Life Beyond the Earth's Environment: The Biology of Living Organisms in Space

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The Biology of Living Organisms in Space

Space Science Board
Assembly of Mathematical and Physical Sciences
National Research Council

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Foreword

The Space Science Board, since its inception in 1958, has been reviewing and evaluating the scientific aspects of space biology and medicine. In 1970, a group under H. Bentley Glass conducted a year-long study and prepared a report entitled *Life Sciences in Space* that recommended a reorganization of the life sciences within NASA. In 1973, the SSB's report on *Scientific Uses of the Space Shuttle* included a chapter on the life sciences prepared by a panel under Robert Forster.

In 1976, NASA issued an Announcement of Opportunities for biomedical experimentation in the Space Shuttle and to which it received over 1500 responses. In the light of this large response, NASA asked the SSB to survey the status of the life sciences in space and to recommend a future strategy. In response to this request, the Board agreed to undertake the study and requested its Committee on Space Biology and Medicine to develop plans for the study, including appropriate terms of reference. The Committee met at Ames Research Center, Mountain View, California, on December 16-17, 1976, approved the terms of reference for the study, and asked Neal S. Bricker, formerly of the University of Miami and currently at the University of California, Los Angeles, to be the study leader.

As planning for the study proceeded, it became apparent that a more extensive effort and, because of the large number of disciplines involved, a larger number of specialists would be required. The principal activity was a two-week-long workshop in August 1977 at Snowmass, Colorado, where some 40 biologists and medical scientists assembled, reviewed the existing data, and, after considerable deliberation, reached conclusions and recommendations.

LIFE BEYOND THE EARTH'S ENVIRONMENT

This is one of a *series* of documents prepared by committees of the Space Science Board that develop strategies for space science during the coming decade. The Board has reviewed this material and adopted this document as policy.

The Board is grateful to the many people who devoted so much work to this study and acknowledges the continuing support of the National Aeronautics and Space Administration.

A. G. W. Cameron, *Chairman*
Space Science Board

Acknowledgments

I would like to express my gratitude to A. G. W. Cameron, Chairman of the Space Science Board, for his guidance and leadership. I would like also to convey the appreciation of the entire committee to Milton W. Rosen, former Executive Secretary of the Space Science Board, and to his staff, headed most expertly by Lally Anne Anderson, for their untiring contribution to the planning and execution of the Study and the preparation of this report. I would like to thank Leon G. Fine, the co-editor of this report for his collaboration and continual search for excellence. Finally, with regard to the Committee, to the members, and to the consultants, I would like to express my appreciation for a task performed in the national and international interest and for efforts that were truly above and beyond the call of duty.

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INTRODUCTION AND SUMMARY

Introduction

Neal S. Bricker

In October 1957, man broke the barriers that had confined him to the surface and contiguous atmosphere of the earth since the beginning of recorded history. The Soviet Union successfully launched an 84-kg sphere named Sputnik into an elliptical orbit, the apogee of which was 900 km. By so transcending the heretofore impenetrable barriers and escaping from the all pervasive gravitational constraints, the inhabitants of earth made the first tentative move toward worlds beyond. In the 20 years following Sputnik I, an escalating effort has been made to determine the effects of the environment of space on the processes of life that had evolved over many millions, and perhaps billions, of years in the environment of earth. Many of our earthbound species, from the simplest microorganisms to the most complicated animals including man, were projected into space, and a multinational aggregate of life scientists began to assemble a body of data designed to determine whether man's remarkable ability to adapt to the vicissitudes of life on earth would extend to life in the weightless environment of space.

This report represents an effort to examine, in a critical and analytic manner, the cumulative data obtained during this two-decade interval. A multidisciplinary group of life scientists participated in the study that culminated in a two-week workshop in Snowmass, Colorado, in August 1977. For practical and logistic reasons, the workshop was limited to six areas of the life sciences, which are listed below. Key areas, such as the psychologic effects of spaceflight and the hemotologic changes in space, were not included. The selection process does not represent a value judgment or the establishment of priorities. Those areas of importance that were not addressed in the study should be examined in a similar fashion in the future.

