosphere at P_b = 258 mm Hg and P_{AO_2} = 100 mm Hg. Deconditioning was prevented by a daily exercise schedule. There was no change in D_L in the four men tested.

At the 2nd Annual Conference on Atmospheric Contamination in Confined Spaces at Wright-Patterson Air Force Base, Hagebusch (1966) reported on lung pathology in dogs, monkeys, rats, and mice exposed to the Apollo atmosphere (P_{IO_2} = P_b = 258 mm Hg) for 235 days. There was no pulmonary pathology in the monkey group. The rats and mice showed considerable lung pathology (chronic pneumonitis) in both control and experimental groups. The experimental dogs showed more pathology (interstitial pneumonia, bronchitis, and destructive emphysema) than controls, and the author suggests that 258 mm Hg O_2 may be toxic to dogs. In a second report from that meeting, Kistler and associates (1966) also failed to find any pathology except some eosinophilia in young rats exposed to 5 psia for 14 days. The authors do claim to have demonstrated by morphometry an O_2 effect on lung growth. However, in another report by Back (1966), the 235-day animals failed to show any effect of the atmosphere on growth or size of organs. The data suggest that 100 percent O_2 at P_b = 258 mm Hg is safe for man up to 30 days but that long-term effects have not been satisfactorily evaluated.

Ernsting (1961) found D_m significantly reduced in men after 3 hours of 100-percent-O_2 breathing at sea level. Vc was not changed. He interpreted these findings as " . . . an increase in the thickness of the [alveolar-capillary] membrane due to inter- and intracellular oedema." An alternate interpretation could be a change in the diffusion coefficient of the membrane. Lee and co-workers (1963) exposed men to 98.5 percent O_2 up to 30 hours and found after 30 hours decreases in D_L consistent with a diffusion block resulting from a change in the alveolar-capillary membrane. Their data have not yet been published in full. The reason for the time discrepancy between Ernsting's and Lee's studies is unknown, although the ultimate changes of D_m are in agreement.

It is worth noting that there is no clear agreement that high-pressure O_2 toxic effects are due to direct action on the lung.

Recent data by Bean et al. (1966) and by Buckingham et al. (1966) suggest that the effects are secondary to central nervous system effects. If this is true there is little reason to suspect

that 5 psia O_2 will directly affect D_L. We should remember that the alveolar-capillary membrane tissue normally lives at P_{O_2} = 100 mm Hg, which is higher than most other body cells.

Toxic Materials

The long-term toxic effects of the many substances that might contaminate the space cabin atmosphere are to be discussed by others. As far as diffusion goes we note one example, that of low ozone concentrations (0.6 to 0.8 ppm) for 2 hours (Young et al., 1964) which caused significant decreases in D_L. The ways to test space cabin contaminant effects will be in actual practice or by simulation.

Other

Small but statistically significant changes in D_L have been noted in situations that might be related to space flight. Cinkotai and co-workers (1966) found that apprehension increased D_L slightly, presumably because of increased Vc. Frayser et al. (1966) found that high environmental temperatures decreased D_L and Vc. Both groups felt that the dominant factor was a change in the systemic vascular volume.

RESEARCH PROBLEMS

If gases of higher-than-normal oxygen partial pressure are to be used in long-term flight, then it is imperative that testing of such atmospheres be done on animals and on humans during progressively longer ground-based and Earth-orbital flights. The reason for mentioning the problem here is that the D_L test, including the subdivisions (D_m and Vc), may be a sensitive early sign of pathology. The test is quite simple and practical for both animals (Young et al., 1963) and humans. Following are three experiments of interest:

1. The single-breath D_L test is relatively simple to instrument and easy to perform. In view of the availability of a space-borne gas chromatograph (Melpar, Inc.) that is programmed to measure the diffusion test gases, it seems desirable to include this test during the Apollo Applications Programs experiments. In addition to D_L, D_m, and Vc, the test can also give expiratory reserve volume, vital capacity (inspiratory), residual volume (single-breath dilution volume), inspiratory and expiratory flow

rates (if a fast response spirometer is available). As a bonus, slight changes in procedure will permit determination of pulmonary capillary blood flow by the soluble inert-gas method during the same breath as the D_L determination.

2. The relation of pulmonary capillary pressure to alveolar pressure as referred to in the text could be handled in astronauts by comparing pulmonary capillary volume during weightlessness with the values (recumbent) at 1 G. A marked increase in Vc in weightlessness would point to capillary pressure greater than alveolar pressure. This procedure does not require cardiac catheterization.

3. Whether or not increased $P_{A_{O_2}}$ has a direct toxic effect on the lung can be tested in ground-based studies with the use of D_L as a sensitive index but with additional pathological studies also. Dogs can be operated on to make chronic lobar bronchial fistula through which O_2 at any desired partial pressure can be given without making any other organ of the body hyperoxic.

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SOLBERT PERMUTT

6

PULMONARY CIRCULATION AND THE DISTRIBUTION OF BLOOD AND GAS IN THE LUNGS

Within recent years, considerable evidence has been accumulated that suggests that gravity is the major factor affecting the distribution of both blood and gas within normal lungs. I propose to review the mechanisms through which gravity works on blood and gas within the lungs and attempt to show how these mechanisms operate under both increased and decreased gravitational fields encountered in space travel. This review is essentially limited to mechanical factors affecting the pulmonary circulation and ventilation of the lungs, and I have concentrated on the relationships between alveolar, intrapleural, and vascular pressures. Some of these relations can be considerably simplified through the use of mechanical models, and the Starling Resistor (see p. 39) is one such model on which I have leaned heavily, fully realizing the dangers and limitations of reasoning from mechanical analogues. Nevertheless, the mechanical model allows the integration of a number of seemingly isolated facts into a coherent picture and suggests a variety of experiments that can be carried out to test its validity.

Of course, the pulmonary circulation and airways will be affected in space by all the factors that are at work on the surface of the Earth. There are hundreds of references on the effects of changes in blood gases and drugs on the pulmonary circulation and airways, some of which are of unquestioned importance, especially from the viewpoint of the composition of the air breathed, but this information is so well understood and the magnitude of the changes expected so small, that this aspect of the picture has not been covered in any detail in the present review.

Starling Resistor Effect

Starling, in his heart - lung preparation, connected the aorta to a thin-walled collapsible tube traversing a chamber in which the pressure surrounding the tube could be controlled. Such a device has come to be called a Starling resistor. Although Starling resistors have been widely used in the laboratory, it was not until the recent work of Banister and Torrance (1960) that it became apparent that the Starling resistor might serve as a model to explain some of the pressure - flow relationships of the pulmonary circulation. More recently, the pressure - flow relationships of Starling resistors have been described in simple quantitative terms (Permutt et al., 1961; Permutt and Riley, 1963), although these quantitative relationships were implicitly set forth in the work of Duomarco and Rimini (1954).

Consider a thin-walled collapsible tube. Let P_I, P_O, and P_S be the inflow, outflow, and surrounding pressures respectively.* The relationships between pressure and flow through such a tube can be characterized, as a first approximation, by the following statements (Permutt et al., 1961; Permutt and Riley, 1963):

1. When $P_S > P_I > P_O$, no flow through the tube occurs.
2. When $P_I > P_S > P_O$, flow through the tube is proportional to $P_I - P_S$, and changes in P_O have no influence on flow.
3. When $P_I > P_O > P_S$, flow through the tube is proportional to $P_I - P_O$, and changes in P_S have no influence on flow.

It is now reasonably clear that the small blood vessels of the lungs are easily collapsible and are surrounded by a pressure essentially equal to alveolar pressure (Permutt et al., 1961; Howell et al., 1961; Banister and Torrance, 1960). Therefore, flow through an alveolus of the lung can be described by the three statements above if the following substitutions are made: pulmonary arterial pressure (P_{PA}) for P_I, pulmonary venous pressure (P_{PV}) for P_O, and alveolar pressure (P_{ALV}) for P_S. A number of studies in excised lungs, intact dogs, and normal human subjects suggest that these pressure - flow relations obtain in normal lungs (Anthonisen and Milic-Emili, 1966; Banister and Torrance, 1960; De Bono and Caro, 1963; Fowler et al., 1966; Permutt et al., 1962; Sheehan, 1966; West and Dollery, 1965; West et al., 1964).

*Throughout this paper, the units of pressure and the reference level are not relevant except when specified. It is assumed, of course, that when relationships between pressures are considered, all pressures are in the same units and are measured from the same reference level.

Starling Resistor Effect on Distribution of Pulmonary Blood Flow at 1 G

Recent work of West and colleagues (1964, 1965), who used excised lungs of dogs, gives considerable support to the concept that the effective driving pressure for blood flow through the lungs is the difference between pulmonary arterial and alveolar pressure whenever alveolar pressure is greater than pulmonary venous pressure, and that changes in pulmonary venous pressure have no influence on flow under these conditions. West divides the lungs into three zones.

Zone 1 is that portion of the lung in which alveolar pressure is greater than pulmonary arterial pressure, which in turn is greater than pulmonary venous pressure. This zone has no flow because of the collapse of small vessels exposed to alveolar pressure.

Zone 2 is that portion in which pulmonary arterial pressure is greater than alveolar pressure, which in turn is greater than pulmonary venous pressure. In this zone, flow increases linearly toward the more dependent regions because $P_{PA} - P_{ALV}$ increases linearly.

Zone 3 is that portion in which pulmonary arterial pressure is greater than pulmonary venous pressure and both are greater than alveolar pressure. In this region flow tends to remain constant because the driving pressure ($P_{PA} - P_{PV}$) remains constant, gravity affecting both pressures by an equal amount. In this zone, West et al. (1964) find, however, that there is still some increase in flow toward the more dependent parts, presumably because the increasing transmural pressure causes distention of pulmonary vessels.

It now appears quite likely that these same factors are in large part responsible for the distribution of blood flow in the erect human subject in a normal gravitational field (+ 1 G_z). Butler and Paley (1962) found that the mean P_{PA} was 6.9 cm H_2O in relation to atmospheric pressure at the angle of Louis in 13 erect normal subjects. Anthonisen and Milic-Emili (1966) showed by radiographs that the angle of Louis was, on the average, 10 cm below the top of the lung. If the pulmonary blood vessels act as Starling resistors, there should be no blood flow above the level at which $P_{PA} = P_{ALV}$. Thus, on the basis of the above average values, P_{PA} should be equal to P_{ALV} approximately 3 cm below the top of the lung, and the upper 3 cm of the lung should be unperfused with blood. Anthonisen and Milic-Emili (1966), using ^{133}Xe in a manner that allowed them to calculate relative blood flow per alveolus at different horizontal levels of the lung, found on the average in six normal subjects that the upper 2.9 cm of the lung was unperfused with blood. These figures suggest that the upper 3 cm of the lung in normal

upright subjects is in West's Zone 1 and compare favorably with the conclusions of Bjurstedt et al. (1962) and Riley et al. (1959) who, on the basis of dead-space measurements, estimate that 6 percent and 14 percent of the alveoli become unperfused with blood on assuming the upright posture.

Butler and Paley (1962) also found that the pulmonary wedge pressure was 11.3 cm H_2O less than P_{PA}. If we assume that the pulmonary wedge pressure accurately reflects the pressure in the pulmonary veins, we can estimate that for a distance of 11 cm below the uppermost level of perfusion (where $P_{PA} = P_{ALV}$ and P_{ALV} is 11 cm above P_{PV}), P_{PA} should be greater than P_{ALV}, and P_{ALV} should be greater than P_{PV}. This is comparable to West's Zone 2; and within this zone there should be a linear increase in blood flow per alveolus as we go down the lung, since flow per alveolus is proportional to $P_{PA} - P_{ALV}$. Anthonisen and Milic-Emili (1966) found a linear increase in pulmonary blood flow per alveolus for a distance of 15.1 cm below the uppermost level of perfusion. Considering the limitations of the methods, the agreement appears to be reasonably good. At any rate, if the pulmonary blood vessels act like Starling resistors, there should be a Zone 2 of vertical distance approximately equal to the difference between mean arterial and left atrial pressures expressed in cm H_2O. Anthonisen and Milic-Emili (1966) found, in contrast with the findings of West et al. (1964) in excised lungs, that blood flow per alveolus did not show a significant increase within Zone 3. Their findings are compatible with those of Bryan et al. (1965), who concluded, on the basis of studies with the macroaggregated albumin technique, that the basal vessels of the lungs in normal subjects are close to the limit of their distensibility at + 1 G_z.

Several other studies in human subjects with the use of radioactive gases have not shown the distinct zones found by Anthonisen and Milic-Emili (1966), but rather have shown approximately linear increases in flow per unit volume of lung from apex to base (Ball et al., 1962; Bryan et al., 1964; Dollery and Gillam, 1963; West and Dollery, 1960). Anthonisen and Milic-Emili (1966) suggest that the distinct zones might have been obscured because the alveoli in the upper parts of the lung are larger than in the lower parts owing to the more negative intrapleural pressure. They, too, found an essentially linear increase in blood flow per unit volume of lung but not per alveolus. The gradient of intrapleural pressure with vertical distance would have presented no problem in West's work (West and Dollery, 1965) on excised lungs where the pleural pressure was uniform.

In the supine posture, there is agreement that the distribution of blood flow from apex to base becomes uniform. Yet the possibility remains that there is a difference in blood flow in the anterior - posterior direction. A recent study of Kaneko et al.

(1966) shows that the blood flow per alveolus is evenly distributed in the anterior - posterior direction in normal men in a supine position. Wood et al. (1963) found in dogs in a supine position that mean left atrial pressure was + 3 cm H_2O in relation to atmospheric pressure at mid-dorsoventral chest level and that the average dorsal - ventral dimension was 20 cm. This would suggest that the upper 7 cm of the lungs were in Zone 2, which theoretically should have increasing flow in the ventral - dorsal direction.

Read and Fowler (1964) have attempted to account for the effect of gravity on the distribution of pulmonary blood flow in a somewhat different manner. They postulate that vascular smooth muscle tone can produce a critical opening pressure within pulmonary vessels. If one then presupposes a critical opening pressure that is relatively uniform throughout the lung, the effect of gravity on pulmonary arterial pressure causes a zone of no perfusion at the upper parts of the lungs above the level where pulmonary arterial pressure is less than the critical opening pressure. Read and Fowler also consider that extrapulmonary veins can act as Starling resistors in areas where the pulmonary venous pressure is less than intrapleural pressure. Under these conditions, the effective driving pressure is pulmonary arterial minus intrapleural pressure, and there should be a decrease in driving pressure toward the upper portions of the lungs even when pulmonary arterial pressure is greater than critical opening pressure.

Apparently Read and Fowler did not consider the possibility of a Starling resistor effect under conditions where pulmonary venous pressure is less than alveolar pressure. Since alveolar pressure is always equal to or higher than intrapleural pressure, the Starling resistor effect from venous collapse as postulated by Read and Fowler is probably irrelevant under most conditions because the Starling resistor that is farthest upstream is the controlling one. Nevertheless, West and Dollery (1965) showed that in excised lungs, under special circumstances where the hilum is considerably above the most dependent portion of the lung, collapse of extrapulmonary veins might be of significance in determining the distribution of pulmonary blood flow. Because the hilum in the human subject is well above the most dependent part of the lung, even in the supine position, a Starling resistor effect from collapse of the veins has to be considered, especially under conditions of increased G.

Effect of Increased Gravity on the Pulmonary Circulation

If we assume that the lungs continue to act as Starling resistors under conditions of increased G, the effects can be easily

predicted if we know the mean pulmonary arterial pressure at heart level. Let $P_{PA'} = P_{PA}$ at the level of the heart. The height in centimeters that the lungs can be perfused above heart level (h) is

$$h = \left(P_{PA'} - P_{ALV}\right)/G \qquad (1)$$

when $P_{PA'}$ and P_{ALV} are expressed in cm H_2O and G is the magnitude of acceleration in relation to the normal gravitational acceleration. The expression is valid only under conditions where G is not equal to zero. For instance, if $P_{PA'}$ remained at 20 cm H_2O at + 5 G_z, the lungs could only be perfused to a distance of 4 cm above the level of the heart. Thus, all parts of the lungs more than 4 cm above the level of the heart would be in Zone 1.

By the same reasoning we can assume that the vertical distance of Zone 2 (assuming that there is a Zone 1), which we shall call h_{Z2}, is given by the following simple expression,

$$h_{Z2} = (P_{PA} - P_{LA})/G \qquad (2)$$

when $P_{PA} - P_{LA}$ is the difference between the pulmonary arterial and left atrial pressure expressed in cm H_2O. Thus, if $P_{PA} - P_{LA}$ is 10 cm H_2O, the vertical distance of Zone 2 would be reduced from 10 cm at + 1 G_z to only 2 cm at + 5 G_z. The overall effect, then, of increasing G can be assumed to be an increasingly sharp division between the upper portions of the lungs with no blood flow and the lower portions of the lungs with relatively even blood flow (those portions in Zone 3). Let us see how these predictions compare with the few studies available.

Glaister (1965), using ^{133}Xe, found that the ratio of blood flow per unit volume of lung in the lower to the upper part was 2.7:1 at + 1 G_z, 5.9:1 at + 2 G_z; and at + 3 G_z blood flow to the upper part of the lungs was absent. Bryan et al. (1965) used equation (1), above, to analyze the result obtained with the macroaggregated albumin technique in normal subjects exposed to increasing + G_z, and found that the results were entirely in keeping with the predictions from the equation. These workers also found that the blood flow in the more dependent parts of the lungs was relatively evenly distributed with increasing + G_z in spite of the increasingly high intravascular pressures toward the more dependent regions.

At the present time it is somewhat uncertain whether the anterior parts of the lungs become unperfused with blood during increasing + G_x. If the work only of Wood et al. (1963) on dogs is taken into consideration, we must assume that the anterior portions of the lungs are not perfused with blood at + 6 G_x. Wood found that the pulmonary arterial pressure 10 cm below the most anterior portion of the lungs averaged 33 cm H_2O. Equa-

tion (1) suggests that the maximum height of perfusion would be only 5.5 cm above the level of the pressure measurement, which means that 4.5 c : of the most anterior portions of the lungs would not be perfused at all. As the average anterior - posterior (or ventral - dorsal) dimension of the lungs was approximately 20 cm in Wood's study, we can estimate that more than 20 percent of the most anterior parts of the lungs was unperfused. On the other hand, Hoppin et al. (1967), using the macroaggregated albumin technique in normal human volunteers, found the same distribution of blood flow in the anterior - posterior direction at + 1 G_X, + 4 G_X, and + 8 G_X. They accounted for their results and explained as follows why they differed from those obtained at + G_Z:

> Under + G_Z, much of the lung being superior to the heart, may have had inadequate perfusion pressure. . . . Under + G_X as in the present study, however, little of the lung would have been "uphill" from the right ventricle which is located forward in chest and is not markedly displaced under + G_X. . . . Furthermore, there has been evidence suggesting that pulmonary artery pressures are elevated under + G_X. . . . In man under + 5 G_X, pressures in the right atrium, radial artery, and esophagus were increased about 20 mm Hg. . . . In dogs under + 5 G_X and + 10 G_X similar though variable increases in aortic, right atrial, and right ventricular pressures were noted. . . .

These same workers concluded that nearly all the lung must have been in Zone 3. They also reported that the blood flow was relatively evenly distributed in spite of changes in transmural pressures, estimated to be from 0 to 88 mm Hg, from the anterior to the posterior portions of the lungs. These findings contrast with those of West and Dollery (1965) who suggested that changes in transmural pressure within vessels in Zone 3 had some influence on the distribution of blood flow. The findings of Hoppin et al. (1967), more than any others to date, point to the relative unimportance of changes in transmural pressures in determining the distribution of blood flow, and this negative finding indirectly points toward the tremendous importance of the Starling resistor effect.

Although the increase in transmural pressure in the more dependent portions of the lungs does not appear to have a great deal of influence on the flow through these vessels, the high transmural pressure would be expected to cause transudation of fluid from the pulmonary capillaries into lung tissue and alveolar spaces. Wood et al. (1963) concluded that considerable transudation of fluid does occur on the basis of hemoconcentration during exposures to forward acceleration (6 G_X for 60 sec). These workers also found a significant decrease in right and left atrial pressures of 1 to 2 cm H_2O during the period of recovery compared with the control. On the basis of similar decreases in right atrial pressure in human subjects, Wood

et al. (1963) estimated a decrease in plasma volume of nearly 400 ml.

Any increase in the extent of Zone 1, which certainly occurs under increased + G_Z and might occur under + G_X, would be expected to increase the extent of alveolar dead space, and minute volume would have to be increased in order to maintain a normal arterial pH and P_{CO_2}. Zechman et al. (1960) have found an increase in minute volume in normal subjects exposed to increased + G_X, and Barr (1962) found the same thing in normal subjects exposed to increased + G_Z. In addition, Barr found that the arterial pH did not change, and suggested that the increased minute ventilation was necessary to maintain the pH at a normal value in the presence of an increased alveolar dead space.

Extrapolation to the Gravity-Free State

It is immediately apparent from the above considerations that under zero G, all the blood vessels of the lung must be in either Zone 2 or Zone 3, but it is not immediately apparent which of the two zones they will be in under ordinary activity. If left atrial pressure were positive in relation to the ambient pressure and therefore in relation to alveolar pressure, all the blood vessels would be in Zone 3, but it is not at all certain that left atrial pressure is positive in relation to ambient pressure under ordinary conditions in the weightless state. The intrapleural pressure is negative, and it is quite possible that the left atrium could be distended sufficiently to provide an adequate filling pressure for the left ventricle during diastole even under conditions where the intraluminal pressure of the left atrium is negative in relation to ambient pressure. Whether this will occur at end-expiration, it is likely to occur at end-inspiration and almost certainly will do so if the subject increases his lung volume sufficiently. The reason is: Assuming constant cardiac output, pulse rate, and myocardial contractility, the left atrial pressure is fixed in relation to intrapleural pressure. With a normal inspiration, assuming no major change in cardiac output, pulse rate, or myocardial contractility, the left atrial pressure would remain constant in relation to intrapleural pressure. At the same time, however, inspiration is always associated with an increase in alveolar pressure in relation to intrapleural pressure. Therefore, inspiration would be expected to cause an increase in alveolar pressure in relation to left atrial pressure. If the increase in alveolar pressure in relation to left atrial pressure is sufficient, the lungs will change from a Zone-3 state to a Zone-2 state.

Regardless of whether the lungs are in Zone 2 or Zone 3, the

blood flow per alveolus would tend to be even because P_{PA} is even throughout and, as will be shown later, the same is likely to be true for ventilation. Therefore, from the point of view of good distribution of blood and gas within the lungs, the weightless state is ideal, and it is reasonable to conclude the alveolar dead space and venous admixture would be at a minimum.

Even though the gravity-free state will insure even distribution of blood flow, the uniformity of the blood vessels' condition is not necessarily an unmixed blessing. Consider some of the problems that might arise if the pulmonary vessels remain in a constant Zone-3 state:

Those portions of the lungs near the apex would have considerably higher transmural pressures than would be present in the upright subject at + 1 G_Z. In fact, the cephalad portions of the lungs at zero G would be in the same state as they would be in a patient with mitral stenosis at + 1 G_Z. It is not inconceivable that this would result in reflex changes and structural alterations.

An increased tendency toward fluid transudation from the capillaries is also possible. When the blood vessels are acting as Starling resistors, the alveolar pressure is higher than the pulmonary venous pressure, and the pulmonary capillaries, which are surrounded by fluid pressure equivalent to alveolar pressure, are in a state of collapse and at virtually zero transmural pressure. We have found that, if a Starling resistor is made of a fairly large collapsible tube, even if the tube has 1-mm holes in it, fluid will still move from the area surrounding the tube into the tube and on into the outflow reservoir. If the flow is increased beyond a certain critical level, depending on the diameter of the collapsible tube, fluid will begin to move out of the collapsible tube into the area surrounding the tube, especially if the holes are placed at the upstream end of the tube. If the transmural pressure is even slightly positive, and the tube is no longer collapsed, fluid flows freely from the tube to the surrounding area. Now here we have a situation in which a change in transmural pressure of an exceedingly small amount can reverse the direction of fluid movement across the wall of the collapsible tube under conditions in which the tube changes from a collapsed to a distended state.

A similar reverse in fluid movement might occur as the pulmonary capillary changes from a collapsed to a distended state when pulmonary venous pressure becomes higher than alveolar pressure. It is even possible that pulmonary edema could occur. It is well known that if a person continues to lie in one position, fluid tends to accumulate in the most dependent portion of the lungs. Frequent movement occurs in the normal person, even when asleep, and this type of fluid accumulation is not often seen in the normal person unless he is highly sedated. At zero

G, however, no matter how the pers turns, he will never change his pulmonary capillary from a distended to a collapsed state. Furthermore, any activity that leads to an increased left atrial pressure will accentuate the condition.

Finally, it is possible that at least some of the capillaries of the lungs have to be in a Zone-2 state to permit the lungs to filter out some of the cellular elements of the blood, which apparently is one of the functions of the lungs. One would expect collapsed capillaries to be better filters than fully distended ones.

The problems that might conceivably arise from uniformly collapsed capillaries relate to a possible increase in their filtering capacity. Might they tend to become plugged with cellular elements ? Might there be an increased tendency for microthrombi ? Is it possible that the blood might become altered in its continuous passage through collapsed capillaries ? Unquestionably, if the capillaries were uniformly in a collapsed state, their diffusing capacity would be reduced. Nevertheless, the reserve under normal activity is so great that it seems unlikely that such a reduction could have any significant influence on blood - gas tensions.

DISTRIBUTION OF VENTILATION AND PERFUSION

Effect of Gravity Upon the Distribution of Ventilation

There now appears to be little question that gravity is the main factor determining the distribution of both blood and gas within the lungs under physiological conditions. Use of the radioactive xenon technique by several independent groups shows that both perfusion and ventilation per unit lung volume are greater in the lower than in the upper portions of the lungs, with more striking difference for perfusion than ventilation (Anthonisen and Milic-Emili, 1966; Bryan et al., 1964; Denison et al., 1964; Glaister, 1965; Kaneko et al., 1966). The differences are increased during positive acceleration (Bryan et al., 1966; Glaister, 1965) and are reversed when the subject is turned upside down (Glaister, 1965; Kaneko, 1966).

The effect of gravity on the distribution of blood flow can in large part be explained by mechanical factors, but the way in which gravity also causes a difference in ventilation between the lower and upper parts of the lungs is not yet generally agreed upon. It is possible that the diminution in blood flow itself causes a reflex diminution in ventilation by bronchial constriction. It now seems likely however, that the major ef-

fect of gravity on the distribution of ventilation is also through mechanical factors.

The mechanical factor influencing the distribution of ventilation in relation to height is the "gradient" in intrapleural pressure from the lower to the upper parts of the lungs with the more negative values in the upper parts (Daly and Bondurant, 1963; Krueger et al., 1961; Milic-Emili et al., 1966; Turner, 1962; Wood et al., 1963). Neither the magnitude of the gradient nor the mechanism governing it has been clearly delineated. Krueger et al. (1961) suggested that the air-filled lung tissue has the properties of homogeneous fluid of the same mean density as the lungs. Mead (1961) and Turner (1962) suggested that differences in supporting forces applied to the surface of the lungs might be responsible for the difference in intrapleural pressure. Whatever its origin, the gradient in intrapleural pressure appears to be gravity dependent and has been shown to increase under conditions of positive acceleration (Milic-Emili et al., 1966; Wood et al., 1963). The magnitude of the gradient at + 1 G has been found to be approximately 0.2 cm H_2O/cm by Krueger et al. (1961), Daly and Bondurant (1963), and Milic-Emili et al. (1966). On the other hand, Wood et al. (1963) have reported gradients in excess of 0.5 cm H_2O/cm.

The mechanism by which the gradient in intrapleural pressure causes differential ventilation between the upper and lower parts of the lungs appears to be related to the relatively greater volume of the alveoli in the upper parts of the lungs. If the compliance of the lungs were homogeneous throughout, the more negative intrapleural pressure at the upper portions of the lungs would cause the air spaces in this region to have greater volumes than identical air spaces in the lower portions of the lungs at end-expiration. The larger airspaces in the upper parts would have a smaller change in volume per unit volume during inspiration; this could account for the smaller ventilation per unit volume in the upper parts of the lungs found by the radioactive xenon technique.

Although this explanation is attractive, the problem cannot be handled so simply, because the pressure - volume curve of an individual unit of the lung is nonlinear, and the compliance is therefore a function of the initial volume of the unit. The larger the initial volume, the less the compliance. Therefore, it might be expected that when a breath is taken from functional residual capacity, the difference in compliance between the lower and upper parts of the lungs would favor greater tidal volumes in the lower parts.

The problem is further complicated when the phenomenon of air trapping is considered. If intrapleural pressure is increased until residual volume is reached, the transpulmonary pressure of units in the dependent parts of the lungs might be sufficiently

low to cause air trapping in these units. If a breath were then taken from residual volume, the trapped units in the lower parts of the lungs would not be expected to take in air until the intrapleural pressure fell below a critical value. Under these conditions, a small breath taken from residual volume would go predominantly to the upper parts of the lungs, unlike a breath of the same size taken from functional residual capacity. Fowler (1964) found that inspired gas was indeed distributed predominantly to the upper parts of the lungs when a breath was taken from residual volume and to the lower parts of the lungs when the breath was taken from an initially high lung volume.

Recently Milic-Emili et al. (1966) studied the expansion of different regions of the lungs at various lung volumes in seated normal men, using ^{133}Xe. They found that the volume per alveolus was always greater in upper than in lower zones. When the lung volume was increased from residual volume to about 20 percent of the vital capacity, the changes in volume per alveolus were greater in the upper than in the lower lung regions, whereas the opposite was true at higher lung volumes. In a further study the same group (Kaneko, 1966) was able to show that the same relationships held for the highest and lowest parts of the lungs regardless of the body position.

The effect of an increased positive acceleration would be expected to magnify the regional differences in ventilation. Bryan et al. (1966) found that increased gravitational force increases the difference in lung expansion between the upper and lower regions. A most interesting discovery of these workers was that if they extrapolated their findings at different $+ G_z$ to zero G, regional lung expansion and regional ventilation were found to be uniform throughout the lungs. Glaister (1965) has shown unequivocally that the dependent portions of the lungs show considerably more trapping during positive acceleration. On the basis of the washout of ^{133}Xe from the dependent part of the lung at $+ 3 G_z$, he described a fast compartment with a half-time of 10 to 20 sec and a slow compartment of more than 2 min, the latter compartment presumably from trapped gas. When repeated with 100 percent oxygen, sufficient collapse of the lung occurred to reduce the vital capacity by 56 percent, and the slow compartment disappeared, presumably from the trapped gas's being rapidly absorbed, leaving only atelectatic areas. That the disappearance of the slow compartment was due to complete absorption of oxygen was shown by a fourfold increase in radioactivity of the systemic blood from shunt with oxygen breathing.

Atelectasis and Trapping

If the transpulmonary pressure in the alveolus falls below a critical level, gas is expelled from the alveolus, and it becomes atelectatic. The critical transpulmonary pressure depends on the surface tension of the liquid - air interface of the alveolus which in turn depends on the nature of the material that accumulates at the interface. Clements (1962) has shown that in the normal lung a special substance, believed to be lipoprotein in nature, is present at the interface and acts to reduce the surface tension under conditions where the surface area is decreasing. This special substance, now called surfactant, reduces the critical transpulmonary pressure at which atelectasis occurs. If surfactant is absent or diminished in amount, the critical transpulmonary pressure is at a higher level.

Another effect of reduction in transpulmonary pressure is a decrease in the diameter of terminal bronchioles and probably of alveolar ducts also. It now appears quite likely that when the transpulmonary pressure of a terminal bronchiole or alveolar duct falls below a critical level, the bronchiole or duct closes. If the critical transpulmonary pressure of the bronchiole or alveolar duct is higher than the critical transpulmonary pressure of the alveoli peripheral to it, closure of the conducting airway occurs when gas is still present in the alveoli, thus producing trapping. If, on the other hand, the critical transpulmonary pressure of the alveoli is higher than the critical transpulmonary pressure of the conducting airways, atelectasis occurs first.

Apparently surfactant has little, if any, influence on the critical transpulmonary pressure of the conducting airways. Thus, if surfactant is present, low transpulmonary pressures produce trapping; if surfactant is absent or diminished, low transpulmonary pressures produce atelectasis (Faridy and Permutt, unpublished material). The critical transpulmonary pressure at which trapping occurs depends on the state of the conducting airways. Any narrowing, increased smooth muscle tone, or secretions within the lumina of conducting airways would be expected to increase the critical transpulmonary pressure at which trapping occurs.

The basic mechanism of producing atelectasis or trapping, then, is a reduction of transpulmonary pressure below a critical level. The effect of gravity is obviously of great importance because of the resulting gradient of intrapleural pressure. In the presence of gravity, the transpulmonary pressures are always lower in the more dependent than in the upper parts of the lungs. With increasing positive acceleration, the transpulmonary pressure becomes less and less. Sooner or later atelectasis or trapping must occur in the more dependent regions of the lungs. In normal subjects, where there should be no

reason to suspect alterations in surfactant, one would expect trapping to occur; and the studies of Glaister, described above, certainly bear this out. It is possible, however, that fluid accumulation in the alveoli, which probably occurs in the more dependent regions, could have some effect in altering surfactant or the surface properties of the lungs (Johnson et al., 1964), but thus far there has been no work to suggest that this is a significant factor in the production of atelectasis during positive acceleration.

Regardless of whether trapping or atelectasis occurs first, the end result is still atelectasis as the trapped gas diffuses into the blood perfusing the trapped alveoli. The rate at which atelectasis occurs from a trapped alveolus is highly dependent upon the type of gas trapped (Rahn and Farhi, 1963). If alveolar gas contains no nitrogen or other inert gas, as would be the case if the person were breathing pure oxygen, the rate of production of atelectasis following trapping would be increased manyfold. The studies of Rahn and Farhi (1963) show that breathing pure oxygen at reduced ambient pressure, as the Mercury and Gemini astronauts have done, increases the rate of production of atelectasis above that which occurs when breathing pure oxygen at 1 atm. Recent studies of Ernsting (1965) and DuBois et al. (1966) demonstrate the importance of even relatively small concentrations of nitrogen in preventing the occurrence of atelectasis. The study made by DuBois and co-workers is especially interesting because they showed that atelectasis occurs in some subjects breathing pure oxygen at 1 G, whether at sea-level or reduced pressures. They also presented evidence that air trapping was probably the causal mechanism.

DuBois et al. (1966) suggest that in the presence of bronchiolar obstruction the airway conductance, which has been shown to decrease with a decrease in transpulmonary pressure, may be virtually nonexistent in the most dependent part of the lungs. In subjects with bronchiolar obstruction, breathing pure oxygen at 1 G would produce atelectasis in the same manner as in normal subjects under positive acceleration. The significant effect of pure oxygen on the production of atelectasis under conditions of increased G favors the idea that trapping precedes atelectasis. In a recent study by Williams et al. (1966) where atelectasis was produced in dogs by decreasing surfactant, breathing pure oxygen had no effect on the rate of formation of atelectasis, because the atelectasis occurred in the absence of bronchiolar closure.

Trapping and atelectasis are unquestionably the cause of the decreased arterial oxygen saturation under conditions of positive acceleration (Barr, 1962; Wood et al., 1963). As far as the effect of desaturation of the arterial blood is concerned, it makes little difference whether atelectasis or trapping is present, for in either situation the alveoli are not ventilated,

and blood passing through these regions is being effectively shunted from the pulmonary artery to the pulmonary veins. Although breathing 100 percent oxygen increases the tendency to atelectasis, it should improve the arterial oxygen saturation; and that this is so has been demonstrated by Wood et al. (1963). If a subject were to be exposed to positive acceleration for only limited periods, it might be debatable whether it would be better to breathe pure oxygen or a gas mixture containing a significant concentration of nitrogen. If the major concern were the prevention of arterial oxygen desaturation, then breathing 100 percent oxygen would be preferable. Not only would the higher oxygen content in the blood from the non-shunting areas be beneficial, but also, a trapped alveolus containing only oxygen, carbon dioxide, and water vapor would not act as a shunt at all until it became atelectatic. On the other hand, if the prevention of atelectasis is considered of primary importance, then the presence of an inert gas is of considerable benefit.

It is possible that the presence of atelectasis is more serious than the limited degree of arterial oxygen desaturation that has been found. Atelectasis unquestionably produces symptoms, consisting of coughing and chest discomfort, that are accentuated by attempting to take a deep breath (Ernsting, 1965). DuBois et al. (1966) discuss the possibility that once atelectasis occurs, the pressure required to open gas-free alveoli might not be reached even during a deep inspiration, which could account for the persistence of atelectasis while the subject continues to breathe oxygen and for the delay in recovery even after he has returned to room air.

In the weightless state, all factors tending to produce atelectasis would be at a minimum. The probability remains that the breathing of pure oxygen for long periods in zero G would produce atelectasis in some individuals, especially those who might develop bronchiolar obstruction either during a respiratory infection or because of unsuspected pre-existing conditions of the lungs (DuBois et al., 1966). Also, the long-term effect of pure oxygen, even at reduced atmospheres, on surfactant is still unknown.

RESEARCH PROBLEMS

In this rather cursory review of the problems of manned space flight in respect to pulmonary circulation and distribution of blood and gas within the lungs, I see no major problems of which we are now aware that must be solved before prolonged trips can be undertaken. Although the risks from positive acceleration

appear considerable, they have already been faced without any serious consequences, and I do not think that they will be increased with prolongation of space flight. In regard to distribution of blood and gas within the lungs, it seems that man will be better off, at least on the basis of our current knowledge, in the weightless state than at 1 G. I suspect that the real problems to be faced in the future in the subject under review are at present unknown, and I suggest that the greatest dividends from money spent at this time will come from the support given to basic physiological investigation. Some of the studies that I would like to see emphasized are:

1. Basic mechanics of flow through collapsible tubes.
2. Factors controlling the distributions of intrapleural pressures, i.e., distribution of pressures at the surface of the lungs, heart, and great vessels within the thorax.
3. Distribution of forces across the heart chambers; studies on heart function under positive acceleration.
4. Measurement of pressures within the heart chambers under a variety of conditions at different G levels.
5. The effect of the Starling resistor phenomenon on the function of pulmonary capillaries with respect to fluid transudation, filtering function, and the passage of blood elements through the capillaries.
6. Use of macroaggregated albumin technique in transient weightlessness.
7. Extension to $-G_X$ acceleration of the type of study carried out by Hoppin et al. (1967). If the reasons presented by these authors for the even distribution of pulmonary blood flow under $+G_X$ are correct, one would expect an uneven distribution of blood flow under $-G_X$.
8. Measurements of the distribution of blood volume within the thorax and lungs. Better methods of measuring the distribution of blood volume throughout the lungs in different gravitational fields are required. We need to know how the pulmonary blood volume is partitioned between arteries, veins, and capillaries.
9. Better measurements of the distribution of blood volume between the systemic and pulmonary circulations in different gravitational fields. We need experiments that will shed light on the mechanisms involved in controlling the distribution. The capacitance of the pulmonary circulation is so small in relation to the systemic circulation that the major factors in this area are more likely to be found in the systemic circulation, but we do need to know more about the effect of perhaps even small volume changes within the vascular structures of the thorax on the capacitance of the systemic circulation through reflex and hormonal changes.

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JERE MEAD

7

REGULATION OF BREATHING

The only severe embarrassment to breathing in connection with space flights occurs during transients of high G. For example, during transverse accelerations in excess of about 10 G, breathing appears to be virtually impossible. In general, such transients are brief and not beyond the limits of breath holding. In contrast, prolonged periods of weightlessness should present no important problems with regard to the regulation of breathing. Anxiety could be expected to increase ventilation during takeoff and re-entry, but should not be a long-term problem for a selected population such as astronauts.

INFLUENCE OF RESPIRATORY MECHANICS

The respiratory system is particularly rugged in its capacity to defend adequate ventilation in the face of mechanical loading. Milic-Emili and Tyler (1963) showed that to increase the mechanical load presented to the respiratory muscles by 100 percent reduced ventilation by only about 2 percent. The experiment of Kellogg et al. (unpublished observations) provided for mechanical assistance to breathing by an amount equivalent to about a 50-percent reduction of respiratory work and produced thereby an increase in ventilation of somewhat less than 10 percent. Accordingly, it may be confidently predicted that the modest changes in respiratory mechanics to be anticipated will have little or no influence on ventilation.

POSSIBLE EFFECT OF HYPEROXIA*

Use of an oxygen atmosphere of 250 mm Hg provides a slight hyperoxia in comparison with sea-level air. Such hyperoxia may depress breathing slightly when it is prolonged for periods of a month to two years. The classic work of Fitzgerald before World War I, in which he measured the resting alveolar P_{CO_2} in normal Americans from the Rocky Mountains down through the Great Smoky Mountains to sea level, seems to indicate that resting alveolar P_{CO_2} is a continuous linear function of altitude. No such thoroughgoing study has been made to investigate whether this relation would extend through sea-level pressures to still higher total barometric pressures. One attributes such variations in the regulation of breathing to the barometric-pressure effect on the total oxygen pressure. Because the oxygen pressure at 250 mm Hg corresponds to a total barometric pressure considerably greater than the normal 760 mm Hg, the matter might be of some interest. There is some experimental evidence that the impulse frequency in the chemoreceptor nerve fibers is a function of oxygen pressure even if the oxygen pressure is above that at sea level.

RESEARCH PROBLEMS

As a preliminary to further studies, chronic exposures to mild hyperoxia should be undertaken with repeated measurements of arterial CO_2 both at rest and during exercise.

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8

EXCHANGE OF FLUIDS IN LUNGS

Transfer of liquid from the lung capillaries to the alveoli (neglecting accumulation in the interstitial space) is caused by the transmural pressure (pulmonary capillary pressure minus alveolar pressure) exceeding the colloid osmotic pressure of the blood. The transmural pressure is normally about 15 mm Hg, whereas the colloid osmotic pressure is about 35 mm Hg. Therefore, for transudation to occur, capillary pressure must increase by about 20 mm Hg, such as it would with increase of left atrial pressure, or alveolar pressure must decrease to about - 20 mm Hg in relation to capillary pressure (- 15 mm Hg has been measured during absorptional atelectasis), or the blood colloids must be lost.

Guyton and Lindsey (1959) found that fluid transudation began at a threshold of left atrial pressure of 24 mm Hg, and that the amount of fluid transuded was progressively greater at greater pressures. When the plasma protein concentration was lowered to 47 percent of control, transudation began at a threshold of 11 mm Hg.

Kylstra (personal communication) suggests that the rate of transudation may be low because, although water passes freely through the alveolar-capillary membrane, salts do not; and owing to their osmotic pressure the salts, passing slowly, delay the passage of water.

Leakage of protein into the alveoli may occur if the alveolar wall - gas capillary membrane is damaged chemically, metabolically, or mechanically. If proteins enter the alveoli, their osmotic effect may facilitate fluid transfer into the alveoli.

Some substances pass rapidly and other substances pass slowly through the semipermeable alveolar-capillary membrane (see Tables 1 and 2). Liquids, solutes, and particulates may accumulate in the interstitial space between capillary endothelium and alveolar epithelium by undefined mechanisms.