This is not the first time that the Space Science Board has been asked to study NASA's medical and biological activities. In 1969, the Board assembled a large group at the University of California, Santa Cruz, under the chairmanship of Kenneth V. Thimann. The group's report, *Space Biology*, dealt largely with various aspects of biologic research in space. In the following year the Board convened a smaller group under H. Bentley Glass to look at the organization of the life sciences in NASA. The major finding of this group was that the life-science activity in NASA was fragmented and should be brought together into one entity under a single director, a recommendation that NASA adopted. In 1973, the Board's study of scientific uses of the Space Shuttle included a chapter on the life sciences, prepared by a group under the leadership of Robert Forster. Despite these reports and extensive efforts by those in NASA concerned with the life sciences, the field appears still to lack sufficient purpose and direction, and, what is of more concern, it has failed to attract a growing complement of outstanding investigators outside the agency.

It is unfortunate that more of the best minds in the biomedical sciences have failed to become involved in NASA's research programs in the life sciences. The reasons seem to be multiple. Though the research, of necessity, was of a screening and exploratory nature, there has been an inordinate element of "ideas in search of problems" or "analytic techniques in search of ideas." In the process of asking questions and designing experiments, expert scientists outside of NASA were too often either not asked, asked and not listened to, or in some instances regarded as antagonists who criticized the activities and the data of the NASA scientists.

Part of the problem in the past, in my judgment, may have been due to an all too powerful role of astronauts in the execution of biomedical research in space. This apparently has included veto power. In the final analysis, the astronauts knew what risks they were taking and did not appear to want to be told that exposure to the environment of their work was hazardous to their health.

The problem also related to the fact that the engineering of the space vehicles, including Skylab* (and unfortunately, probably the forthcoming Spacelab as well), not only precluded last-minute changes in experimental design but mandated that the protocols be fixed months to years in advance, at times without a solid scientific basis.

This then was the background; the study proceeded in the following manner.

*An experiment in long-duration manned spaceflight undertaken by the United States in 1973 in which three teams, each consisting of three astronauts, lived and worked in a space station called Skylab for successively longer periods of time, i.e., 28, 54, and 84 days, respectively.

The areas we addressed were limited to six. Thus some important areas were defined for future studies. The areas covered were

1. Renal and body fluid
2. Cardiovascular
3. Endocrinology including bone
4. Vestibular
5. Genetics and developmental biology
6. Ecology

After in-depth consultation with members of the SSB's Committee on Space Biology and Medicine and others, the chairmen of the six groups were selected. They, in turn (again with consultation), selected the members of their respective panels.

The group of scientists numbered 40, including 5 consultants. They came from the United States, Canada, the United Kingdom, and the Federal Republic of Germany. In addition, there were eight consultants from NASA, including scientists, administrators, and one astronaut (Owen Garriott).

A preliminary meeting of a number of the principals within the full Committee was held at the Johnson Space Center in May of 1977, to see the mock-up of the Spacelab to be carried in the Shuttle and to review the medical data obtained from Skylab. The full Committee met at Snowmass, Colorado, during the last two weeks of August 1977.

The charge to the Committee according to A. G. W. Cameron, Chairman of the Space Science Board, was as follows.

We were to attempt to set directions for a ten-year period, speaking primarily to the following two questions:

1. Does the weightless environment provide a unique opportunity for designing experiments that can lead to a better understanding of fundamental physiological and biochemical mechanisms operative on earth in a wide variety of organisms, including man?

2. Are there specific medical problems relating to a weightless environment that pose a threat to health or to life in long-term spaceflight?

The existing plans for laboratory facilities and the "hardware" planned for Spacelab were not to limit our decisions or recommendations; nor were we to restrict ourselves to the Space Shuttle program.