Current knowledge indicates that the alveolar-gas interface is lined with a layer of lipoprotein, thus allowing a surface pressure sufficient to overcome the aqueous surface tension which otherwise might collapse the alveoli. This lipoprotein lining is sometimes absent, inhibited, or ineffective, whereupon those parts of the lungs so affected collapse from surface tension.

Life can be sustained in mammals (rats, dogs) by liquid ventilation of the lungs, using balanced saline solutions. These

TABLE 1
Permeability Characteristics of the Pulmonary Blood-Gas Barrier[a]

Entering Barrier		Excluded from Barrier	
Respiratory gases:	O_2, CO_2	Ions:	Na^+, K^+, Cl^-, HCO_3^-, p-aminohippurate, SCN^-, SO_4^{--}, phosphate, lactate, pyruvate
Hydrocarbons:	ethylene		
Inert gases:	hydrogen, krypton, xenon		
Alcohols:	methanol, ethanol, propanol	"Neutral" substances:	urea, thiourea, ethylene glycol, glycerol
Water		Macromolecules:	inulin, proteins

[a]From F. P. Chinard (1966).

TABLE 2
Permeability Coefficients, Blood-Gas Barrier[a]

Substance	Permeability Coefficient		
	Mean	Standard Deviation	Units
^{24}Na	7.2	$\pm$ 2.1 $\times 10^{-7}$	cm/sec
^{42}K	56.5	$\pm$ 3.5 $\times 10^{-7}$	cm/sec
Urea	22.9	$\pm$ 9.2 $\times 10^{-7}$	cm/sec
Glucose	3.14	$\pm$ 0.72 $\times 10^{-7}$	cm/sec
D_2O	> 400	?[b] $\times 10^{-7}$	cm/sec
DNP	> 400	?[b] $\times 10^{-7}$	cm/sec

[a]From Taylor et al. (1965); based on left lower lobe of dogs.

[b]Too fast to measure.

fluids have been oxygenated under high ambient pressure (4 atm) and contain a low concentration of a buffer [THAM = tris(hydroxymethyl)aminomethane or 2-amino-2-hydroxymethyl-1,3-propanediol] to increase their CO_2-absorbing capacity.

FLUID IN THE LUNGS

Causes

The causes of extra liquid in the lungs during manned space flight may be as follows:

1. Liquids may be aspirated from the nose or throat into the larynx, bronchi, or alveoli.
2. Liquids may pass from the lung capillaries into the alveoli during sustained periods of acceleration.
3. The negative alveolar pressure that occurs during absorptional atelectasis might produce a small amount of liquid transudation into the alveoli.
4. Hydrostatic pressure in the lung capillaries during severe acceleration may cause rupture of blood into the alveoli. Similarly, such forces may tear the lung tissue.
5. Secretions from glands in the walls of trachea and bronchi or upper airways could cause blockage during increased G. One deliberate cause of liquid in the lungs might be artificial ventilation of the lungs with liquids, rather than with gases, to support the pulmonary blood vessels and lung tissues with hydrostatic pressure, thus preventing lung hemorrhage or lung rupture and inequalities in ventilation or perfusion during high accelerations.

Consequences

The consequences of fluid in the alveoli would be as follows: Increased surface tension at the liquid - gas interface would make it difficult to re-expand the "wet" parts of the lungs and would thus lead to decreased arterial oxygen saturation. Blockage of alveoli with liquid or bubbles would impair the diffusion of oxygen and contribute to arterial oxygen desaturation. Lungs when artificially ventilated with liquids would require special life-support systems to pump the liquid into and out of the lungs, to dissolve enough oxygen in the liquid, and to absorb and buffer the CO_2 that must be eliminated.

RESEARCH PROBLEMS

These lie in the area of the mechanism of arterial oxygen desaturation, which occurs during forward acceleration. Subjects have some pain in the chest and find it hard to breathe. At 8 to 10 G, ear oximeter readings may fall to 75 percent saturation. The lungs, afterward, may show some atelectasis. At still higher-G loads, hemorrhage and lung rupture have occurred in animals, and perhaps in man. Some rather radical, speculative, and possibly impractical schemes to prevent these effects are given:

Scheme 1: Liquid Ventilation

The techniques and benefits of liquid ventilation, possibly with exotic fluids (Clark, 1966), under high G need to be explored. Theoretically this should allow very high acceleration (for example 100 G) for long periods (hours). The transition from breathing liquid back to breathing air requires further study.

Scheme 2: Collapsing the Lungs

Induce a bilateral hydrothorax of 0.75 liter each side. Breathe 95 percent O_2, 5 percent He or N_2 at 3 atm absolute pressure for 5 to 10 min. Breathe out slowly as far as possible, and hold the breath just before high-G forces begin. External support of the body would be needed. After a minute, or after high-G forces subside, breathe again. Positive pressure at the mouth may be needed to help expand the lungs. This method is predicated on the recent findings that the lungs can be emptied of gas almost completely (Cavagna et al., in press). Hyperbaric oxygen should prolong the state of consciousness to about a minute after cessation of cerebral blood flow (Saltzmann, personal communication) and therefore probably during apnea; 5 percent inert gas should facilitate re-expansion of the lungs (Farhi and Rahn, personal communication). Hydrothorax would be necessary to empty human lungs without collapsing and breaking the rib cage, a danger pointed out by R. E. Davies (personal communication), based on diving accidents.

Scheme 3: Draining Blood from the Brain

If apnea were prolonged, tissue hypoxia would cause irreversible brain damage. Neely and Youmans (1963) found that first drain-

ing a dog's brain of blood allowed survival of hypoxia and recovery of cerebral function even after 25 min of hypoxia. This finding needs to be confirmed. An astronaut might find that re-entry would cause brain tissue hypoxia for a period beyond that compatible with recovery of brain function. He might elect to re-enter in a partly sitting position to drain the blood from the brain—re-entering unconscious, and recovering later.

Certain basic physiological problems bear on the questions at hand. One fundamental question is whether the inside walls of the alveoli are dry, or wet with free water. Another problem consists of finding out whether it is the capillary endothelium or the alveolar epithelium that offers the main barrier to diffusion of salts and particles. Furthermore, there is some evidence (Kylstra, 1958) that heparinized plasma leaves the alveolar space more rapidly than does citrated plasma. Thus, Kylstra found interstitial edema after placing tap water, 5-percent-glucose solution, or heparinized plasma within the alveoli, but did not find interstitial edema after he placed Ringer's solution plus 1.25 percent glucose in the alveoli. Dr. Earl Wood is said to have found (conference deliberations) interstitial edema in the lungs after centrifugation studies.

Scheme 4: Extracorporeal Oxygenation of the Blood

In this scheme, the lungs would have to be collapsed or filled with liquid. Oxygenation of the body would be carried out by passing part of the blood stream through a device such as an artificial lung, and pump, outside the body.

Scheme 5: Breath-Holding Diving Reflex

Cold water placed on the face will produce bradycardia and peripheral vasoconstriction not unlike that found in diving animals. Induction of this reflex might be useful under circumstances where long breath holding is required.

PROMISING LINES OF RESEARCH

Additional knowledge is needed about causes of arterial oxygen desaturation under gravity, the amount of fluid filtered into alveoli under gravity, and the rate of resorption afterward. Labeled dye or protein (albumin tagged with ^{131}I) may be used for this purpose. Also, we need to have more advanced techniques

for liquid ventilation. Studies on the basic physiology of surface tension of alveoli and additional studies of surface layer in alveoli (lipoprotein layer) are required. A better understanding is required about mechanisms of exchange of substances across the alveolar membrane and routes of resorption of proteins: lymphatic, veins, macrophages, and fibrinolysis. Investigators should consider the use of computer simulation of forces acting on the lungs to facilitate their researches.

Bioinstrumentation is needed to determine pulmonary vascular pressures, intrapleural (esophageal) pressure, alveolar pressure, osmotic pressure of blood, arterial O_2 saturation, and the pressure-volume curve of lungs. Bioinstrumentation will be necessary in a life-support system for experiments involving immersion in liquid or liquid ventilation or for voluntary exhalation to minimal air volume, coupled with previous hyperbaric oxygenation to prolong consciousness and 5 percent inert gas to prevent complete or irreversible atelectasis during this maneuver.

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9

RESPIRATORY TRACT CLEARANCE MECHANISMS FOR NONGASEOUS MATERIALS

In considering the physiology of the respiratory tract, primary emphasis is usually given to the lungs' mechanical function of moving air and to the exchange processes in the alveoli that permit air and blood gases to equilibrate. There is another important function associated with respiration, namely, a self-cleaning capability that is responsible for maintaining the epithelial surface of the respiratory tract relatively free of contaminants.

There are three clearance mechanisms of special interest to respiratory physiologists: ciliary mucous transport, endocytosis, and lymphatic drainage. Of these, least is known about lymphatic drainage. Presumably it depends on just two components: (1) selective permeability, controlled by the alveolar epithelium and/or the capillary endothelium, which governs the material transported by lymph; and (2) the lymph flow. Evidence from dust clearance studies indicates that the lymphatics normally account for only a few percent of the total clearance (Morrow et al., 1966a). There are circumstances, however, where the role of lymphatic drainage is increased, for example, during protein absorption and the clearance of certain colloidal substances such as transuranic oxides (Courtice and Simmonds, 1949; Drinker et al., 1937; Thomas, 1965).

CILIARY MUCOUS TRANSPORT

Ciliary mucous transport is one of the major clearance mechanisms of the respiratory tract in that it directly serves to remove material deposited in or arising from the ciliated areas of the respiratory tract, that is, virtually all the conducting airways from the nares down to the respiratory bronchioles. Indirectly, through some coupling mechanism, much of the cellular debris, dust particles, and bacteria that are deposited in or arise from the parenchymatous areas of the lungs are also presented to the ciliary mucous "escalator." The rate of presentation is far slower than the ciliary mucous process, so the coupling quickly becomes rate limiting.

Quantitative assessments of the ciliary mucous transport as a self-cleansing process are far from exact, but data are consistent with the view that the ciliary mucous transport is ordinarily the dominant mechanism for the removal of "insoluble" particulate matter from the respiratory tract.

Although ciliary activity has been the subject of hundreds of investigations in a great numer of species, most of the older work is not particularly useful given the modern view that ciliary activity and mucous transport are an integrated function. Many recent studies have shown that ciliary activity per se may appear to be unaltered while mucous transport or some manifestation of integrated ciliary-mucous function ceases (Dalhamn, 1956). This would suggest that changes in the properties and amount of mucus* can have a profound effect on transport when other indexes of ciliary activity, such as beat frequency, fail to reveal any change. Further, the current literature is full of indications that, unless a close technical control is exercised, extraordinarily variable performances of ciliated epithelia are to be expected. This is less true in the case of mussels and other aquatic animals, including the flagellates.

Most of the important historical studies of ciliary activity, including many relatively modern contributions, have been summarized by Sleigh (1962) and in the symposium edited by Rivera (1962). Another more recent symposium on ciliary mucous transport (Symposium on Structure, Function and Measurement of Respiratory Cilia, 1966) probably represents the best single source on the bioenergetics of cilia, physiology and structure of cilia, and the actions of drugs and air contaminants on cilia. Most of the studies reported in this volume, however, unlike most earlier works, do give necessary attention to the role of mucus.

*In this paper, mucus denotes the superficial fluid lining of the respiratory epithelium.

The information we have on ciliary mucous transport, even in modern terms, mainly stems from measurements of tracheal cilia in experimental animals. Despite the acknowledged problems of environmental control, such as the need for the proper and constant temperature, humidity, composition of media, and the like, experimental results vary disconcertingly. Interspecies variations, such as those reported by Kensler and Battista (1966), are no greater than those found in the same species by different investigators. For example, Baetjer's work (1966) with the chicken trachea indicated approximately 6 mm/min for mucous transport; Carson et al. (1966) reported 0.25 ± .08 mm/min for cats, while transport values ranging between 17 and 45 mm/min have been described in several species including the chicken and the cat (Kensler and Battista, 1966; Battligelli et al., 1966; Dalhamn, 1955; Hilding, 1957; Barclay and Franklin, 1937). The most likely explanation for these variations is still to be found in differences in technique. Most investigators have apparently striven only for a reliable performance in their particular preparation and technique; consequently, comparisons among various investigators' results remain, at best, qualitative.

Human and animal studies have been made with the use of intact preparations. In both groups the many contributions of Hilding (1956, 1961) rely on direct measurements. The human studies of Proctor (1965, 1966), Albert and Arnett (1955), Albert and co-workers (1965), Luchsinger and co-workers (1966), and Morrow and co-workers (1962, 1965) have utilized the clearance of radioactive dust particles. Similar approaches have been made in animals (Bair, 1960; Friberg and Holma, 1961; Friedberg et al., 1965). Although it is not possible when using radioactive dust to determine ciliary mucous transport to express the findings in terms of finite velocities, it is practical to express them in terms of effective clearance half-times. These are generally greater than 0.5 hour and less than 2.5 hours for the tracheal, upper bronchial, and nasopharyngeal areas, regions that appear to be cleared more quickly than the rest of the respiratory tract. In vivo measurements of dust clearance give much slower transport values than those obtained from direct visualization of limited regions of the respiratory tract. There are several possible explanations: The human measurements by in vivo counting are generally complicated by the uncertain nature of the original deposition pattern; that is to say, there is no discrete measurement of single particles starting from specific points and passing to others. Rather, there is a more or less continuous deposition pattern that extends well beyond the area measured to regions where ciliary mucous activity may be quite different (Proetz, 1951). With the in vitro method, the most likely pitfall is use of the dominant or most

rapid ciliary-motion pathway and the rejection of areas outside the mainstream of mucous movement. In other words, there are normally areas that are being rapidly cleared within a fairly localized region, but close by, the mucus might not be so rapidly or completely removed; this "uncooperative" area is rarely studied for fear that it is abnormal. There is a tendency, therefore, to report maximal values. This tendency is partially justified in view of the rather fragile nature of the preparations and the multitude of factors that affect ciliary activity and mucus production. Nevertheless, for toxicological considerations, the in vivo measurements are probably more acceptable and relevant.

Temperature and humidity are regarded as major factors affecting ciliary mucous transport, particularly in the case of in vitro preparations. Under most environmental conditions the human respiratory mucosa is well protected from changes in temperature and humidity except for the nasal passages. Here the ciliary mucous transport is apt to be more variable, not only because of its susceptibility to environmental changes, but also because of the rather nonuniform arrangement of cilia within this region. Studies by Proctor and Wagner (1965) clearly demonstrated zones in the nasal pharynx that are cleared in a few minutes, whereas others remain unchanged for hours.

Ciliary mucous transport in the respiratory tract moves toward the esophagus. There is possibly an exception in the anterior portion of the nasal passages where movement of mucus toward the external nares has been reported by at least one investigator (Proetz, 1933).

Although it is common to the respiratory tract in general, one is struck by the relatively slight responsiveness of the mucus production and ciliary control systems to drugs (Antweiler, 1958; Sleigh, 1962; Rivera, 1962). Certainly a major difficulty in this field is the absence of basic information on mucus secretion and ciliary activity. Tobacco smoke and many irritants appear to be at least temporary ciliastatics (Falk et al., 1959; Dalhamn and Rylander, 1964); where chronic or high doses of irritants and other toxic agents are administered, there frequently is damage to the stratified epithelium with loss of ciliary function (Falk et al., 1963).

The effects of unipolar gaseous ions have received considerable attention in Europe, where many clinics offer inhalation therapy based on ions; in this country interest is primarily due to the work of Krueger and Smith (1958a, 1958b). Krueger and Smith reported that positive ions are ciliastatic and depress mucous flow, whereas negative ions are actually cilioaccelerators. There are also reports that negative ions affect the "acceptability" of the air being breathed (Krueger and Smith, 1958b).

On the basis of existing evidence, it is difficult to understand how the effects attributed to gaseous ions are produced, particularly on the mucous transport process. Considering the large diffusion coefficients of gaseous ions and their propensity to interact with water vapor and aerosols, their penetration beyond the upper respiratory tract seems unlikely. In view of the enormous ion fields and fluxes that are present in the mucous layer, the extracellular fluid, and the membrane interfaces, it seems extremely improbable that a specific substrate for negative ions could exist. Another point of contention, and certainly a most formidable one, is that some investigators have been unable to demonstrate "ion effects" on cilia (Kensler and Battista, 1966). It is appropriate to emphasize that only unipolar ions are involved in this controversy. The production of unipolar ions is not a circumstance expected in space capsules unless there happens to be an electric field present to accelerate one ion species while scavenging the other. There is no evidence that this combination of factors may occur, but very high atmospheric ion concentrations do exist in space (Clamann, 1965); estimates vary from a factor of 10 to 1,000 times normal levels. In this context some reports have indicated that the atmospheric ion concentration has effects on man (Davis, 1963; Barron and Dreher, 1964; Clamann, 1965), but these effects do not appear to be directly pertinent to ciliary mucous transport.

ENDOCYTOSIS

Another important clearance mechanism in the respiratory tract is provided by cells that have the ability to engulf materials, migrate from the engulfment site, and thereby affect the removal of materials. The general term covering cellular activities of this nature is endocytosis. This process is of primary interest in matters of inhalation toxicology because it is recognized as the dominant clearance mechanism in the lung parenchyma for particulate material of molecular, colloidal, or even microscopic dimensions.

In many qualitatively similar ways, endocytosis occurs at different sites within the body, for example, monocytes in circulating blood, endothelial cells in blood vessel walls, Kupffer cells in the lining of the liver sinusoids, and epithelial cells of the small intestinal mucosa. Wilbrandt (1963) in a recent review has described a variety of cells that engage in endocytotic activity. The same engulfment phenomenon is known to occur with most cells in tissue culture and with many unicellular organisms.

The various terminologies describing this phenomenon differ according to Holder (1959) only with respect to the material ingested by the cells, not the mechanism of the process. Thus the terms "phagocytosis" and "pinocytosis" (which covers all forms of engulfment phenomena wherever they occur) may be regarded as identical or at least indistinguishable cytological functions.

The term "pinocytosis" was first used by Lewis (1931) to describe the discontinuous engulfment of environmental fluid by cells. The pseudopods, intracellular invaginations, and vesicules produced during pinocytosis were generally small, although variable in size. In contrast, phagocytosis is a term that has been widely used to describe the uptake of solid materials by the cell, and it also involves pseudopod formation, invaginations, and the formation of inclusions or vesicules, all of which are substantially larger than those produced in pinocytosis (DeRobertis et al., 1960). Nevertheless, we conclude that no important qualitative distinctions are known between the two processes.

A modified form of endocytosis, or at least a special case, has been reported by Moore and Ruska (1957) and termed cytopempsis. This alludes to the phenomenon of the transcellular movement of vesicules that have originated at a cell surface, and thereby describes a special type of transport mechanism. It is not surprising, therefore, that discussions of endocytosis (phagocytosis or pinocytosis) generally appear in recent symposia and literature reviews under the heading of membrane transport (Wilbrandt, 1963; Holder, 1959). It is especially appropriate to consider the phenomenon of cytopempsis as one explanation of how particulate material can be moved from the alveolar cell - air interface to an interstitial position. It is well established that this translocation occurs, but it is poorly understood and has been subject to many interpretations (Hatch and Gross, 1964).

The pioneering studies of Fenn (1921), the investigations of Robertson (1941) and others, on to the work of the modern biochemists (Roberts and Quastel, 1963; Iyer et al., 1961; Kessel et al., 1963) provide a good understanding of endocytotic events, although many gaps exist. The primary event in endocytosis is generally conceived to be the adsorption or contact of the material with the cell surface. This leads to a process called induction, which triggers the endocytotic event. There is good evidence that induction varies according to the material and the media (Holder, 1961). Because induction probably takes place in a liquid layer (mucus, lining complex, or other) both the particle and the cell interface have been subjected to a host of ionic and molecular ligands so that particles, at least, are usually endowed with an adsorbed layer, probably of protein. The interaction of the particle with the cell surface appears to

modify the membrane, that is, provoke induction at fairly localized areas, perhaps through changes in specific binding sites (Marshall et al., 1959).

There is also the possibility that the cell is normally producing vesicules in response to dissolved materials in the external media rather than in response to direct contact of foreign substances with the cell surface (Holder, 1961). In other words, by the first view, there must first be an induction to which the cell responds by engulfing the inductant and surrounding it with an appropriate amount of cell surface membrane; by the second view, there is a normally discontinuous pattern of changes occurring on the cell surface, which leads to a more or less passive uptake of media (which could contain particles). This uptake would be restrictive in terms of the size of the vesicules formed and of the orientation and adsorption of various ligands to cell surface before or as the process occurs (Bennett, 1956). In this regard, Csaky (1965) reports quite different protein and electrolyte concentrations, in comparison with the general environmental medium, along the cell surface and within the pinocytotic vacuoles.

Despite the fact that there are different views on induction, they are not mutually exclusive and may represent the same basic response to inductants of different physical states and potency.

There is very active research on the problem of the fate of the vacuoles or vesicules produced during the endocytosis of materials. This research impinges upon many undeveloped topics, such as lysosomes, endoplasmic reticulum, the so-called internal micropinocytosis, and modifications of permeability in vacuolar and other membranes. Interest in these concepts is tied to the general proposition that the material moved into the cytoplasm is still surrounded by the (external) cell membrane and that there must be some way for the material to be either dissipated, disposed of, or absorbed into the cytoplasm (Siekevitz, 1958; Beaulay and Berthet, 1963; Chapman-Andresen and Nilsson, 1960). In dust phagocytosis, one investigative team has reported particles within alveolar cells that were not surrounded by a vesicular membrane and that presumably entered by mechanical or passive penetration (Schlipkötter and Linder, 1961).

Biochemical studies have clearly shown that energy is required during the process of endocytosis, although the exact events in which the energy is expended are still somewhat controversial (Csaky, 1965; Karnovsky, 1962). It is clear from these studies and from the classic studies already cited that different materials have different endocytotic potentials, that is, macrophages appear to exhibit different affinities for different materials. Also, macrophages appear to differentiate between large and

small particles of the same substance (Schoenberg et al., 1963), although the restrictiveness is not so great as was once believed (Wilson, 1962).

Finally, many reports support the view that pulmonary macrophages respond to the absolute amount of dust deposited in the pulmonary region (Heppleston, 1963; LaBelle and Brieger, 1959; Ferin et al., 1965). Several of these investigators have used this effect to modify the clearance of one dust by administering another. On the other hand, examples exist of dust clearance from the pulmonary region in which the absolute dust burdens varied by more than an order of magnitude without any effect on clearance (Gibb and Morrow, 1962). Finally, relatively continuous dust exposures to some materials may lead to a prolongation of clearance but without appreciable pathological changes (Morrow et al., 1966a).

Macrophages have various origins, but how many origins and the nature of their migratory ability are outstanding points of ignorance and controversy in this field. Both these issues are dramatically relevant to the lung macrophage (Easton, 1952; Heppleston, 1963; Hatch and Gross, 1964; Casarett, 1964).

Phagocytosis has also been studied in animals after particulate exposures by having the "free" cells washed from the lungs (LaBelle and Brieger, 1959). Indirectly, phagocytosis has also been studied by measurement of the disappearance of radioactive colloids and particles that have been taken up by phagocytic cells in a specific area, but in these cases the relation is often more inferred than demonstrable (Nicol and Bilbey, 1960).

RESEARCH PROBLEMS

On the basis of the omnidirectional mucous-flow patterns in the lower respiratory tract, it is reasonable to suppose that gravity ordinarily plays only a minor role in mucous transport. In some conditions, postural drainage is used to augment mucus removal. It is possible that drainage of the nasal passages and the sinuses depends more on gravity than does the lower respiratory tract. In the medical reports of astronauts, a frequent complaint is nasal congestion (Gemini Mid-Program Reports, 1966). Whether this congestion is related to poor drainage caused by the zero-G state or to other factors such as abnormal humidity, atmospheric contaminants, high oxygen tension, low barometric pressure, and the like, or a combination of these factors, is uncertain (Herlocher et al., 1964; Ohlsson, 1947; Roth, 1964). Information to clarify the basis of this respiratory ailment should be obtained.

Gravity-free studies of sinus drainage and mucus clearance seem impracticable at the present time, but 1-G studies in man as a function of humidity, postural changes, drugs, high O_2, etc., are becoming technically feasible and should be encouraged.

In view of the high concentration of ions presumed to be present in space capsules, for example, up to 10^3 times greater than normal (Clamann, 1965) and of the reported effects of both unipolar and mixed ions, it may be necessary to undertake studies of such effects on a broader base than that suggested by ciliary mucous transport alone.

In vitro and in vivo preparations suitable for quantitative measurements of mucous transport should be utilized in toxicological evaluation of atmospheric contaminants.

There is no evidence that gravity plays any role in endocytosis or in the movement of phagocytic cells from one locatio another. However, insufficient studies of endocytosis have been made in mammals. Where such studies have been undertaken they have usually utilized tissue culture, in which the cellular morphology and function alter rapidly, or have employed harvested macrophages, which may not be representative of alveolar macrophages. There is no information in the literature of endocytosis that appears to have any special relevance to man under conditions existing in space capsules.

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10

DIFFUSION OF GASES IN PERIPHERAL TISSUE

The following review of present knowledge on the diffusion of gases in peripheral tissue is based almost entirely on considerations of diffusion of oxygen through tissues. There are few data on diffusion of other gases.

OXYGEN DIFFUSIVITY

Diffusion refers to translocation of a substance in response to an acting force, the gradient in chemical potential. For oxygen, it has been assumed that the acting force is the gradient in partial pressure of O_2, that the capillary wall is a relatively trivial barrier to diffusion, that the tissues are isotropic, and that diffusion through any tissue under any given set of circumstances can be characterized by a single diffusion coefficient. The fact is that most of these assumptions have not been tested critically, and there are even experimental results that appear to challenge some of the assumptions, although in every case the experimental conditions were not free of defects. Nevertheless, on the basis of the classical assumptions, diffusivity of O_2 through tissues has been estimated by one of two methods:

1. A tissue, such as frog abdominal wall, is used as a membrane across which a fixed P_{O_2} gradient is imposed. This is the method used originally by Krogh (1919b) and contemporarily by Thews (1963). The diffusion coefficient, D or D′, is calculated

from the classical equations for unidirectional isotropic flux through plane sheets with invariant diffusivity,

$$\text{flux} = J_x = -D(\partial C/\partial x) = -D'(\partial P/\partial x), \quad (1)$$

where J_x is flux per unit area in the x direction, C is concentration, P is partial pressure (both as differences over the interval of length ∂x), D is diffusivity (area per time), and D' is diffusivity in terms of gas pressure ($D' = \alpha D$), where α is the solubility coefficient of the gas. Table 1 lists some values for D and D' from such experiments. In general, D in tissues is half of or slightly less than that for O_2 in water. Because α is rather temperature sensitive, D' varies more markedly with temperature than D.

Experiments of this sort give no information on the path O_2 takes through the tissues. It is conceivable that nearly all the O_2 diffuses through selective paths having high permeability, and that those portions of the tissue with low permeability go undetected. In particular, these observations do not rigorously define diffusivity of O_2 as it flows out of capillaries through tissues between capillaries.

2. The second method, originally proposed by Warburg, depends on the relation between O_2 consumption by a tissue and P_{O_2} surrounding it. The notion is that, in a multicellular tissue in a bath, the outer regions of the tissue, exposed directly to the bathing solution, have the highest P_{O_2}, and that P_{O_2} decreases toward the center of the tissue. It is supposed that, above a certain critical P_{O_2} for a cell, cellular O_2 uptake is constant and independent of P_{O_2}. For the multicellular tissue, as P_{O_2} is decreased, O_2 uptake remains constant as long as all cells are exposed to P_{O_2} above the critical level. As P_{O_2}

TABLE 1[a]
Oxygen Diffusivity at 20°C

	D	D′	D″
	$cm^2 \cdot sec^{-1} \times 10^5$	$cm^2 \cdot min^{-1} \cdot atm^{-1} \times 10^5$	$cm^2 \cdot sec^{-1} \cdot (mm\ Hg/cm)^{-1} \times 10^5$
Water	1.7	3.2	7.0
Albumin 7%	1.7	3.2	7.0
20%	1.2	2.0	4.4
Frog muscle	0.9	1.4	3.1
Rat heart	1.0	1.6	3 5
Liver	0.6	1.0	2.2
Rat brain (gray)	1.2	2.0	4.4
Rabbit brain (gray)	0.9	1.5	3.3

[a]Adapted from Thews, 1963.

in the bathing solution falls farther, a point is reached at which P_{O_2} in the center of the tissue falls below the critical P_{O_2} for cells. The observed O_2 consumption by the tissue begins to fall at this point, which defines the critical P_{O_2} for the tissue (more precisely, the P_{O_2} in the bathing solution that just fails to maintain zero order O_2 uptake for the whole tissue). Warburg's equation is simply a modified form of Fick's second equation for diffusion:

$$\partial C/\partial_t = D(\partial^2 C/\partial x^2) = D'(\partial^2 P/\partial x^2). \quad (2)$$

Warburg presented the equivalent equation,

$$\dot{Q}/V = D'[(P_t - P_c)/(x^2/2)], \quad (3)$$

where $\dot{Q}/V$ is O_2 uptake per time per unit volume of tissue, x is tissue thickness, and P_t and P_c are critical P_{O_2} values for tissue and cell, respectively. Longmuir (1964) has calculated D' from such experiments on rat liver, kidney, and heart slices. His values are about 10 times greater than those given in Table 1. Since they are about 5 times greater than the diffusivity of O_2 in water they suggest that either there is something wrong with the experiments or there is something wrong with the equation, including the unlikely possibility of active transport.

The possibility that diffusion of O_2 may be enhanced by myoglobin was raised in a number of reports, chiefly in those by Scholander and Hemmingsen (Hemmingsen, 1965) and by Wittenberg (1965), as the result of observations on movement of O_2 through hemoglobin or myoglobin solutions in Millipore filters. Flux of O_2 through such myoglobin membranes is greater than through metmyoglobin membranes. The mechanism remains in dispute, and the relevance of the observations to O_2 diffusion in vivo is questionable. It is noteworthy that cellular localization of myoglobin is undetermined.

Solubility of Oxygen and Oxygen Stores

At 37°C the solubility of O_2 in physiological aqueous solutions is about 3×10^{-5} ml/gram of tissue per mm Hg pressure. O_2 is about 5 times more soluble in olive oil than in blood. If this ratio applies to solubility in adipose tissue, there are about 30 ml of O_2 in the 10 kg of total body adipose tissue at a tension of 20 mm Hg. This is about half the O_2 capacity of all the myoglobin in the body of an adult man.

Models of Distribution of Tissue P_{O_2}

If the partial pressure of an inert gas in arterial blood is kept constant, the gas will be distributed eventually throughout the body (except for tissues at gas interfaces) at a family of constant concentrations in each tissue depending on its solubility; there will be no differences in arteriovenous concentration and no pressure gradients along capillaries. However, because oxygen is consumed by peripheral tissues, there is an arteriovenous concentration difference, there are O_2 pressure gradients along capillaries, and O_2 tension in tissues between capillaries is not expected to be uniform.

Beginning with Krogh (1919a), many geometric models have been constructed to illustrate more or less plausible distributions of tissue P_{O_2}. Krogh's model was a cylinder of tissue coaxial with a lesser cylinder of capillary. Both cylinders were considered to be of infinite length with unidirectional diffusion in only the radial direction, independent of the radial angle, and with zero flux at the circumference of the outer tissue cylinder. The further assumption, implicit in Krogh's model, is that O_2 uptake is zero order and is distributed evenly throughout the tissue. The model considers only the steady state; that is, the spatial distribution of tissue P_{O_2} is independent of time. These conditions lead at once to the statement that the O_2 flux (per unit area multiplied by the area) across any cylinder of radius r within the tissue cylinder is exactly equal to the quantity of O_2 remaining to be consumed by the volume of tissue beyond that cylinder, or

$$2rJ_r = 2rD' (dP/dr) = \dot{Q}/V (b^2 - r^2), \qquad (4)$$

where $\dot{Q}/V$ is O_2 uptake per unit volume of tissue, J_r is flux per unit area in the r direction, and b is the radius of the tissue cylinder. Integration of this equation leads immediately to the equation Erlang presented to Krogh for P_{O_2} at any distance, r, from the capillary:

$$p(r) = p_a - (\dot{Q}/V)/(D') [(b^2/2) \ln (r/a) - (r^2 - a^2/4)], \qquad (5)$$

where p_a is P_{O_2} at the wall of the capillary, a is capillary radius, and b is tissue radius.

The pressure drop, $p_a - p(r)$, is therefore the same for any given r along the length of the capillary. The three-dimensional representation of tissue P_{O_2} is then obtained by constructing a model of P_{O_2} decay along the length of the capillary. The assumption of uniform extraction of O_2 along the capillary leads to a linear decrease in O_2 content along the capillary. When the linear decrease in O_2 content is reflected off the hemoglobin saturation-tension curve, a curvilinear representation of capillary P_{O_2} drop is obtained.

Other models have been discussed by Hill (1965), Roughton (1952), Crank (1957), Caligara and Rooth (1961), and Hudson and Cater (1964).

Of interest is the time necessary for a transient change in tissue P_{O_2} to disappear following a change in arterial P_{O_2}, assuming no change in O_2 uptake. Roughton has calculated that, for the Krogh model, the time necessary for the transient to disappear to within one percent of steady state is:

$$t = (5\alpha/D'\gamma_1^2), \tag{6}$$

where γ_1 is the smallest root in the solution of a rather complicated function. For a capillary radius of 4×10^{-4} cm and for a tissue cylinder radius of 40×10^{-4} cm, γ_1 is 275, and t is about 5 sec.

For the following reasons it is worthwhile to express the average tissue P_{O_2}: (1) No technique has been developed for measuring the spatial distribution of P_{O_2} accurately enough to test the models; (2) because blood flow is likely to be distributed in a continuously changing fashion, intercapillary gradients will be reduced; and (3) longitudinal diffusion within the tissue will reduce the gradients.

Mean tissue P_{O_2} along the radius of the tissue cylinder at any given point, x, along the capillary is:

$$\overline{p_x}(r) = 1/b - a \int_a^b p_x(r)dr \tag{7}$$

$$\overline{p_x}(r) = p_x(a) - [(\dot{Q}/V)/(b - a)\, D'][b^3/2 \ln (b/a) - (7b^3 - 6ab^2 - 3a^2b + 2a^3/12)] \tag{8}$$

Mean tissue P_{O_2} is then taken as the mean, $\overline{p_x}(r)$, along the length of the capillary

$$\bar{p}(x, r) = 1/L \int_0^L \overline{p_x}(r)dx, \tag{9}$$

where L is capillary length. The integration is performed numerically.

For human skeletal muscle at rest, from data on O_2 uptake and arteriovenous concentration differences observed in the forearm of man, if the tissue cylinder is selected so that the most remote point just falls to zero O_2 tension, it can be calculated that intercapillary distance is 144 μ and mean tissue P_{O_2} is 23 mm Hg.

Measurements of Tissue P_{O_2}

Three main types of measurements have been used: (1) P_{O_2} in body fluids such as urine and lymph, (2) P_{O_2} in artificial interstitial gas pockets, (3) P_{O_2} by polarography with needle electrodes placed on or within solid tissues. No method is completely satis-

factory. P_{O_2} in lymph has been reported in anesthetized dogs to be about 8 mm Hg regardless of the site (Bergofsky et al., 1962). It is not known whether lymph P_{O_2} is in equilibrium with any solid tissue P_{O_2} and, if so, with what P_{O_2} it is in equilibrium.

Gas tensions in artificial pockets apparently do not reach a steady state. According to Rahn (1957) there is extensive vascularization about the gas pocket, and the P_{O_2} in the pocket has no obvious relation to P_{O_2} in solid tissues.

There have been many critical discussions of so-called O_2 electrodes. The electrodes damage the tissue into which they are inserted. They sense P_{O_2} in an uncertain volume surrounding the electrode, but it is a volume that is relatively large in comparison with the size of the electrode tip. In general, tissue P_{O_2} measurements by O_2 electrodes are characterized by very large variations; whether they are spurious or mirror genuine tissue P_{O_2} gradients is unknown. For example, Cross and Silver (1962) stereotaxically placed two electrodes 1 mm apart in rabbit forebrain. P_{O_2} varied from 5 to 20 mm Hg with great divergencies between the two electrode readings. An example of average P_{O_2} measurements made in a variety of tissues by the one group of observers is given in Table 2.

TABLE 2
Tissue P_{O_2} Measurements, mm Hg[a]

Liver	13	Cerebrospinal fluid	35
Kidney	20	Spleen	17
Subcutaneous	23	Intraperitoneal	17
Brain	37		

[a]Measurements by Jamieson and Van den Brenk (1965) in anesthetized rats with 60-μ-diameter gold electrodes.

Intercapillary Distance

There have been a number of estimates of intercapillary distance based on capillary counts per unit area of tissue in fixed preparations. This morphological intercapillary distance represents the minimum. In many tissues, owing to action of pre-

capillary sphincters, most capillaries are not perfused vigorously at any given moment under resting conditions, although it is unlikely that any capillary is unperfused for very long.

For example, Myers and Honig (1964) estimated the number of functioning capillaries in the heart after injection of radioiodinated serum albumin (RISA) and ^{51}Cr-tagged RBC's

counting of myocardial sections. With certain assumptions they estimate that there are only 750 capillaries per mm^2 in apical superficial myocardium and about 1,100 in apical deep myocardium, or about 20 percent of the morphological capillary count. This means that functional intercapillary distance is much greater than morphological intercapillary distance except under maximal blood flow. Since intercapillary distance is the most potent determinant of mean tissue P_{O_2}, mean tissue P_{O_2} depends critically on the number and distribution of functioning capillaries.

RESEARCH PROBLEMS

The entire subject of the diffusion of gases in peripheral tissue is riddled with uncertainties. Tissue P_{O_2} at any point depends more or less linearly on arterial P_{O_2}, on blood flow, on oxygen consumption, and on diffusivity, but it depends to a greater extent on intercapillary distance.

Physical diffusion of O_2 from one extravascular region of a tissue to another depends on local P_{O_2} gradients and on the diffusion coefficient, which is not apt to be changed by conditions of space flight. If arterial P_{O_2}, total blood flow, and oxygen consumption are maintained, the real problem is the distribution of capillary blood flow.

Measurement of mean tissue P_{O_2} gives no information on the distribution of P_{O_2} and can conceal the fact that some regions may be below a critical level of P_{O_2}. The assumptions that critical P_{O_2} is very low, less than 1 mm Hg and that O_2 uptake is zero order are based largely on observations on the cytochrome system. They ignore the possibility that qualitatively crucial, though quantitatively minor, mechanisms for O_2 uptake may require higher P_{O_2}. Information on the role of O_2 in maintaining integrity of mammalian cells is fragmentary.

Even if reliable methods for spatial resolution of tissue P_{O_2} existed, it would be important to check for evidence of cellular hypoxia under the circumstances appropriate to space flight. The rules of evidence have not been established clearly but include signs of increased leakiness of cells, such as a rise in certain extracellular enzyme concentrations, best detected by measurement of arteriovenous differences.

Methods for measuring capillary blood flow in various organs are not completely settled, but the mo' promising methods are those that employ tracer dilution techniques or tracer washout in conjunction with local injection and external monitoring.

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DAVID MINARD

11

TEMPERATURE REGULATION

Heat exchange by way of the respiratory tract will be negative under the environmental temperatures planned for space cabins and pressurized space suits, that is, the body will lose heat by warming and humidifying the inspired gas. Under resting conditions at ground level at 75° F and 50 percent RH, this heat loss constitutes approximately 12 percent of total body heat. About half the respiratory heat is lost in warming the inspired air (sensible heat) and half is lost as latent heat in humidifying the air (insensible heat). During activity, the increase in respiratory heat loss will be proportional to the minute volume, with the result that the fraction of the total heat production thus accounted for will remain comparatively unchanged. It should be emphasized, however, that heat loss via the respiratory tract in man is subject to control not by the thermoregulatory center but by the respiratory center and is thus driven by ventilatory needs rather than needs for control of body temperature.

In atmospheres contemplated for post-Apollo flights, hypobaric pressures will reduce sensible heat loss via the respiratory tract because of the lower (as compared with ground level) density of the atmosphere. Since the specific heat of the gas is also a determining factor of sensible heat exchange in the respiratory tract, heat loss will vary depending on the composition of the cabin atmosphere. Insensible heat loss via the respiratory tract is dependent not on atmospheric pressure but rather on the vapor pressure of the inspired air and its dry bulb temperature.

Exposure to heat may influence respiratory function by inducing hyperventilation in some subjects and by reducing blood

volume in the pulmonary vascular bed. The latter response appears to reduce pulmonary diffusion capacity ($D_{L_{CO}}$) both at rest and during exercise.

Studies on heat and water exchange via the respiratory tract have recently been reviewed by Webb (1964), Webb and Annis (1966), and by Wortz et al. (1966).

Webb and Annis (1966) emphasize the role of the upper airway as a heat exchanger, first cooled by incoming air during inspiration and then warmed by expired air from the deeper regions of the lung. These authors studied sensible and insensible respiratory heat exchange in man at rest and at work. The subject breathed mixtures of gases of different specific heat (O_2 + He, O_2 + N_2, O_2 + SF_6) at 1 atm in an air environment, and at 4 and 8 atm in a hyperbaric wet chamber. They concluded that factors determining sensible heat loss in atmospheres of the same dry bulb temperature were respiratory minute volume and the product of the density and specific heat of each gas mixture. Insensible loss was a function only of minute volume and vapor pressure of the inspired gas. Under the two hyperbaric conditions that they studied, respiratory heat loss amounted to as much as 25 percent of heat produced. In confirming earlier studies, Webb and Annis point out that expired air is not fully saturated and is below body temperature. Consequently, to assume that expired air is fully saturated and at body temperature is to introduce an error in estimating respiratory heat loss from computations with the use of temperature and humidity of the inspired air and the minute volume alone.

Wortz et al. (1966) measured water loss in expired air with subjects at rest and while walking at 2 and 4 mph on a treadmill. Their subjects breathed oxygen at one of three dew points (40° F, 60° F, and 80° F), at one of three ambient pressures (3.5, 7.0, and 14.7 psia), and at one of three dry bulb temperatures (95° F, 75° F, and 55° F). The authors concluded that each of the variables affects water loss. Reduced ambient pressure reduces water loss apparently because of the lower minute volumes at the reduced pressures to which the authors ascribed reduced respiratory work. Water loss was proportional to the minute volume and thus revealed an essentially linear increase with work rate. Increasing the humidity of inspired gas reduced water loss; increasing dry bulb temperature produced greater water loss. The amount of water added to the respired air was observed to vary from 0.0067 gm/l to 0.0268 gm/l. Wortz et al. (1966) supported the findings of Webb and Annis and of earlier authors, that expired air approached but did not reach body temperature, being less than 97° F even when inspired air was maximal (95° F). Moreover, it was never fully saturated.