The overall conclusions were as follows:

1. It would be untenable to permit research in Space Life Sciences to die either by omission or commission.

2. Zero-g does provide a unique environment for investigating certain physiological and biochemical processes.

3. There are large and substantive areas of uncertainty about the biological connotations of long-term (months to years) missions.

4. Many of the background experiments can and should be done on earth.

5. There are important questions in the disciplines considered that can be addressed in two- to four-week missions.

6. However, the major questions, enumerated in the text, require long-term missions. The most compelling question is: Can man, and other organisms, remain alive and healthy in a weightless environment for months to years?

7. There was unanimity of opinion that any major adverse effects of spaceflight could probably be prevented by creating an artificial gravitational field within the spacecraft.

The report is, in effect, a compilation of the results of the deliberations of six separate investigative panels. As such, inevitable areas of overlap have been retained in the editorial process so as not to obscure the fact that many problems appear to be of mutual interest to scientists drawn from seemingly disparate disciplines and that points of contention have arisen over common problems approached from different points of view.

The questions that may be amenable to resolution include the following.

SHORT-TERM MISSIONS (DAYS TO WEEKS)

1. Both the renal and cardiovascular groups were concerned with the translocation of blood and interstitial fluid from the lower extremities into the more cephalad parts of the body (particularly the chest) that appears to occur within a relatively short period of time after entrance into a zero-g environment. These fluid shifts are believed to initiate a loss of sodium and water into the urine, and the latter accounts for the uniform loss of weight that has occurred in all spacefliers early in their missions and has borne no correlation to time in flight. The renal and electrolyte group believes that the increased urinary excretion is compensatory and restores central volume to or close to normal; the cardiovascular group believes that increased central blood volume (hypervolemia) may persist. The renal and electrolyte group, therefore, believes that the translocation of fluid should pose no risk in long-term flights; the cardiovascular group believes that persistence of hypervolemia could lead to serious consequences, including heart failure, in prolonged spaceflight. Resolution of this conflict may well be possible by simple measurements (e.g., venous pressure) in the upcoming Shuttle Program.

2. The vestibular group raised a number of questions regarding the type of motion sickness that has afflicted many individuals in space. A number of experiments was described to uncover the mechanism of space motion sickness and to develop means for protection against it. Many of these involve ground-based studies of the underlying physiology and pharmacology. An integrated plan for vestibular research to be undertaken in space was considered. Although some of the zero-g studies considered require long-duration flights, some of the suggested studies could be undertaken in two- to four-week flights. Although space motion sickness is self-limited, it diminishes work performance, and it is a source of considerable annoyance to those affected. It could be of more importance to future nonastronaut space voyagers and represent a definite threat to astronaut safety during extravehicular activity.

3. Demineralization of the bones of the lower extremities has occurred uniformly in a weightless environment and could represent a serious problem on prolonged missions. Up to this time, none of the preventive measures has modified the loss of bone mass; but several of the factors known to influence both formation and dissolution of bone have not been adequately studied, and measurements could be made in two- to four-week flights. There are certain other hormonal measurements that have been suggested for short flights. At least part of these relate to the inability to interpret existing data.

4. The role of *stress*, particularly as it influences the interpretation of certain of the endocrine studies, was underscored, and experiments to evaluate this factor were suggested. One avenue would involve the use of nonastronaut experimental subjects in order to eliminate the variable introduced by the rigorous and tightly programmed schedule of activities that the astronauts carry out.

5. In the area of genetics and developmental biology, experiments designed to test the influence of a *zero-g* environment on certain of the very early events in the maturation of the fertilized ovum, particularly in mammalian species, were suggested. Other short-term experiments on both animal and plant species were considered feasible, but with varying priorities.

LONG-TERM MISSIONS (MONTHS TO YEARS)

1. For long-term studies, the question of the persistence of central hypervolemia and of its significance if it does persist could be answered definitively.