Changes in pulmonary ventilation as a result of acute heat exposure have been reported by Iampietro (1963) and more

recently by Murray (1966). Although a rise in body temperature increases metabolic rate by approximately 13 percent per 1°C, this mechanism would not explain hyperpnea under heat stress because hyperpnea is often observed before a significant rise in mean body temperature has occurred. Moreover, a rise in ventilation resulting from increased metabolic rate would be associated with a normal alveolar P_{CO_2}. Iampietro (1963), on the other hand, describes extreme hyperventilation leading to respiratory alkalosis and tetany.

Hyperventilation is occasionally seen in unacclimatized men undergoing recruit training in hot weather. Symptoms are sometimes confused with those of heat exhaustion or heat syncope (Leithead and Lind, 1964).

Thus, the mechanism of hyperpnea observed during acute heat exposure is by no means well understood. Although anxiety may be a factor in unacclimatized and inexperienced men, heat hyperpnea may also be observed in subjects accustomed to experimental conditions in heat chambers (Iampietro, 1964; Murray, 1966).

Other respiratory responses to heat exposure are less apparent. A recent study by Frayser et al. (1966) indicates that heat exposure reduces blood volume in the pulmonary vascular bed. Associated with this shift is a reduction in diffusion capacity for CO measured by the single-breath method. In resting subjects the D_{LCO} measured at room temperature at rest was 33.1 ml/min mm Hg. This dropped to 29.4 during exposure to an ambient temperature of 49°C. After 2 hours' exposure to 49°C, D_{LCO} was found to be 40.3 two minutes after the subject began working on a bicycle ergometer. At room temperature, the D_{LCO} at the same work level was 46.8.

RESEARCH PROBLEMS

Mechanisms of water loss via the respiratory tract deserve study for improvement of the design of space ventilatory systems, particularly in pressurized suits. It is recalled that fogging and frosting of the facepiece was reported during the extravehicular activity of the Gemini IX flight. For example, respiratory flow could be coupled directly to a heat exchanger exposed to the space environment. Removal of sensible heat and water vapor from expired air with return of cold dry air would make maximum use of the airway as a heat exchanger. In any event, the physical process of evaporation of water into a closed space at zero G, in the absence of any convective forces and under varying atmospheric pressures, should be determined.

The mechanism of heat hyperpnea is not well understood. One question that might be asked is whether this response is adaptive with respect to tolerance to heat exposure. If unrelated to mechanisms of body temperature regulation, hyperpnea would be expected to diminish as heat acclimatization develops. Such a change would suggest that emotional factors may play a role. Investigations of heat hyperpnea should include (1) its possible modification during acclimatization; (2) a behavioral assessment of subjects displaying the response; and (3) experimental efforts to elicit the response in susceptible subjects by limiting heat exposure to the upper airway, to various skin areas, and to carotid blood (with the use of diathermy).

An important gap in knowledge in thermal physiology is the cause of redistribution of blood under heat stress in subjects at rest or at work. A search for reflex or hemodynamic causal mechanisms should be made. A promising lead is given in the report of Frayser et al. (1966), which indicates that an interaction may exist between pulmonary circulation and the increase in cutaneous circulation that occurs on heat exposure. (The significance of this finding in terms of exercise capacity in the heat remains obscure.) Interrelations between neural and humoral factors affecting respiration and those concerned with cutaneous circulation should be sought. A question here is whether there is a physiological association between the hyperpnea of exhausting work and the peripheral cutaneous constriction often observed to precede collapse.

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PART III

THE ATMOSPHERE

ROBERT E. DAVIES

12

OXYGEN TOXICITY AT NEAR-NORMAL PARTIAL PRESSURES

Because a decision must be made concerning the nature of the atmosphere to be used in long-duration manned space flight, it is necessary to know the toxicity of oxygen at slightly above normal partial pressures and to evaluate the possible hazards of oxygen at somewhat reduced partial pressures.

Our information concerning the biochemical changes associated with the development of oxygen poisoning is quite unsatisfactory. Despite great efforts (for review, see Davies and Davies, 1965), it has not been possible to find a chemical reaction that is clearly associated with the observed physiological changes, although recently Chance et al. (1966) found that changes in the intracellular oxidation-reduction states of reduced pyridine nucleotide in general, and on the energy-linked pathway for pyridine nucleotide reduction in particular, have been found to occur quite rapidly in rat liver and pigeon heart mitochondria. One of the problems has been that the tissues in descending order of oxygen sensitivity are brain cortex, > spinal cord, > liver, > testes, > kidney, > lung, > muscle. This refers to the acute effect of high partial pressures of oxygen on the oxygen uptake of isolated slices of these tissues. However, in the intact animal the lung, either directly or indirectly, is extremely sensitive to increases in the partial pressure of oxygen (DuBois, 1962; Lambertsen, 1965).

Our current information on the possible toxicity of 100 percent oxygen at 5 psi is incomplete. There is no evidence that it cannot be tolerated for periods of 14 days, but the information is inadequate for coming to a clear decision about exposure for long periods. There has not been agreement among the workers

in the field. Thus, Sharpe (1964) wrote,

There is no physiological reason why 100 per cent O_2 at 5 psi cannot be used for 30 days. Prior simulation studies using 100 per cent O_2 at 5 psi have reported such effects as renal aberration, tunnel vision, substernal pain, hematological changes, ocular and respiratory irritation, and aural atelectasis. These changes are not believed to be of consequence because they are (1) non-reproducible, (2) inconsequential, or (3) they may have been coincidental.

McNerney (1965) found that

A 90-day continuous exposure of mice, rats, beagles and monkeys to a 5 psia and 100 per cent oxygen environment produced the following pertinent results: 1) A Wistar-derived strain of rats proved to be sensitive to altitude conditions early in the exposure (15 per cent mortality within 14 days of exposure) whereas a Sprague-Dawley-derived strain proved resistant. 2) A possible association of increasing SPGT levels in beagles with length of exposure.

Except for these factors, the experimental animals gave no apparent indication of being stressed throughout the exposure. A one-year study has been initiated to determine if the enzyme change was due to sampling or is indicative of an accumulating stress.

No significant increase in the toxic response of animals to inhaled atmospheric contaminants under conditions of 5 psia and 100 per cent oxygen was noted when compared with animals exposed under normal atmospheric conditions (except in the case of mice exposed to carbon tetrachloride).

Roth (1966) wrote,

At a recent NASA conference on Selection of Post-Apollo Atmospheres, it was reported that electron microscopic changes in mitochondrial structure have been seen in the liver and kidney of several animal species after prolonged exposure. . . (7 days). . . to 5 psia 100 per cent O_2. There were no specific symptoms or clinical chemistry findings associated with these lesions and their meaning is not clear. The USAF toxicology studies at the Aero-Medical Laboratories at Wright-Patterson AFB have recently revealed that most of the abnormal blood chemistries seen in dogs and monkeys early in exposure to 5 psia 100 per cent O_2 return to normal within 6 months. Only blood lactic dehydrogenase (LDH), serum pyruvic-glutamic transaminase (SPGT), and serum glutamic-oxalacetic transaminase (SGOT) remain slightly above the upper limits of the normal range. These slight abnormalities may represent adaptation to 5 psia 100 per cent O_2.

Harper and Robinson (1966) stated that

Dogs, monkeys, rats and mice were exposed for periods up to 92 days at an atmosphere of 93-98 per cent oxygen at approximately 258 mm Hg. During the study 20 per cent of the rats and two mice died of overwhelming pulmonary edema and congestion. Uniformly pre-existing infectious disease in rats increased in severity during the exposure. Edema of the pulmonary artery media was noted in 55 per cent of the exposed rats and 36 per cent of the exposed mice examined, while control animals were free of this change. The high incidence of endemic disease in rats, dogs and monkeys is emphasized, with a caveat to investigators attempting to evaluate results when using these species in inhalation work. No dose-

response relationship was found between any pathological finding and exposure to a single gas oxygen atmosphere at this pressure.

Back (1966) noted that, in rats exposed to 5 psia 100-percent-oxygen environment for periods up to 235 days, deaths were strain dependent, Wistar rats being much more sensitive than Sprague-Dawley rats. Hagebusch (1966) in experiments on the pathology of oxygen exposure at 5 psia for 230 plus 40 days concluded

> On the basis of this small group of animals it is suggested that at 258 mm Hg 100 per cent oxygen for 230 days may be toxic for the dog. There was no evidence that this concentration was toxic for mice or monkeys under the same experimental conditions. . . . It is the considered opinion that when dogs are exposed to 258 mm Hg 100 per cent oxygen for 230 days, pathological changes are present in the lungs. It is thought that subtle changes may be present in rats at this same exposure, but that more work is necessary before this can definitely be determined.

These data lend weight to the view of the Space Science Board's Report of the Working Group on Gaseous Environment for Manned Spacecraft (1965):

> A partial pressure of oxygen of 250 mm Hg is an abnormal environment for man, and one that is potentially injurious. We were not satisfied that the simulated flights and the pressure-chamber studies performed to date have validated the selection of 100 per cent oxygen at 5 psi as a suitable cabin atmosphere for space flights of longer than a few days. At present there is inadequate scientific information about the extent to which subclinical oxygen toxicity may lead to serious impairment of itself, and may be exacerbated by weightlessness, by exposure to ionizing radiation, by infection, or by other factors peculiar to space flight.

RESEARCH PROBLEMS

Owing to the very different responses of different animal species, and even strains, to atmospheres containing oxygen at increased partial pressures, it is not possible to conclude without long-term testing that such atmospheres, that is, 5 psia, are safe for humans.

On the other hand, normal partial pressures of oxygen are known to be safe and acceptable. Reduced partial pressures may also be acceptable and in some cases unavoidable, but the circumstances and limits must be investigated.

It may be that a partial pressure of oxygen somewhat less than that found in air at 1 atm would be even more advantageous than that in normal air. The effects of radiation on tissues would theoretically be lessened, the leak rate would be decreased if the total pressure were lowered, the fire hazard would be reduced (Fenn, Chapter 14, p. 102), and acclimatization would permit a lower cabin P_{O_2} in case of emergency. The present

requirement for a total ambient pressure of 5 psia appears to be predicated largely on heat exchange of astronauts and of instruments. The use of newer (liquid cooled) methods may obviate this atmosphere requirement. Studies on the advantages and disadvantages of a cabin atmosphere containing oxygen at less than 150 mm Hg should be carried out.

SUMMARY

It is not certain that atmospheres containing increased partial pressures of oxygen are safe for humans during long-duration space flights (more than 30 days). Reduced partial pressures of oxygen may be acceptable and in some cases unavoidable. The circumstances and limits of the use of reduced rather than normal partial pressures of oxygen ought to be examined carefully.

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ROBERT E. FORSTER

13

CONSIDERATIONS OF CARBON DIOXIDE CONCENTRATION

The ambient [CO_2] in the spacecraft is a function of the rate of CO_2 production by the astronauts (plus a negligible amount produced by materials oxidizing) and the rate of CO_2 absorption by the air conditioning system. The latter in turn is determined by the efficiency of the CO_2 absorber and the flow rate through it. Theoretically, by increasing the air flow and the action of the absorber, the CO_2 in the inspired gas can be reduced to any desired level, but it is at the cost of increased energy consumption and increased weight (Roth, 1966). To maintain the inspired P_{CO_2} at approximately normal atmospheric levels, the air flow through the CO_2 absorber must be extremely high, the relations between [CO_2] in gas and flow being reciprocal. Therefore, a reasonable limiting gas [CO_2] is chosen, and the absorbing - circulating system is designed to keep the cabin gas concentration below this limit.

Alveolar P_{CO_2} under steady-state conditions is proportional to rate of CO_2 production x alveolar ventilation. Thus alveolar, and, because it is in equilibrium with is, arterial P_{CO_2}, will rise whenever alveolar ventilation falls in relation to the metabolic rate, because of either a relative fall in minute ventilation or an increase in the physiological dead space. Of the two components of physiological dead space, the anatomical should decrease because of the expected reduction in lung volume (Mead, Chapter 4, p.26). As discussed by Permutt in Chapter 6 (p. 38), the uniformity of alveolar ventilation to capillary blood flow will probably be improved

during zero G, although there will be transient gross abnormalities during launch and re-entry. Thus, we expect no significant changes in physiological dead space in flight, and because there also appears no reason to expect important changes in the regulation of minute ventilation, alveolar P_{CO_2} should be in the normal range.

Once it becomes necessary to determine a safe level of inspired CO_2, the effect of chronic exposure to different concentrations of this gas must be known in order to make a reasonable choice. This immediately raises the problem of investigating the multitude of effects of CO_2 upon the body.

Workers have performed studies on inspiration at 21 torr (3 percent) CO_2 in which there was deterioration of performance (Schaefer, 1961). Even at 10 torr (1.5 percent) there were difficulties with adaptive processes. Thus, from physiological considerations alone the inspired P_{CO_2} should be less than 8 to 10 torr; on the basis of these considerations a similar limit was set, perhaps arbitrarily, by the Space Medicine Advisory Group (NASA, 1965).

It is essential to distinguish between the scrubbed gas entering the atmosphere of the space suit or capsule and that inspired in the astronaut's upper airway. Under steady state conditions, space into which a man breathes, be it cabin atmosphere or helmet, must contain enough CO_2 so that the total CO_2 carried away by the ventilating stream equals the rate of his CO_2 production. In other words,

$$CO_2 \text{ production rate (ml STPD/min)} = \text{gas flow (ml STPD/min)} \times [CO_2] \text{ in fractional atmosphere.} \quad (1)$$

This simple relation is often helpful in estimating the actual inspired $[CO_2]$ from knowledge of only the CO_2 production rate and the flow of ventilating gas. Note that inspired $[CO_2]$ is independent of the volume of the space into which rebreathing occurs.

We are told (E. Michel and J. Billingham, personal communication) that the $[CO_2]$ of the scrubbed gas entering the suit is monitored by an instrument that registers only when the partial pressure rises above a predetermined value; in the Gemini program that value was 7.6 torr (although continuous in-flight records are preserved at the Manned Space Flight Center in Houston). However, this is not the same as the inspired $[CO_2]$, which is probably higher. Apparently the inspired P_{CO_2} during flight has not been measured.

RESEARCH PROBLEMS

1. Determine the normal operating inspired P_{CO_2} in spacecraft, in pressure suit, and under conditions of varying activity.
2. Determine the possible effects of inspiring low concentrations of CO_2 (such as 7.6 torr P_{CO_2}) over extremely long periods.
3. Determine the effects of a breakdown in the CO_2 absorbing system, such as the rate of rise of P_{CO_2}.
4. Measure alveolar (expired) P_{CO_2} when subjects are awake and asleep, at zero G.
5. Determine time-concentration curves of increased inspired CO_2 for use in emergencies.

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WALLACE O. FENN

14

INERT GASES

Man can survive in spite of large variations in the composition and pressure of the inspired air, the partial pressures of oxygen and carbon dioxide being the most critical. The optimum composition is not necessarily the same for launch, re-entry, in-flight maintenance, or extravehicular activities. The selection of the best mixture is also complicated by engineering and environmental factors not directly related to the physiology of the astronaut. This chapter will endeavor to consider all these factors, with special reference to the physiology of the man himself. The particular problem of the best partial pressure of oxygen is considered in Chapter 12 of this report. We recommend that for prolonged use the oxygen tension of the inspired gas in the spaceship should be no higher than that found in air at sea level when both atmospheres are saturated with water vapor at 37°C. Starting with this as a basis, the amount and nature of the inert gas to be added must be decided. We hope to predict on the basis of the information now available just what the physiological risks may be and what emergencies might be encountered in a space mission with different gases in the various circumstances.

PHYSIOLOGY OF THE INERT GASES

Before considering the advantages and disadvantages of adding inert gases to the atmosphere of the space capsule, a brief review

of the physiology of the inert gases is in order. Under normal conditions the only inert gas of any importance is nitrogen.

Nitrogen gas, when inhaled, can always be recovered as nitrogen gas in either the excreta or the expired air. It might however, have some physiological effects even at the concentration found in air. In a sufficiently high concentration of 3 or more atm it has a narcotic effect that is well recognized by deep-sea divers and has been demonstrated in many laboratory studies. Synapses are more sensitive to nitrogen narcosis than are isolated nerves and muscles (Marshall, 1951). In Drosophila, at least, high pressures of nitrogen are more narcotic in the presence of 1 atm than in 1/5 atm of oxygen (Fenn, 1965). The same is true of xenon and argon, but helium has a narcotic effect only in very high concentrations. Similarly, the inhibitory effect of the narcotic inert gases on the growth of Streptococcus faecalis is greater in the presence of 1 atm of oxygen than in a strictly anaerobic environment (Fenn, unpublished observations). Mice and men are more sensitive to nitrogen narcosis than paramecia and insects, possibly because the CO_2 tension is higher in mammals.

Nitrogen narcosis is attributed to the physical effect of a sufficient number of molecules of N_2 in solution in the water, proteins, or lipids of the body cells, especially those in the brain. This narcotic state develops very quickly, apparently as soon as a threshold concentration of nitrogen in the tissues is attained. According to Bennett (1966), in his excellent monograph on inert gases, the time required for blocking of the alpha rhythm of the electroencephalogram in man is inversely proportional to the square of the pressure. There is no evidence of adaptation to high concentrations of nitrogen, although there seems to be some diminution in the subjective effects after the first onset of high pressure. This may be due to disappearance of an initial increase in CO_2 tension because of pressurization. As far as we know now, the body reacts to a second exposure to high pressures of nitrogen exactly as it does to the first exposure, with neither increased tolerance nor increased sensitivity.

There is at present no good evidence that the nitrogen we inhale plays any essential role. At least for periods of a few weeks, men and other animals tolerate a nitrogen-free atmosphere without any untoward effects as long as the oxygen tension does not exceed the normal value. Fruit flies have also tolerated such nitrogen-free environments without obvious decrement in their life span. In Neurospora, however, Schreiner et al. (1962) have shown that growth is accelerated when helium is substituted for nitrogen; the growth rates were inversely proportional to the square roots of the molecular weights of the gases. Under high pressures, nitrogen was unusual in being less inhibitory to growth than helium (Schreiner, 1965). These experiments do suggest that even at 0.8 atm pressure the inert gases may have some effect.

It was reported by Volskii (1960) and confirmed at least partially by Allen (1963) that chick embryos do not hatch normally if the nitrogen of the air is replaced by helium. This conclusion, however, was not confirmed by further work in the Soviet Union by Savin (1965), who reported that development was normal provided the eggs were properly cared for. It is doubtful at present, therefore, whether any effect of sea-level nitrogen can be deduced from this work. Further, South and Cook (1954) reported some inhibition of oxygen consumption and some acceleration of anaerobic glycolysis of mammalian tissue slices by N_2 in comparison with helium at 0.8 atm, but recent efforts by Rodgers (1966) failed to confirm these findings. Finally, MacHattie and Rahn (1960) have raised a litter of mice successfully at 1/5 atm of 100 percent oxygen without ever permitting any significant amounts of N_2 to enter the lung. Again, there remains no reliable evidence that sea-level N_2 is physiologically active.

REASONS FOR AND AGAINST INCLUSION OF INERT GASES IN SPACE CAPSULES

Advantages of including inert gases are:

1. Less danger of fire
2. Atelectasis of the lung inhibited
3. Possible but still unproved effects of low pressures of nitrogen for long periods

Disadvantages of including inert gases are:

1. A double monitoring system needed to stabilize the atmosphere
2. Extra cost of carrying a supply of inert gas to replace gas lost by leakage
3. Danger of developing the bends
4. Engineering requirements for the ventilation system

These arguments will be considered in turn, beginning with the factor considered by us to be of first importance—the danger of fire.

ADVANTAGES OF ADDING INERT GAS

Inert Gases and the Hazards of Fire

It seems impossible to rule out completely the danger of fire in a space capsule. It is possible, however, to reduce substantially the chances of a dangerous fire without seriously incapacitating

the astronaut. Unfortunately, for engineering reasons it is desirable to reduce the total cabin pressure so that the percentage of oxygen is increased, perhaps to 100 percent, and this increases the fire hazard (Clamann, 1965; Hall and Fang, 1963; Roth, 1964). In a pure oxygen atmosphere at 5 psi, fires have burned with unexpected speed, so that the temperature rises very quickly to very high levels. At a sufficiently high temperature, even stainless steel will burn (Parker et al., 1964). Under such circumstances the usual fire-fighting methods are useless. In a space capsule the process is to some extent self-limiting if the O_2 supply is automatically turned off because there is a limited supply of oxygen, and when that is used up the fire will stop. In the meantime, however, very high temperatures and pressures have been generated, and noxious gases may be produced. Events develop so rapidly that there may hardly be time to institute any fire-fighting procedures and even less to get into a space suit. It is extremely doubtful whether an astronaut could survive if the fire started in a shirt-sleeve situation.

To our knowledge there have been no serious efforts to incorporate in space vehicles appropriate methods for fighting oxygen fires, and without them the situation is hazardous for the astronaut. Apparently the only method now envisaged is to decompress the whole capsule immediately (Space Science Board, 1965), and this is a safe procedure only if the astronauts are already in their space suits. If the atmosphere is dumped promptly enough, a single astronaut, in his suit, might conceivably be able to cool the burned location and recompress the capsule quickly enough to permit the resuscitation of his anoxic comrades, but the chances of success in such a venture seem very slim indeed. Several fires have already developed in simulated space flights despite precautions that seemed adequate at the time. It is perhaps impossible to anticipate every contingency; any local heating from electric apparatus, meteoroid impact, inadvertent focusing of the sun's rays, or an electrostatic spark might start a fire.