2. Loss of bone mass appears to represent the most important potential hazard of long-term spaceflight. Efforts to determine the cause, and to develop techniques for prevention of bone demineralization (and an associated loss

of muscle mass) would require missions considerably longer than those contemplated for the Shuttle program. An interesting adverse trade-off of the skeletal demineralization is the high concentrations of calcium in the blood and the abnormally high excretion of calcium in the urine that have been observed uniformly to date. The increased rate of calcium excretion could pose a hazard to the kidneys by leading to (a) the formation of kidney stones, (b) calcification of the kidney, and (c) direct toxic effects on renal function.

The foregoing list of investigations is a selected one, and a number of other suggested studies is described in the full report.

SPECIFIC SUGGESTIONS

1. Partnership: An ongoing organic relationship between the NASA life scientists and life scientists working in universities, institutes, and medical schools seems essential. The partnership should begin with the questions asked; it should continue with experimental design; and it should extend to the choice of the analytic and other procedures employed, the types of technology used, and the requirements for quality control.

2. A peer review system for assessing the merits of projected studies should be strengthened; a section on peer review is included in the report (see Chapter 7).

3. There should be consideration of methods to effect more cohesion and closer communication both within NASA and between NASA scientists and the scientific community outside the Agency.

Among the more exciting results of the Summer Study was the birth of what could represent a new scientific discipline. A group of ecologists was asked to come to grips with the concept of an environment that might conceivably house thousands or even hundreds of thousands of earth's inhabitants in an enclosed capsule that would remain in orbit for many decades. In approaching their deliberations about how to close an environment, the ecologists recognized that the only real model of an enclosed environment was the surface of the earth. They found, moreover, that there were few ground rules that they could extract from standard ecological principles and very limited experimental data were of immediate pertinence. Their work during the summer convinced them that the study of closed ecosystems was relevant not only to the development of regenerative systems for space travel but also to the analysis of the origin of life on earth, of the possibility of life on other planets, and of present terrestrial problems, including the management of our environment and improvement in agricultural techniques. What evolved was a commitment to a continuing process of creating a series of hypotheses and designing experiments that would permit the testing of the hypotheses.

Summary

This chapter presents summaries of the six chapters of the report that deal with medical and scientific matters. These chapters were prepared by six separate panels during the course of the workshop. Five of the chapters deal with separate medical disciplines, but, as would be expected, there are correlations and, as will be seen, a major difference of opinion (with respect to the long-term effects of body-fluid redistribution in zero-*g*). All the chapters were discussed and reviewed by all participants in the course of the study so that the correlations and differences were known to all of them. It is hoped that these summaries will assist the reader by giving an overview of the subject before presenting the details of each medical discipline. A sixth chapter is devoted to the study of closed ecological systems. Finally, Chapter 7, approved by the entire study group, comments upon NASA's advisory structure in life sciences.

OVERVIEW OF THE REPORTS OF INDIVIDUAL PANELS

Renal and Electrolyte

During the first 24 to 48 hours of spaceflight, the absence of gravity is associated with a translocation of fluid from the lower limbs into the central vascular compartment. This results in loss of sodium and water through the urine, a reduction in body weight, and the rapid attainment of a new steady state. It is postulated (but remains to be tested) that this diuresis begins immediately after a person enters the weightless state. The fact that plasma protein concentration and hematocrit have been found to rise within the first 3 days of flight suggests that the bulk of the fluid translocated from the legs is excreted. Re-entry leads to the reverse phenomena, i.e., reaccumulation of blood and interstitial fluid in the legs and a postflight period of fluid and salt retention. Existing information does not allow the precise mechanisms of these adaptations to be described with certainty. However, the panel believes that central blood volume is restored and thereafter maintained at approximately a normal level during flights of up to 3 months in duration and that central congestion and cardiovascular overload probably do not constitute a threat to continued well-being in long-term voyages. However, the panel emphasized the extreme importance of subjecting this postulate to test.

A small, continued potassium loss occurs in the urine and is attributed to the slow release of potassium from a breakdown of muscle mass. There is also an increased urinary and fecal excretion of calcium, which is attributed to demineralization of the bones. The potential hazards of persistently high blood and urine calcium levels could include a deleterious effect on kidney function and also the formation of kidney stones. Studies must be conducted to clarify these issues.