In a gravity-free environment, the danger of fire is somewhat diminished because there is no convection to bring a fresh supply of oxygen to the flame, and the available oxygen may be largely replaced by carbon dioxide and water vapor. Under such conditions a candle burns with a small round flame rather than the familiar elongated flame (Clamann, 1965). Tests in gravity-free parabolic airplane flights have shown, however, that the candle, at 100 percent O_2 in 5 psi, is not extinguished thereby, at least not during the short period (28 sec) of weightlessness available for such experiments (Hall, 1964). This gravity-free factor is naturally most effective in a completely static atmosphere; it may be supposed that in a space vehicle the currents of gas produced by the ventilating system and the movements of the astronauts in

their efforts to escape from or to extinguish the fire, might stir up the atmosphere sufficiently to neutralize the protective effect of the gravity-free environment. On the whole, more studies of fires in such an environment would be exceedingly helpful in appraising the fire hazards to be expected.

Every possible precaution should be taken to minimize the chance of ignition, to slow the rate of burning, and to install in the vehicle the most effective fire-extinguishing measures. One method that might be considered is a stream of any inert gas, because even helium is as "heavy" as carbon dioxide in a gravity-free situation and much less toxic. Quick automatic pressurization of the whole capsule (up to its maximum pressure tolerance) with nitrogen might also permit use of more familiar fire-fighting methods and reduce the conflagration to manageable dimensions.

An excellent and very comprehensive review of fire hazards and methods of extinguishing fires has been made by Roth (1964), but several fires have occurred more recently, and the danger of fire might now be given even more weight than the author gave it at that time. Since that report, further studies have been made by Parker et al. (1964) and Huggett et al. (1964, 1965). All these authors and others agree that the presence of an inert gas and a decrease in oxygen partial pressure slow the rate of burning and the energy required for ignition, although the results vary somewhat with different combustible materials. Helium and nitrogen appear to be the inert gases of choice, although neon might serve equally well. Helium requires less ignition energy than nitrogen, but nitrogen seems more effective in retarding the spread of fire in spite of the higher thermal conductivity of the helium. On the whole, nitrogen seems slightly preferable. A jet of nitrogen gas mixed with water could be effective by cooling the burning surface and surrounding the flame with oxygen-free water vapor and nitrogen. Water should not be used for this purpose, however, without due consideration of the damage to the lungs that results from inhaling hot steam at a temperature that would be innocuous in a dry gas. Pressurization with nitrogen could be continued to the limit of the pressure tolerance of the vehicle without physiological hazards. Meanwhile, the fire itself would reduce the oxygen tension if the cabin supply were turned off, and the astronauts could use oxygen masks from a separate system. Whatever method proves most feasible, we strongly recommend that a fire-extinguishing system be installed in space vehicles.

Mention should also be made of the possibility of fire in a space suit ventilated by oxygen. One such fire has already been experienced during an ejection from a disabled high-performance experimental airplane (Yeager, 1965). One would conclude that a suit should be ventilated with water or nitrogen rather than a combustible mixture.

Prevention of Atelectasis by Inert Gases

The physiology of atelectasis is considered in more detail by Permutt in Chapter 6, (p. 38). Here it is only necessary to state that even in normal breathing any small branch of the airway may become occluded by fluid or mucus, thus trapping some gas beyond that point. If that gas contains only O_2 and CO_2 it is absorbed by the blood within a few minutes, and that part of the airway will collapse, gas free. If the collapse is sufficiently widespread it can be detected as a decrease in the vital capacity, a condition often observed in aviators breathing 100-percent-oxygen mixtures (Ernsting, 1960, 1965). This collapse can usually be opened up again easily by a few deep breaths, but it may last for 24 hours in spite of all efforts to correct it (DuBois et al., 1966). Trapped gas of this sort disappears more rapidly at high altitudes or low pressures because there is less gas to absorb. The tendency toward trapping of gas is also favored by breathing at low lung volumes and by exposure to high-G forces. The presence of any inert gas greatly delays the absorption of trapped gas. Owing to its lower solubility, helium provides more delay than nitrogen. In general, trapped gas disappears rapidly at first, but in a short time it disappears much more slowly and at a constant composition. At this point every gas in the mixture attains a concentration just enough higher than that in the venous blood entering the lung that it is absorbed at a rate proportional to its own percentage concentration. Thus, the composition of the trapped gas remains constant after this point, until all the gas has disappeared (Rahn and Farhi, 1963). Such atelectatic areas are useless for gas exchange and tend to lower the oxygen saturation of the arterial blood.

A similar situation obtains in the inner ear. Astronauts breathing 100-percent-oxygen mixtures find it necessary to clear their ears frequently, and may even have to be awakened at intervals during the night for that purpose. While neither of these effects is usually serious, it is at least an annoyance and can be avoided by even small amounts of any inert gas.

Possible Effects of Low Pressures of Nitrogen for Long Periods

This problem has already been discussed, and it is evident that further experiments are required. To determine conclusively whether any such effects exist, it would be necessary to keep animals in a nitrogen-free atmosphere at normal oxygen pressures for their full life-span, or for several generations. It would

also be useful to carry out this experiment at different oxygen tensions to discover whether the life-span is longest at the oxygen tension of air or at some slightly higher or lower tension. In Drosophila, at least (Fenn, unpublished observations), the partial pressure of air seems to be optimum, although there are probably no statistically significant differences between 0.1 and 0.25 atm. It is well known, however, that nitrogen does have physiological effects at higher pressures, and an extrapolation to a pressure for no-effect is subject to considerable error. Lacking good evidence to the contrary, therefore, it might be wise to include some nitrogen in the cabin atmosphere; from this point of view, a nonnarcotic gas like helium would not be expected to serve the same purpose.

Engineering Requirements for the Ventilation System

It is reported that the weight of the blower needed for ventilation in the capsule increases markedly with decrease in pressure. A study carried out by Parker et al. (1964) indicates that the total required weight of the capsule reaches a minimum at a pressure of about 7.5 psi rather than 3.5 psi. It is thus for weight considerations that engineers have recommended the inclusion of an inert gas. If other ways of cooling could be found to avoid this large weight penalty, the conclusion might be quite different.

DISADVANTAGES OF ADDING INERT GAS

The principal disadvantage of including an inert gas is that it seems to be an unnecessary added expense. It requires a store of nitrogen or helium large enough to replace all the inert gas lost by leakage, an amount that could equal perhaps 30 percent of the oxygen consumed by the astronaut. Total weight is thus greatly increased, and a double monitoring system, with an oxygen sensor to keep the P_{O_2} constant and a total pressure system to control the addition of inert gas, is also required. This, of course, can easily be done, but it does add to the total weight and the total cost.

The only real physiological disadvantage to the inclusion of an inert gas is the danger of producing the bends when the pressure is reduced for extravehicular activities. This danger could, of course, be reduced by breathing 100 percent oxygen for 3 hours before making the transition from, say, 7 psi of a 50/50 nitrogen-oxygen mixture to 3.5 psi of 100 percent oxygen. One would expect this procedure to be reasonably safe because the total

pressure is not reduced to less than about 60 percent of the inert gas pressure; in practice, however, it has been found that about 5 percent of the astronauts do develop the bends under these conditions (Parker et al., 1964). Most cases of the bends could be treated satisfactorily by returning the victim to the original atmosphere at 7 psi until more of the nitrogen could be removed by more-prolonged breathing of pure oxygen, but the bends sometimes leads to difficulties not easily treated in a space capsule.

It might be pointed out also that with a pressure lower than 7 psi, the tendency to develop the bends on launch is increased if the preliminary period of denitrogenation by the breathing of oxygen were not continued for the full 3 hours usually considered necessary. This might be listed, therefore, as one of the advantages (rather than a disadvantage) of including an inert gas in the capsule atmosphere.

We believe that the advantages of including an inert gas definitely outweigh the disadvantages, and strongly recommend an inert gas-oxygen mixture for long-term flights. The only problem remaining, then, is the selection of a suitable gas for this purpose, and the determination of the optimum pressure of the chosen gas.

SELECTION OF BEST INERT GAS FOR USE IN SPACECRAFT

There is no apparent reason to use any gas other than nitrogen. There are certainly no advantages to argon, xenon, or SF_6, and not enough is known as yet about the physiological effects of neon. If absence of N_2 (as such) is likely to be a hazard for long-term flights, then helium presumably could not be a substitute. Nitrogen is somewhat better than helium in controlling fires. Helium, on the other hand, is said to be less likely to cause the bends because its low solubility and more rapid diffusion should permit its more rapid elimination from the body. This notion is not borne out in the experience of divers, however. (See Roth, 1965, for references.) Further, Brestkin (1958) has reported that helium tends to initiate bubble formation at a substantially lower level of supersaturation than does nitrogen. Helium is certainly nontoxic and has been found to be no worse than nitrogen with respect to speech intelligibility at low pressures and perhaps even slightly better because of the lower noise level (Cooke and Beard, 1965).

Helium is said to be preferable to nitrogen because it does not lead to dangerous radioactive isotopes like carbon-14 when bombarded by neutrons secondary to cosmic rays impinging on

the capsule or its contents (Bond, 1963). This, however, seems a minor consideration because there is more nitrogen in one adult man than in a space cabin atmosphere, and there are so many other ways, even in a helium-oxygen atmosphere, by which radiation can cause damage to man. Nitrogen also offers a better substitute than helium for the formation of ions in the space cabin atmosphere. Such ions have been considered beneficial, but the evidence is that there will be more than enough ions at the expected radiation levels with either inert gas (Clamann, 1965).

It has been calculated that under certain conditions the extra weight required to store the necessary amount of inert gas is appreciably less for helium than for nitrogen. Apart from such engineering considerations, N_2 seems somewhat preferable to helium. Since N_2 has more narcotic effect than He at high pressures, it may well have a small effect at low pressures; and since the body is adapted to the presence of N_2, this small effect might be important. Admittedly, no evidence of such an effect has yet been demonstrated in man.

A preference for helium has been mentioned on the grounds that it delays the absorption of trapped gas in the lung longer than nitrogen, but either gas provides so much delay in relation to 100 percent oxygen that the slower absorption of helium is probably not significant. On the other hand, nitrogen has been recommended because it provides more protection against ionizing radiation. [This is based on the experiments of Ebert et al. (1958) who found that relatively high pressures of the inert gases protected bean roots against damage from ionizing radiation, nitrogen being more effective in this respect than helium. A similar protection has been observed in Drosophila (Chang et al., 1959).] This protection actually seems to represent an elimination of the potentiating effect of oxygen, and it is supposed that the inert gases act by somehow displacing oxygen from combination on some site where it can effectively enhance the damage from radiation. Still, the protection afforded by either nitrogen or helium at pressures of less than 1 atm appears to be negligible and thus provides no basis for preference.

In conclusion, it is suggested that nitrogen is somewhat better than helium as an inert gas to be added to the necessary oxygen in the cabin atmosphere. A pressure of 2 or 3 psi is suggested as a reasonable concentration.

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JOSEPH C. ROSS

15

TRACE CONTAMINANTS

Safely sustaining man in a closed system for a relatively long period is not particularly new or unique. This problem has been handled by the Navy for many years, and many successful missions have been performed in which prolonged periods of submergence in the nuclear-powered submarine have been required. The experience and data compiled on submarine contamination problems have direct application to space cabin function. While the problems are similar in the two systems, the environmental control problems in the spacecraft are greatly accentuated by the internal and external environments of the vehicle. It has already been shown that there are no major difficulties with regard to trace concentration of toxic contaminants in missions up to 14 days. The major problem, then, appears to be associated with missions lasting longer than 2 weeks and with those that could not be aborted easily into the friendly atmosphere of Earth. The major needs with regard to trace contamination, then, are as follows:

1. Prevention, as far as possible, of contamination with trace concentrations of toxic substances
    a. Determination of the origin of trace contaminants
        i. Degradation and gas-off products of materials used within the confined space
        ii. Contaminants from man himself
        iii. Contaminants from the acute failure of systems and equipment
    b. Identification of the nature of possible contaminants
    c. Selection of materials with regard to their gas-off and degradation products

2. Adequate knowledge of man's long-term tolerance to various trace contaminants

3. Rapid detection of trace contaminants in confined spaces

4. Removal of the contaminants from the closed environment

Possibly because of its high leakage rate, no significant trace contamination of the Gemini vehicle has been noted. However, since near-zero leakage is necessary to conserve the atmosphere on extended manned missions, the buildup of contaminants from the equipment and from man himself could become a serious problem. Some trace contaminants may be irritating but not life threatening, while others, by a cumulative effect, may actually be life threatening. Some trace contaminants may be directly irritating to the skin, eyes, or upper or lower respiratory tract, while others may produce a systemic toxic effect after being absorbed into the body. Although many trace contaminants may have no effect on respiration, they are important in relation to respiration because the majority of them are in the gaseous phase and are most commonly taken into the body by that means. It is for this reason that trace contaminants must be a part of the consideration of respiratory physiology during prolonged manned space flight.

ORIGIN OF TRACE CONTAMINANTS

A great deal of knowledge has been accumulated concerning the origin of trace contaminants. It is well known that carbon monoxide is produced endogenously (Coburn et al., 1965; Root, 1965) and is also a gas-off and degradation product of many materials. More than 50 different gases from the several hundred believed to be present in the sealed environment of nuclear-powered submarines have been isolated (Schulte, 1964). This complex mixture of gaseous atmospheric contaminants comes from many sources. Neither the acute nor chronic symptoms of intoxication attributable to exposure to any of these compounds has been reported in submarines; it would appear that such control methods should be sufficient in the sealed environment of the future space vehicle. At least 46 contaminants were identified in the internal environment of the Mercury spacecraft as a result of stripping the atmosphere of contaminants by means of activated charcoal for post-

flight analysis (Saunders, 1963). The major constituents, accounting for 99.5 percent of the total, were carbon dioxide and Freon-114. The pattern of the contaminants was similar in all flights analyzed, and practically all evolved in the outer cabin atmosphere as distinct from the separate atmosphere of the pilot's pressure suit.

Hodgson and Pustinger (1966) have a program to establish the

off-gassing and oxidation products from individual cabin materials. They have tested 150 materials and over 1,500 gaseous environments to identify and estimate concentrations of gas-off products. They also found that at 25 °C, little increase in gas-off products occurred after the first 30 days if there was no purging and if the chamber was not recharged, but if the chamber was purged and recharged, additional gas-off products accumulated after the first 30 days.

The atmosphere to which four human volunteers were exposed for 56 days during a study designed to describe the effects on man of oxygen-helium at 258 mm Hg total pressure (oxygen, 175 mm Hg; helium, 74 mm Hg) was analyzed for major and minor constituents by Adams et al. (1966). Sixty-eight minor constituents were detected, and concentrations were below the level thought to cause a physiological effect. Another study with four men in a closed system for 30 days showed the maximum concentrations of CO, CO_2, NH_3, SO_2, H_2S, NO_2, Cl, hydrocarbons, aldehydes, cyanide, and phosgene to be well below alert values (Toliver and Morris, 1966).

These investigations have not, in general, been specifically designed to study contamination. Conkle et al. (in press) have conducted a study to define the contaminants associated with human occupancy of a sealed environment in an oxygen-nitrogen atmosphere at 760 mm Hg total pressure with an oxygen partial pressure of 165 mm Hg. The study consisted of an 11-day background (unmanned) and a 14-day manned period. A total of 97 compounds was identified, with 22 noted only during the manned portion. Methane production was within the limits of flatus production. Carbon monoxide was produced at the rate of 0.37 ml/man/hour and was the only compound produced by man at such a rate that it clearly would require removal in long-term sealed atmospheric habitation.

In summary, then, numerous trace contaminants have been identified in the atmospheres of confined spaces. Their origins have been determined to be from degradation and off-gassing of materials within the space, from endogenous production within the body, or from some breakdown of equipment or system. Some trace contaminants have been identified, and others have been recovered but not identified. It is likely that a great many others will be noted as further studies proceed.

KNOWLEDGE OF MAN'S TOLERANCE TO TRACE CONTAMINANTS

Although much is known about the toxicity of various trace contaminants, the deficiency lies in the fact that most of this knowl-

edge has been obtained on the basis of industrial exposure. Much of it has also been obtained from animal studies and extrapolated to man. As already pointed out, a majority of these trace contaminants are taken into the body by inhalation, although most are not known to have any direct effect on respiration. Some, however, have their toxic effect directly on the lungs and respiratory tract. Of these, some common examples are carbon monoxide, ozone, nitrogen dioxide, and sulfur dioxide. Some information has been derived from the industrial threshold limit value (TLV). The TLV represents the upper limits of toxic concentration to which nearly all workers can be exposed day after day without ill effect, and it is designed to be used only for 8-hour exposures in a 5-day work week for a 30-year-or-more work span.

Carbon monoxide is one of the most common trace contaminants. Its commonest source in small amounts is ordinary smoking. Large concentrations of CO, possibly lethal, may be produced by fire in a confined space. With about 50 percent saturation of the hemoglobin with carbon monoxide (which may occur after breathing 0.21 percent carbon monoxide for 70 min) the subject will be on the verge of unconsciousness. Carbon monoxide has been identified as one of the trace contaminants in a closed system, as expected, because it is endogenously produced within the body and exhaled in the expired air. The rate of carbon monoxide production in the closed-system study noted above (Conkle et al., in press) is 0.37 ml/man/hour. The TLV in industry for 8 hours/day of exposure to carbon monoxide is 0.01 percent carbon monoxide (100 ppm) for 480 min (Coburn et al., 1965; Root, 1965).

The primary targets of ozone (O_3) are the lungs and respiratory tract; 4 to 50 ppm for 3 to 4 hours causes death in laboratory animals from pulmonary edema (Young et al., 1964). Exposures to 9 ppm have produced severe pneumonitis in humans. Young and co-workers also found that, after breathing 0.6 to 0.8 ppm ozone through a mouthpiece for 2 hours, subjects had a decreased vital capacity, $FEV_{0.75}$, MMEF, and D_{LCO}, suggesting thickening of the alveolar wall be edema fluid and tracheobronchial irritation. Other investigators found that 0.34 to 1.35 ppm ozone decreased tidal volume and increased respiratory rates in guinea pigs (Murphy et al., 1964). McNerney and MacEwen (1965) exposed monkeys, dogs, rats, and mice to continuous inhalation of constant concentrations of ozone at different oxygen tensions for 14 days and found a definite reduction to the toxic response of ozone at higher oxygen tensions.

Ozone is much more acutely toxic than NO_2, but exposures to NO_2 are common and have resulted in a large number of injuries and fatalities. With acute exposure at concentrations of 500 ppm or greater for short periods of time (from a few minutes to an hour) the development of acute pulmonary edema and possibly bronchopneumonia occur, with a very high mortality. With exposure to 150 to 200 ppm, bronchiolitis fibrosa obliterans de-

velops; 50 to 100 ppm induces bronchiolitis with focal pneumonitis lasting from 6 to 8 weeks with, usually, spontaneous recovery. Chronic intermittent exposure to NO_2 in the range of 10 to 40 ppm may result in a type of chronic pulmonary fibrosis (Stokinger, 1965). Concentrations of 5.2 to 15 ppm NO_2 decrease tidal volumes and increase respiratory rates in guinea pigs (Murphy et al., 1964). Hine et al. (1965) have studied the toxicity of NO_2 to rats and rabbits. Secondary infection with diffuse bronchopneumonia is an important complication of NO_2 gassing in man (Stockinger, 1965). McNerney and MacEwen (1965) also found that monkeys, dogs, rats, and mice exposed for 14 days to continuous inhalation of NO_2 had reduced toxic response at higher oxygen tensions.

Sulfur dioxide, formaldehyde, and acrolein cause increased tidal volume and increased respiratory rates in guinea pigs (Murphy et al., 1964). Lester and Adams (1965) found that concentrations of 5 to 40 ppm of oxygen difluoride for 5 to 15 min caused lung pathology in animals. Harper and Robinson (1966) found a greater mortality in dogs, monkeys, rats, and mice from exposure to carbon tetrachloride vapor when in combination with high oxygen tensions than with ambient air. Back et al. (1962) exposed rats, mice, and monkeys to 90 days of continuous toxic vapors and gases including carbon tetrachloride (25 ppm), phenol (4 ppm), indole (10 ppm), skatole (3 ppm), hydrogen sulfide (20 ppm), and methyl mercaptan (50 ppm). The concentrations of test gases were those recognized as industrial TLV's. Methyl mercaptan, indole, and the mixture of several compounds caused the greatest mortality in monkeys. Hydrogen sulfide caused no deaths in monkeys but did cause a significant mortality in rats and mice. Carbon tetrachloride produced weight loss and liver damage, and indole produced hematological changes in rats and mice. These studies made it fairly obvious that inducstrial TLV's cannot be used as criteria for long-term exposure. Saunders (1966) found that the crew of manned environmental systems assessment developed symptoms of appetite decrease, nausea, vomiting, itchiness around the eyes, headaches, sore gums, and painful jaws. This was in the first few days of a 30-day study with five men in a closed system. The mission was aborted on the fourth day. The trace contaminant producing these symptoms was determined as dichloroacetylene.

DETECTION OF TRACE CONTAMINANTS

Most of the above studies have been carried out in chambers or in environments where the concentration of the trace contaminant can be rigidly controlled. Identification of many of the trace con-

taminants has been made by removing all the noxious gases from the atmosphere by means of activated charcoal, with analysis and separation being carried out later. Detection of the contaminant and determination of its concentration have been carried out primarily by gas chromatographic mass spectrometry, but the ability to sense the complete spectrum of the spacecraft contaminants has not yet been achieved.

Removal of Contaminants

Conventionally, activated carbon has been used to remove aerosols, and a catalyst is used to remove contaminants such as carbon monoxide. Cryogenic trapping systems are being studied (Conkle et al., 1965).

RESEARCH PROBLEMS

Manned spacecraft are faced with a unique problem in the need to measure confined, continually recycled atmospheres and the trace contaminants therein. These minute samples present a problem, for although initially they may have little significance, they will probably have a cumulative effect on the astronaut. As they are compounded, the problem becomes more perplexing. The cabin materials that give rise to noxious gases and vapors may not be too different from those found in undersea craft. The differences that will be present, however, have been mentioned. There are payload limitations requiring a closed ecological system for supplying a habitable environment during prolonged manned space flight. The cabin will probably be operated at less than 15 psi pressure, thus enhancing greatly the problems of "boil off" from such common substances as paints, varnishes, adhesives, plastics, oil solvents, fluids, and even metals, to mention only a few. Zero-G conditions will also give rise to problems with particulate matter such as dust and aerosols, which will have a tendency to clump into larger and larger aggregates and be harmful to both man and filtering systems.

Another, and possibly the most important limitation, is the electric and mechanical power supply. Submarine engineers were able to deal satisfactorily with most of the problems noted above as a result of the advent of nuclear power, which allowed almost unlimited power for air conditioning systems, air filtering beds, air pollution instrumentation, and contaminant warning systems. Even then cabin air became contaminated. The requirements for space cabin design are thus very stringent, and the objective

must be to prevent significant contact with trace contaminants from occurring, or when it does, to provide acceptable protective procedures.

With regard to trace contaminants there are many problem areas and gaps in knowledge.

1. All probable contaminants in space vehicles have not yet been identified, nor have concentrations been determined. The gas-off products of a variety of materials under different environmental pressures, temperatures, and oxygen concentrations are being studied (Hodgson and Pustinger, 1966). No studies, even short-term, have been made during simulated flight to determine the trace contaminant levels in a manned space vehicle.

2. Because studies are being carried out to determine the off-gassing of materials used in the space vehicle, the identification of these substances will be forthcoming. However, there is little information concerning methods to prevent the release of these toxic contaminants from the materials used. Because it will probably not be feasible to remove all contaminants completely, an area of concern should be that of preventing the production and release of the contaminants.

3. The knowledge of man's tolerance to trace contaminants over long periods is not complete. It is obvious that extrapolation of a TLV figure for 30, 60, 90, or more days of continuous exposure is not valid even though TLV's may have large built-in safety factors. As it will not be possible to prevent the production of certain toxic contaminants in low concentrations, and as it may not be feasible to rid a space vehicle's environment of all contaminants, it is necessary to know man's tolerance to long-term exposure. To be applicable, these tolerances must be determined in large animals under conditions as closely simulating flight as possible, for extrapolation to man. Studies up to the present time have not, of necessity, taken into consideration the problem of zero G.

4. Little is known about individual hypersensitivities to inhalation of many of the trace contaminants. There are many individual hypersensitivity reactions, and initial exposure to some substance may sensitize a susceptible individual to any future exposure.

5. The effect of zero G on the accumulation and toxicity of trace contaminants has not been determined. Some light on this problem might be obtained by comparing (with all conditions being otherwise equal) the contaminants accumulated during a simulated manned space flight with those of an actual space flight of the same duration.

6. There is no information about the effects of combinations of toxic contaminants under space flight conditions or the microcontaminant problem under conditions of stress.

7. The ability to sense the complete spectrum of spacecraft contaminants has not yet been achieved. Another problem area, then, is the development of appropriate instrumentation.

8. Further development of systems to remove a variety of trace contaminants from the space vehicle atmosphere is needed.

PROMISING LINES OF RESEARCH

Ground-Based Studies

1. Studies of the off-gassing properties of the materials used in the spacecraft. Certainly much additional information on what can be expected in the way of trace contaminants would be obtained thereby.
2. General broadening of investigations in the field of environmental toxicology.
3. Determination, for many of the common trace contaminants, of TLV's based on a 24-hour-day 7-day-week exposure in small and large animals, for extrapolation to man. These studies should include considerations of different atmospheric pressures and oxygen tensions.
4. Extension to much longer periods of study such as those of Conkle et al. (in press) to determine the toxic contaminants associated with human occupancy of a sealed environment.
5. Studies to identify the toxic trace contaminants that may be produced by fire, or the materials that may be used for fire fighting within the space vehicle cabin.
6. Studies of individual hypersensitivity reactions to various trace contaminants in space vehicle environments.
7. Trace contaminant study of the actual space vehicle with crew aboard during prolonged simulated flight prior to actual flight. Actual flight conditions, except for the gravity-free state, could be closely simulated and the results compared with an actual flight of the same duration.
8. Continuation of the development of a system (e.g., cryogenic) for more effective removal of contaminants.

In-Flight Studies

1. Studies of the effect of zero G on the accumulation and toxicity of trace contaminants
2. Studies in primates or other large animals of the effects of combinations of contaminants and/or the stresses of actual space flight on their toxicity
3. Trace contaminant studies during an actual manned space flight to compare with a simulated flight in the same vehicle for

the same duration to determine the effects of the gravity-free state on toxic contaminant accumulation

Gas Analysis

Gas analyzers with versatility and reliability must be perfected so that ultimately a suitable instrument may be available to serve as a space-borne gas analyzer for more advanced manned probes into deep space. Several methods have been proposed, including optical absorption, mass spectroscopy, and gas chromatography. It appears now that a combination of two or more systems will be found optimal (Weber, 1963). Instrumentation requirements almost certainly will include the capability of either continuous analysis of space vehicle environment or the early detection of the presence of any trace contaminant above the level that is determined to be tolerable to man for long-term exposure.

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16

PARTICULATE MATTER: GENERAL CONSIDERATIONS AND AEROSOL DEPOSITION IN MAN

Particulate matter is always a component of the air we breathe. Concern for the health of workers in the so-called dusty trades and, in more recent times, the growing public health problem associated with radioactive fallout and generalized air pollution, have stimulated much aerosol research, especially in the realms of engineering control and biological effects.

In the summary report of the Space Science Board's Working Group on Gaseous Environment for Manned Spacecraft (1964), a recommendation was made to study the contaminants of spacecraft atmospheres, including dust and other aerosols. Virtually nothing has been done so far to determine, with respect to aerosols, the nature and extent of the air contamination problem in space capsules, although statements by Jones (1966) and Roth (1966) clearly indicate that a variety of aerosol sources has been either identified or speculated upon and some type of aerosol removal system has been utilized.

Both the Mercury and Gemini vehicles have rather high atmospheric leakage and turnover rates. Gemini capsules with their ~ 2,270-liter volume, for example, have ~ 795 liters/min turnover rate and a leakage rate specification of 0.5 liters/min. The Gemini atmospheric filters consist of a trap for solids (40-μ Dutch-weave cloth screen), two 5- to 10-μ filters on the ends of the lithium hydroxide (CO_2 absorption) canister, followed by a thick granular charcoal filter (Billingham, personal communication, 1966).

These factors and equipment, of course, determine to a considerable extent the aerosol concentrations, characteristics, and

persistence in Gemini capsules. Apollo and future spacecraft will be larger and have lower leakage rates in terms of percentage of total volume. Greater reliance will be placed on regenerative systems. All these developments indicate that new and different aerosol sources and removal systems will continue to emerge. It is therefore useful to treat all particulate-matter considerations in the broadest possible terms.

Particulate matter in the air originates from diverse sources, but broadly speaking it is generated by:

1. Thermal phenomena, including combustion and other rapid exothermic chemical reactions; electric arcs; and high-temperature modifications of physical state such as boiling.

2. Condensation and coalescent phenomena in which supersaturated vapors form droplets; vapors and gases adsorb to nuclei; and atoms, ions, and nuclei interact to form stable particles.

3. Disruptive phenomena, consisting of a variety of physical interactions in which surfaces are eroded and disrupted; in all such cases materials are fractured, ground, or otherwise reduced in size and increased in surface area.

The major forces affecting the airborne stability of dusts are:

1. Gravitational sedimentation. This follows the classical relationship between gravitational acceleration and the viscous resistance of air described by Stokes' law, corrected by a slip correction factor (Rosenblatt and LaMer, 1946; Green and Lane, 1964) where particles of less than 1 μ in diameter are concerned.

2. Inertial impaction. This deposition phenomenon is brought about by a high-velocity aerosol stream being directed against an obstacle or caused to change direction abruptly. The particles with sufficient inertia fail to follow the air flow and are intercepted by a surface.

3. Diffusion or Brownián motion deposition. This phenomenon is governed by the kinetic energy of the gas molecules according to the Einstein equation (Green and Lane, 1964). The slip correction factor is of great importance in the diffusion of small particles whose diameter is approximately the mean free path of the gas molecules; these are the only particles with appreciable diffusion coefficients.

Fundamental to all biomedical questions and problems associated with aerosols is the matter of deposition (dust removal from the air during respiration) and of retention (persistence of dust in the respiratory structures after deposition). Many valuable experimental studies (Van Wijk and Patterson, 1940; Landahl et al., 1952; Dautrebande et al., 1957; Brown et al., 1950; Hatch and Kindsvater, 1947) and some theoretical models (Findeisen, 1935; Landahl, 1950; Davies, 1961) have been reported on dust deposition, and agreement is substantial. This agreement is probably an expression of the fact that the instability forces

affecting a dust particle are qualitatively identical whether the deposition occurs outside or within the respiratory tract and implies that the anatomical and physical characteristics of the respiratory tract are sufficiently well established to permit an understanding of its dynamic interplay with the physical properties of the aerosol.

Many of the experimental and theoretical relationships described have been organized into deposition curves according to particle size (Hatch and Gross, 1964). An example is given in Figure 1. Such curves are useful not only for depicting the deposition probability of particles of different aerodynamic size but also to predict regional deposition patterns. The major shortcomings of these particular relationships are twofold: (1) They are based, both experimentally and theoretically, on normal respiratory patterns, i.e., approximately 700-ml tidal volume at 10 to 15 respirations a minute. Deep breathing, prolonged inspiratory phases, hygroscopic and electrically charged dust, etc., will all tend to increase deposition beyond the predictions indicated. (2) They fail to give a clear picture of the deposition probabilities of a dust cloud, that is, in the state of dustiness normally encountered. In these cases, a heterodisperse-sized distribution, usually of several orders-of-magnitude range, is

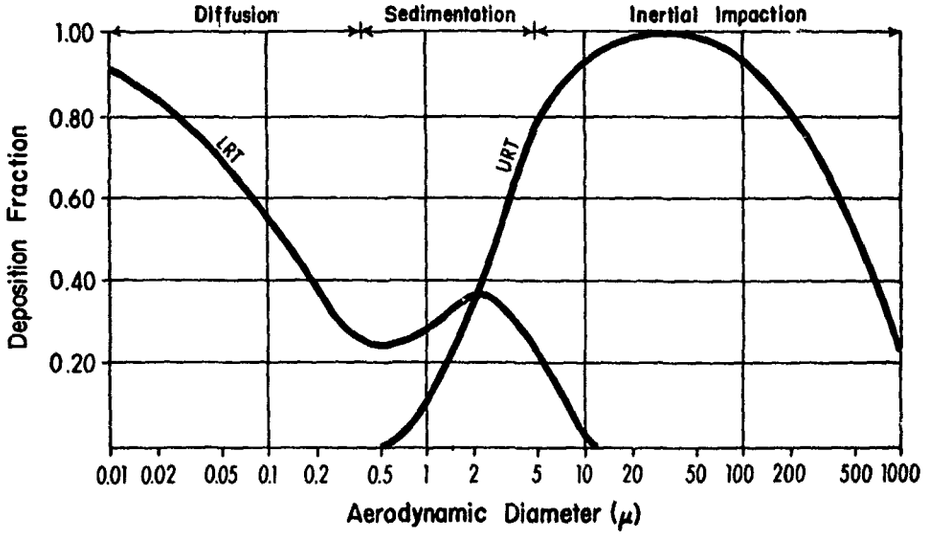

FIGURE 1

Particle - Size Deposition Relationships on Earth. These curves represent the deposition probabilities for particles of the stated sizes during normal respiration. The principal deposition forces involved are indicated; however, they are not to be construed as being exclusive or only pertinent to the size ranges indicated. Aerodynamic size utilizes the particle's terminal velocity and expresses it in terms of a unit density sphere with the same terminal velocity.

breathed so that the relative numbers of each particle size (number in a limited-sized interval) has to be considered. Moreover, in toxicological considerations, both chemical and radioactive, the mass distribution of the aerosol is likely to be more significant than the frequency distribution, and this particular relationship is obscure in such presentations as Figure 1. To this last point is the quite common circumstance whereby 90 percent or more of the particles constitute less than 10 percent of the aerosol mass.

CONSIDERATIONS FOR MANNED SPACE FLIGHT

With the foregoing concepts, predictions, and limitations in mind, we now transfer our considerations to the zero-G state and hypobaric pressures, for example, ~ 3 psia. The sources of aerosols in spacecraft will be diverse, and many, if not most, will be linked to the activities of the astronauts and to the astronauts themselves. Among the aerosols that should be suspected and have been to some extent identified are lubricants, oils, fibers, chemical dusts, food, skin, dandruff, and dried saliva.

There are two essential differences in the behavior of an aerosol in space in contrast to Earth: (1) Sedimentation, which is totally due to gravitational force on the particle, will not occur; consequently, a considerable range of particles of biological interest on Earth, i.e., > 0.5 and < 10 μ, will be stabilized. (2) The mean free path of the air molecules will be increased by the reduced barometric pressure, thereby increasing the slip factor. This, in effect, lowers the resistance of the air to particles of all sizes (i.e., increases their mobility), and is important for enhancing diffusion deposition, the dominant factor for deposition of submicronic particles. Predictions of this general nature have been described by Busby and Mercer (1965), Muir (1966), and Beekmans (1966).

The deposition of particles by inertial impaction will not be decreased in space; in fact, particles that pass through the nasal passages and ordinarily sediment in the tracheobronchial tree or pulmonary spaces will now remain airborne and be expired again. There will thus be an additional, although lower, probability of impaction as the particle moves back through the upper respiratory tract (Busby and Mercer, 1965).

As already stated, where reduced pressures exist, dust deposition due to the Brownian motion of the gas molecules will be enhanced in space; this will primarily affect particles below half a micron and produce an increase in pulmonary deposition. In terms of mass deposition, this effect is not particularly important,

but in terms of aerosols serving as vectors for toxic materials and for considerations of the type that are normally applied to "clean rooms," these particles take on special significance.

Under gravity-free conditions, another deposition phenomenon will prove important although comparatively rare on Earth, namely, interception. This type of deposition in the respiratory tract depends upon the dimensional similarity of the particle and the airways. In the 1-G situation, it is exemplified by the deposition of fibers (asbestos, glass, vegetable, etc.) within the bronchial tree. Such fibers are characteristically a micron or less in diameter, with a length up to several hundred microns. They are especially interesting because of their low sedimentation velocities and the fact that they usually deposit at bronchiolar branch points where they are unable to keep a coaxial alignment; hence, they are intercepted.

Another aspect of this phenomenon also has a considerable probability in space, namely, the aspiration of objects of millimeter ($> 10^3\ \mu$) size and their interception by small bronchioles. This will be very likely if the object can be inhaled through the mouth or aspirated from the throat, for example, during eating.

These several modifications of dust deposition in the respiratory tract based on a reduced atmospheric pressure and gravity-free state are graphically summarized in Figure 2. The same physiological values used in Figure 1 are assumed.

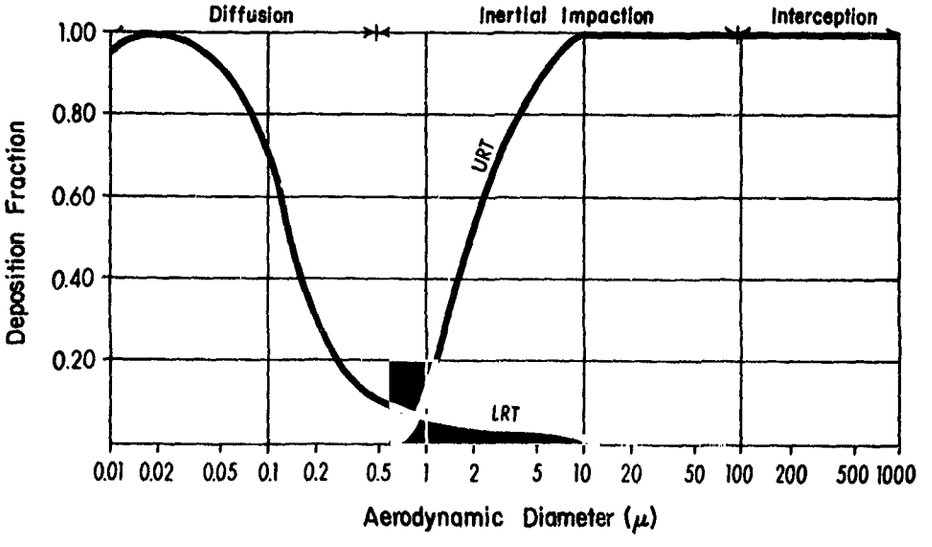

FIGURE 2.

Particle - Size Deposition in Space. Under zero G and in 100 percent oxygen at 160 mm Hg pressure, aerosol deposition during normal respiration is modified. The dominant deposition forces affecting different particle sizes are again generally indicated, but, as before, they are neither definite nor exclusive.

There may be additional minor distinctions between space and terrestrial conditions, including a difference in the viscosity of the atmosphere depending on the gas mixture used, but these and other factors are of relatively little theoretical importance. Dust deposition at intermediate gravitational states such as that on the Moon or that produced artificially can be interpolated from the Figure 1 and Figure 2 data. A discussion of this phenomenon was also made in the recent article by Beekmans (1966).

RESEARCH PROBLEMS

1. Additional information should be obtained on the aerosols in space capsules. Of particular importance is the relation between atmospheric contaminants and the aerosols present. It would be useful to analyze for aerosols in capsules during unmanned pre-flight testing with all systems functioning, but certain measurements during manned space flight are essential. Plans have been made to measure aerosols in a future spacecraft by a light-scattering instrument, a nephelometer (Jones, 1966). This instrument has special design features that permit quantitative estimation of the aerosols present in intervals of several sizes from 0.5 to 10 μ in diameter. It is unfortunate that this instrument has such a limitation on size, for the range measured may not be of the greatest relevance.

It is pertinent to point out that other types of aerosol sampling equipment such as electrostatic and thermal precipitators and filters have been tested at reduced pressures (DiGiovanni et al., 1958; Orr and Wilson, 1964; Stern et al., 1960). Because they do not utilize gravity, the barometric effect is singularly important; however, no important limitations have been reported in hypobaric studies on the efficiencies of the instruments if they are properly designed and operated.

2. Compositional analyses should be obtained under the same circumstances as described in 1, above. They should provide information on the sources of aerosols within the capsule and their toxicity. Related to this task is the procurement of information on bacterial aerosols.

3. An investigation should be made into the design and application of selective samplers to simulate the deposition characteristics of the upper and lower respiratory tracts. Such samplers can give a meaningful account of the aerosol exposures (Morrow, 1964) and probably can be engineered to indicate excessive exposures on either a cumulative or a prevailing basis.

4. To avoid the irritation due to alkaline CO_2 absorbents such as Li OH becoming airborne, glass fiber filters or other deep-bed

filters having good efficiency for particles < 5 μ should be interposed in the system, or alternatively, an acid scrubber could be used.

5. Particle size - deposition relations should be experimentally verified in parabolic flight with the use of selected monodisperse particles, especially from the 1-G sedimentation range, for example, 1- to 5-μ diameter. One-breath analysis utilizing light-scattering methods is a possible procedure.

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PART IV

LUNG INFECTION AND TREATMENT

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17

INFECTION

Experience already gained, particularly in submarines, in combating infection and safely sustaining man in closed systems for relatively long periods has direct application to manned space flight. Nevertheless, while the problems are similar in the two systems, they are again made different by the internal and external environments of the vehicles. The human body is an excellent growth medium for viruses, bacteria, fungi, and other microorganisms. These may be present in nasal secretions, sputum, urine, feces, sweat, and other secretions, and on the surface of the skin. Both small droplets and dried material will be dispersed in the atmosphere of the space cabin. There are many reasons why infection must be included in any consideration of respiratory function during prolonged manned space flight. Some of these reasons are:

1. Microbial infections could become a serious problem when space crews are expanded to more than two members, living in a confined space for extended periods of time.
2. Personal hygiene facilities will not be optimum.
3. Alterations in the viability of microorganisms, the autoflora, the mechanisms of challenge, or individual susceptibilities could be affected by the space cabin environment (i.e., gaseous concentrations, total pressure, temperature, humidity, trace contaminants), or the gravity-free state.
4. Both respiratory and nonrespiratory infections may occur, with the respiratory tract as the route of entry of the microorganisms into the body.

5. Respiratory infections may alter respiratory function.

6. Any illness, respiratory or otherwise, may seriously endanger the success of the mission by physiological or psychological effects on the crew.

It is expected that dust particles, owing to zero G, will accumulate in the cabin atmosphere to higher concentration than they would under similar conditions on Earth. Condensation droplets like dust are retained in the respiratory tract. It is possible that some toxic trace substances in the inspired air by being soluble in these droplets, will be concentrated from subthreshold to threshold levels. Droplets also spread microorganisms from the respiratory tract. The particle - size distribution of droplets expelled during a sneeze range from about 1.5 to 100 μ (Wells, 1955). To quote from Riley (personal communication):

> At 1 G the larger droplets are removed from the air by settling. At zero G the large as well as the small droplets will remain airborne. At 1 G, droplet nuclei are formed in a fraction of a second by evaporation of the water in the small droplets. At zero G, the large droplets will also evaporate to dryness even though the procedure takes an appreciable period of time. The dried residues of larger droplets, though fewer in number, will contain more microorganisms per particle. At 1 G, the most important mechanism for removal of infectious particles from the air is the ventilation of the room (air changes per hour) (Riley and O'Grady, 1961). In a capsule there are no air changes at all, and the dried residues of respiratory droplets will accumulate to much higher concentrations. The concentration of infectious particles will eventually be limited by the biological half-life of the microorganisms. Equilibrium will be established when a balance between production and removal of viable organisms is reached. With no settling out and no dilution by air changes, a very high equilibrium concentration of infectious particles would be expected if a disseminator of infectious organisms should be aboard.

Condensation droplets have shown ten- to twenty-fold increase in the atmospheres of submarines during submergence. Microbial infections may become a serious problem when space crews are expanded to more than two members. This will be intensified by the increasing number of condensation droplets that may carry the infectious agents and by weightlessness, which may impose difficulties with natural drainage. It is anticipated that ciliary action will sustain many of these functions. The clinical syndromes might be those of cross-infection with respiratory, intestinal, and central-nervous-system viruses, with bacterial and protozoal intestinal organisms, and with respiratory staphylococcus, streptococcus, and meningococcus.

Naturally controlled studies give evidence that respiratory illness rates are very closely related to the methods of handling men in the subsequent environment in which they are placed. Arlander et al. (1965) found that the methods of processing new

recruits and the extent to which susceptible men were allowed contact with an ill population were of great significance, at least for acute respiratory disease, in the determination of the subsequent illness patterns. It is well known that there is an increase in respiratory illnesses, particularly acute respiratory diseases (ARD) and the common cold, when a group of men is first placed in a confined area such as on board ship or in a submarine. The incidence of these illnesses increases soon after the men are brought together, but subsides with the development of cross-immunity. Rosenbaum et al. (1965), on the basis of ten years' experience with respiratory disease at the Great Lakes Naval Training Center, indicated relative endemicity of adenovirus and streptococcal agents. The influenza virus types changed, but influenza A and B appeared with yearly frequency in late winter and early spring. The increased ARD rates had no effect on the incidence of pneumonia. Pierce and Miller (1965) found that routine nonrespiratory disease immunizations given to naval recruits during their early weeks of training increased the incidence of reported and surveyed respiratory disease by 20 percent. This suggests increased susceptibility because of the immunization, and certainly gives a hint of what one might expect with the stresses of space flight.

Since the space traveler may be exposed to stresses that lower his resistance to infections, stress factors in spacecraft must be controlled insofar as possible. The effects of diet, temperature, relative humidity, ionizing radiation, noxious gases, fatigue, and seasonal variation on susceptibility to infection have been considered by many investigators. It is well known that ozone exposure decreases resistance to respiratory infection (Stokinger, 1965). Nitrogen dioxide exposure before or after infection with Klebsiella pneumoniae increased mortality in mice (Stokinger, 1965). The resistance of mice to respiratory infection due to Klebsiella pneumoniae is reduced at altitude (atmospheric pressure of 179 mm Hg—approximately 35,000 ft—and a gaseous environment of 85 percent oxygen, 10 percent carbon dioxide, and 5 percent nitrogen), with the greatest mortality occurring when the mice were at altitude before and after the challenge (Mieszkuc and Ehrlich, 1964).

Green and Kass (1965) studied strains of Staphylococcus albus, Staphylococcus aureus, and Proteus mirabilis in a pulmonary aerosol system to determine the rate of inactivation by the murine lung. In untreated animals the order of effectiveness of inactivation was S. albus, S. aureus, and P. mirabilis. In ethanol-intoxicated mice the inactivation of S. albus and S. aureus was depressed, whereas the clearance of P. mirabilis was completely inhibited. With hypoxia, the clearance of S. albus and S. aureus was inhibited. With exposure to cold, the clearance of these organisms was inhibited equally.

Muir (1966) recently commented:

The deposition of aerosols in the lungs of man during breathing constitutes an important mechanism for the entry of toxins or pathogenic organisms to the body. The respiratory tract is protected by an efficient ciliary mechanism for the rapid removal of particles deposited in the upper airways. Particles reaching the alveolar regions are removed more slowly. There are three mechanisms whereby inhaled particles are deposited on the walls of the airways—inertial impaction, sedimentation by gravity, and diffusion due to Brownian motion. The dimensions of the airways are such that large particles are deposited in the upper airways and have no opportunity to reach the alveoli. In the absence of gravity, as in orbiting spacecraft, one may anticipate the particles normally deposited in the lungs by sedimentation (principally those particles of 1-8 μ diameter) will be exhaled again with no deposition. Under the conditions of a reduced gravitational field an important distinction arises. While the deposition of particles in a range of 1-8μ diameter will be less than normal, the particles of this size which are deposited will do so in a deeper region of the airways than normal. One effect of a reduced gravitational field may thus be to allow the access of large particles to the nonciliated alveolar region of the lung. Particles of this size are important in the airborne spread of infection because they include the droplet nuclei carrying bacteria which is produced by coughing or talking. The importance of this hazard to astronauts remains to be established.

According to Riley (private communication):

The depth of penetration of airborne particles into the respiratory tract would not be expected to be very different at zero G than at 1 G. Impingement of particles on the respiratory mucosa is the chief factor limiting penetration and this depends on momentum rather than gravity. Large particles would be taken out in the nose and upper respiratory tract as usual. Because large particles would be increased in number and might contain large numbers of infectious organisms, the danger of direct infection of the upper respiratory tract would be increased.

Particulate matter and the problems of deposition and retention and mucociliary clearance are discussed in detail by Morrow in Chapter 16 (p. 123).

It has been pointed out by Laurenzi et al. (1964) that the antibacterial mechanisms responsible for clearance may involve primarily alveolar macrophages. He administered a predictable number of aerosolized bacteria to small animals and found that the bacteria disappeared rapidly in the post-exposure period so that within 6 hours 95 percent of those originally found had disappeared. The size of the droplet generated by the apparatus suggested that a large share of the bacteria was deposited distal to the bronchial tree—thus the previously stated conclusion.

Levashov (1966) points out that personal hygiene measures must be effective under altered gravitational conditions and

with minimum water consumption. His studies have indicated that the personal hygiene measures that must be used during space flight will not adversely affect the autoflora of the astronaut. Alekseyeva (1966) studied natural immunity factors and cosmonaut autoflora during the training period and following the flights of Vostok 1, 2, 3, and 4. She felt that immunological changes were transient and, for all practical purposes, insignificant because they did not result in weakening the cosmonauts' resistance to microbes. Signs of stimulation either did not appear at all or were compensated for by the end of the flight, and her opinion is that astronauts can adapt during a 3- to 4-day flight.

Since the oxygen concentration of the gas within a space capsule is not likely to differ greatly from that on Earth at sea level, the viability of infectious particles suspended in the air of the capsule should not be greatly altered (Riley, personal communication). Riley believes that at 1 G, respiratory infection is transmitted predominantly by droplet nuclei, which, being in the 1- to 2-μ range, are for the most part deposited in the lung rather than the upper respiratory tract. In the absence of gravity, the percentage retention of small droplet nuclei would probably be low. He implies that the lungs are ordinarily more susceptible to the common respiratory viruses than the upper respiratory tract since they can be infected with fewer organisms, an implication that fits with epidemiological evidence, suggesting that droplet nuclei, rather than larger particles, are primarily involved in the transmission of respiratory contagion.

In a recent study, four Air Force crew members, ranging in age from 27 to 29 years, lived in a test cell for 68 consecutive days (Hargreaves et al., 1966). It was operated at ground level for 8 days, at 258 mm Hg for 56 days, and again at ground level for 4 days. During the 56 days at 258 mm Hg, the atmosphere consisted of 175 mm Hg P_{O_2} and 74 mm Hg P_{He}. There were no changes to indicate that this atmosphere produced any impairment of man's pulmonary function (Robertson and McRae, 1966). Fecal samples were collected during the various phases of the study and examined to determine changes that might have occurred in the bacterial flora (Cordaro et al., 1966). Counts of all microorganisms except enterococci remained within the normal range. There was a decrease in the number of enterococci as the subjects went on the experimental diet, but the values returned to normal when the regular diet was resumed. The change observed was not considered to be of clinical significance.

Studies were also initiated to determine the numbers, distribution, and types of microorganisms encountered under conditions of a sealed environment for an extended period such as would

occur during space exploration (Moyer et al., 1966). Quantitative counts of the aerobic microorganisms present in the circulating atmosphere and those present on the skin of the subjects were made. Distribution of coagulase positive, phage typable Staphylococcus aureus strains and predominant microbial types in throat, nasal, skin, and aerosol samples were determined. Evidence of staphylococcal transfer between subjects was obtained, but the cutaneous studies suggested that no buildup of the aerobic microflora of the skin occurred during the course of the experiment. No cumulative increase or decrease in the numbers of aerobic microorganisms present in the circulating atmosphere was noted. The investigators concluded that for aesthetic purposes and odor problems, a sponge bath daily is sufficient to keep resident skin microorganisms in check. No significant medical abnormalities developed that could be directly attributed to the oxygen-helium, 258 mm Hg environmental conditions (Zeft et al., 1966).

Kennedy et al. (1965) found a decrease in the indirect MBC and Vc in recruits with an acute respiratory illness, which was more pronounced in those with evidence of pneumonia. Berven (1962) found that the steady-state diffusing capacity (D_L) was still impaired months after the chest x ray became normal following a viral pneumonitis, but found no impairment of D_L after bacterial pneumonia. It has also been demonstrated that with lobar pneumonia there is hypocapnia and decrease in arterial blood oxygen saturation, functional residual capacity (FRC), vital capacity, and compliance.

In summary, current knowledge suggests, among other things, the following:

1. Microbial infections, respiratory and nonrespiratory, could be a serious problem during prolonged space flight.

2. Altitude, cold, hypoxia, and other stresses increase the susceptibility of some animals to infections.

3. Some noxious trace contaminants (e.g., ozone, nitrogen dioxide) are known to increase susceptibility of man to respiratory infections.

4. Studies carried out thus far for up to 56 days in a confined oxygen-helium environment at a reduced atmospheric pressure have given no indication that man's susceptibility to infection is altered.

5. No immunological alterations have been found in those who have been studied before and after actual space flight.

6. No changes in autoflora have thus far been detected.

7. Some effects of weightlessness on the airborne spread of infection can be postulated, but actual studies have not been conducted.

8. Respiratory illnesses, when they do occur, may certainly alter pulmonary functions.

RESEARCH PROBLEMS

The major gaps in knowledge concern the effect of prolonged weightlessness on the spread of airborne infection, individual susceptibility to infection, the viability and pathogenicity of organisms, the microbial content of space cabins, and the possible hazard of aerosol deposition in the lungs. The question of the effect of + G_x acceleration on take-off and the gravity-free state in flight on susceptibility to aspiration from the mouth, teeth, gums, etc., is yet to be settled.

The effects on infection of prolonged exposure to high O_2 concentration at less than ambient pressure in a confined space must be clarified. Studies have thus far been carried out up to 56 days, but our knowledge about the alterations to be expected on long-term missions is incomplete. High O_2 tension may increase susceptibility to secondary tuberculosis and localization of tuberculosis in the lungs elsewhere than usually expected.

Additional knowledge is needed on the technical aspects of disinfecting the capsule air or biological filtering during prolonged space flight. As few studies on the microbial content of the astronauts or space cabin have yet been carried out during or immediately after space flight, there is little information concerning what disinfection or filtering may be required for prolonged missions.

RECOMMENDATIONS FOR RESEARCH AND NEEDS IN BIOINSTRUMENTATION

Ground-Based Bioinstrumentation

1. Effect of low ambient pressure on the production of respiratory droplets.

2. Extension to much longer periods of time of studies similar to those in which four men were in a confined space for 68 days. Such studies, possibly with animals and human subjects, should include complete bacteriological and immunological analyses of both the occupants and the cabin atmosphere. This confinement could be preceded by + G_x acceleration take-off profile.

3. Studies of the effects of possible space vehicle cabin environments (i.e., gas concentrations, total pressure, temperature, humidity) on viability and pathogenicity of microorganisms.

In-Flight Bioinstrumentation

1. Bacteriological and immunological studies on the space crew and cabin atmosphere during actual flight under zero G, including (a) sequential samples of capsule air for concentration of bacteria and viruses, (b) effect of capsule atmospheres and zero G on viability and pathogenicity of microorganisms, (c) effects of space vehicle cabin atmosphere and the gravity-free state on mucociliary function and resistance to infection.
2. Investigation of susceptibility to aspiration of particulate matter in the gravity-free state.
3. Evaluation of technical aspects of disinfection or biological filtering of cabin air.

General Recommendations

A filtering system and a detector of the organisms present will probably be necessary so that the microbial content of the space cabin can be carefully controlled. Electrostatic precipitation of dust and particles may also be effective. At any rate, a certain amount of dust and some condensation droplets must be removed during space flights of long duration.

In consideration of the foregoing discussions, the major criteria for controlling infection on prolonged space missions would appear to be as follows:

1. To prevent, insofar as possible, the incidence of significant infections during flight by
   a. selection of crews with similar immunological patterns
   b. isolation of crew prior to prolonged space flight to prevent exposure to infections and to allow cross-immunity to develop. Newer techniques that provide predictability of an individual being susceptible or likely to develop an infection may be found as an alternative to pre-flight quarantine
   c. adequate knowledge of the effects of vehicle cabin environment and zero G on the autoflora, mechanisms of challenge, viability and pathogenicity of microorganisms, and individual susceptibilities to infection
   d. determination of the microbial content, and development of techniques for maintaining control of it, in the space vehicle
   e. methods for personal hygiene that prevent change in autoflora and susceptibility to infection
   f. extension of present knowledge on particle size and deposition in the respiratory tract to include the effects of zero G
2. To develop techniques for handling the infections that do occur

3. To determine the effects of respiratory infections on respiratory function in the space vehicle environment

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PAUL E. MORROW

18

RESPIRATORY DRUGS AND MANNED SPACE FLIGHT

Although it is difficult and perhaps premature to attempt to establish the drug requirements of the manned space flight program, it is possible to draw certain tentative conclusions about drug needs and problems based on general principles and on the information available about space flight conditions and astronaut performance. To some extent, the experience of aviation medicine can also be drawn upon.

It can be anticipated that drug requirements in space medicine will be designed to (1) meet rather common complaints and disorders such as headache and diarrhea; (2) offset certain conditions that are related to space flight such as sleeplessness and motion sickness; (3) reduce the risk associated with severe infections and accidents such as antibiotics and analgetics; and (4) meet the specific requirements of each astronaut based on individual medical histories and indications of drug sensitivity, idiosyncracy, or intolerance. Obviously, these same bases are appropriate to the selection of respiratory drugs.

GENERAL CONSIDERATIONS

The pharmacology of the lung circulation was recently described in a two-volume treatise by Aviado (1965). In an earlier publication, Aviado (1963) dealt with the more comprehensive subject of the pharmacology of the lungs. The textbook by Harris and

Heath (1962) on the pulmonary circulation, the large compilation of drug effects in the Handbook of Respiration (Altman et al., 1958), the recent report by Lambertsen (1966), the review by Widdicombe (1963) on tracheobronchial smooth muscle, the allusions to respiratory drugs in many clinical books, for example, Bates and Christie (1964) and Pullen (1955), together with some of the standard pharmacology texts (Goodman and Gilman, 1965; Wilson and Schild, 1959; Gaddum, 1959), constitute the major source material on respiratory pharmacology.

Those familiar with the pharmacological literature on respiratory structures will find that the material in the major sources cited is very similar in the sense that few, if any, drug actions are without their controversial side. Most of the difficulties stem from the technical problems of studying the pulmonary region and the enormous variability of responses. To this last point is added the fact that the responsiveness of respiratory structures to drugs in reasonable doses is comparatively unremarkable and depends upon the pre-existing tone, which, of course, is highly related to the type of experimental preparation. It is not uncommon to find the same drug producing opposite effects in the same species (Aviado, 1963; Goodman and Gilman, 1965).

Behind this rather confusing picture is the further complication of an incomplete anatomical and functional description of the respiratory tract, particularly on points of innervation, mucous production, the distribution of smooth muscle, and the lymphatics in the terminal portions of the bronchial tree (Weibel, 1963; Aviado, 1963, 1965; Widdicombe, 1963; Liebow, 1962).

In any case, there appear to be no drugs with highly specific and beneficial actions on the respiratory structures per se. Through topical application, a measure of localized action is obtained with nasal decongestants, local anesthetics, and bronchial dilators, particularly if they are administered in aerosol form. Otherwise, most of the drugs having actions on respiratory effectors have a comparatively broad spectrum of effects, often involving the cardiovascular system.

DRUG REQUIREMENTS OF NORMAL INDIVIDUALS

Almost anyone can compile a group of complaints that appear to have widespread and frequent incidence. Most of these are treated by across-the-counter remedies (nonprescription), and the drugs involved are, by and large, safe irrespective of their efficacy. In terms of respiratory tract disorders there are many

such drugs, but in the context of the needs of a selected group of young men in excellent health and under constant medical surveillance, the list dwindles almost to the vanishing point, leaving, possibly, nasal decongestants.

DRUGS IN AVIATION MEDICINE

The needs of the astronauts for medication will clearly differ in some important respects from the needs of men in aviation, but there are some important similarities. For example, they differ in that the astronaut cannot easily dissociate himself from his continuous operational status nor his state of isolation. On the other hand, the need for unimpaired motor and cortical functions is identical for both.

The Federal Aviation Agency's Guide to Drug Hazards in Aviation Medicine (1962) lists commonly used drugs having undesirable primary actions or side effects insofar as aviators or aviation personnel are concerned. It further provides instruction for their use. For example, dextroamphetamine (dexedrine) is described as producing "wakefulness, nervousness, impaired judgment . . . [and consequently, air duties are contraindicated in aviation personnel] for 24 hours after use." Presumably something akin to the foregoing publication will be required or desirable for space medicine. Otherwise, or in addition, a list of useful drugs must be established which, in a positive sense, meets the needs of prolonged space operations.

DRUGS IN THE MANNED SPACE FLIGHT PROGRAM

Schmidt and Lambertsen (1965) and Schmidt (1965) have prepared a general list of possibly useful drugs and their indications for space medicine. Also, a substantial list of drugs has already emerged in the manned space flight program. These were described in part at the NASA briefing of the Space Science Board's Working Groups on Respiratory and Cardiovascular Physiology in May 1966 and have been reported for the Gemini VII mission in the Gemini Mid-Program Conference (National Aeronautics and Space Administration, 1966b).

Drugs carried on space missions to date include the following:

GENERIC NAME	CLASSIFICATION
d-amphetamine	CNS stimulant
cyclizine (tablet & injection solution)	anti-motion sickness
meperidine (tablet & injection solution)	analgetic
d-proproxyphene	analgetic
APC	analgetic
tripolidine	nasal decongestant
pseudo-ephedrine	nasal decongestant
atropine sulfate	antidiarrheal
dephenoxylate	antidiarrheal
tetracycline	antibiotic
chlortrimeton	antihistaminic

Some of these drugs have been taken during flight, namely, APC's, chlortrimeton, and an antidiarrheal mixture; in one case just before re-entry cyclizine was taken when it was known that rough sea conditions existed in the recovery area.

The creation of medical kits to date has been the responsibility of physicians at the NASA Manned Space Flight Center in Houston, Texas. No special panel for the selection of drugs has been organized or used, but something of this nature is being considered (C. Berry, personal communication). Moreover, NASA has also put into effect a pre-flight drug-testing program in which each astronaut is examined for sensitivity to each drug carried in the spacecraft; NASA is committed to continue this testing procedure irrespective of the changes in medical kits. The drugs carried by astronauts have, according to Dr. Berry, been chosen to deal with the most likely complaints. The Gemini VII kit (National Aeronautics and Space Administration, 1966b) was based on an analysis of the expected complaints under space flight conditions. In terms of respiratory drugs, only the nasal decongestants and antibiotics are relevant.

RESPIRATORY PROBLEMS FOR WHICH DRUGS MAY BE REQUIRED OR CONTRAINDICATED

1. Nasal congestion, obstructed sinuses, and similar problems appear to be part of a rather common upper respiratory tract syndrome among astronauts. Similar symptoms and signs have been reported where weightlessness has not been involved but where hyperoxic and hypobaric states have (Ohlsson, 1947; Roth, 1964; Zeft et al., 1966). The causative factors are thus not clear, and their study is suggested.

2. The spread of infection may possibly be facilitated by the gravity-free state (Ross, Chapter 17, p. 133). In any case, antiviral drugs (Sadler, 1963) and antibiotics for respiratory disorders and infections such as pneumonia are clearly indicated, particularly on long-duration flights.

3. Because likelihood of aspirating food or airborne material is greatly increased in weightlessness, the possibility of having to treat bronchial obstruction must be entertained. This clearly indicates a requirement for medical training and the need for special equipment and drugs, such as local anesthetics and bronchial dilators.

4. Certain types of drugs, at least on superficial examination, appear to be contraindicated by virtue of their adverse respiratory effects, for example, methemoglobin producers, bronchial constrictors, and respiratory depressants; in the final analysis, however, drugs from these categories must be judged in their totality. Atropine, for example, is a useful bronchial dilator under certain circumstances, but it is also apparently ciliastatic and affects vision. On the other hand, morphine derivatives, for example, meperdine, are respiratory depressants in that they reduce chemoreceptor sensitivity to carbon dioxide, and yet they are incomparable as analgetics.

RECOMMENDATIONS

1. Many types of drugs, particularly those that affect respiration and respiratory structures and the closely allied cardiovascular responses, should be investigated in primates during the condition of weightlessness.

2. A panel of experts should be created to study the space flight data and the use of drugs by astronauts. Associated with this investigation should be a study of isolated small groups in which self-medication problems are experienced and dealt with. Finally, the basic medical training needed for different types of missions and the occasions where a qualified physician would be required on board must be determined.

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