The panel believes that the renal and electrolyte problems that have been encountered during spaceflight are probably of limited consequence. Immersion of normal volunteers to the neck in a tank of water, in order to simulate weightlessness, provides a useful technique for studying the redistribution of fluid from the lower extremities into the upper parts of the body. Additional ground-based studies using this technique are indicated in order to facilitate the interpretation of the fluid shifts in zero *g*. Measurements of pressure changes in various parts of the vascular tree, volume-related hormones (plasma renin activity, catecholamines, for example) and natriuretic hormone excretion rates could clarify the physiology of the fluid shifts in space and also contribute to a broader understanding of the biological control system that regulates volume homeostasis in health and disease on earth.

Cardiovascular

The Cardiovascular Panel concluded that the cephalad (headward) redistribution of fluid during the early phase of spaceflight could result in a persistent engorgement of the central circulation (rather than the initiation of an early and complete compensatory diuresis). They believe also that inflight measurements of parameters, such as central venous pressure, would be of great importance in evaluating the magnitude and potential hazard of this phenomenon. It was the panel's view that if substantial central venous congestion were to persist over a period of many months, in a weightless environment, space voyagers with no underlying heart disease would become vulnerable to the development of cardiovascular and hemodynamic abnormalities that are closely comparable with those seen in patients on earth with congestive heart failure.

Among the ground-based techniques that may simulate the weightless condition are prolonged bedrest and the previously mentioned water immersion. Both procedures lead to significant increases in central blood volume and in the atrial filling pressure in the right side of the heart. Both are also associated with alterations in pulmonary function, which could become clinically meaningful in prolonged spaceflights.

The panel believes that there is a need for measurements of cardiac and pulmonary function in animals exposed for periods of days to many months to a zero-*g* environment. The provision of inflight artificial gravity could provide a basis not only for confirming the role of weightlessness in producing any observed abnormalities in cardiac or pulmonary function but possibly for preventing and/or reversing these abnormalities.

Endocrinology

BONE AND MINERAL METABOLISM

Perhaps the most significant hazard of spaceflight thus far documented is a seemingly inexorable and progressive loss of skeletal mass. This abnormality is associated with a persistent loss of calcium in the urine and stool. Loss of bone has been found to occur predominantly in the lower limbs, and neither exercise nor any other remedy so far attempted has been found to block this demineralizing effect of exposure to zero-*g*. Comparable findings have been reported in volunteer subjects exposed to the immobilization of prolonged bedrest.

An extensive series of mechanisms that might be responsible for the skeletal changes was addressed by the panel. These include factors known to influence both bone formation and bone reabsorption. It was felt that existing data are incomplete and inadequate and that insights into the mechanism of bone loss would require more sophisticated evaluation of bone physiology under zero-*g*. Although some of the studies can be performed on earth under conditions that simulate zero-*g*, and some but not all of the experiments can be performed on animals, the critical studies will probably require long-term exposure to a weightless environment.

Therapeutic approaches to the problem of bone dissolution in space were considered, but no specific preventive measures were found. It was felt that the consequences of loss are not a major health hazard in flights of up to 3 months' duration but could become serious in more prolonged flights.

MUSCLE-METABOLIC-ENDOCRINE

A consistent finding in spaceflight has been increased protein catabolism (i.e., breakdown) and muscle wasting, which, as in the case of bone dissolution, was not prevented by a vigorous exercise program. Similar findings have been described during prolonged bedrest. The panel believes that it is important to establish whether the absence of gravitational stress is the main cause of the muscle atrophy. If the provision of simulated gravity does not prevent the atrophy, a wider range of studies, including evaluation of the behavior of numerous hormones will be required. Programs of extended exercise and dietary regimens, as well as measurements of muscle performance and metabolism would be part of the approach to this problem.

Increased activity of the renin–angiotension–aldosterone system and the pituitary–adrenal axis (two hormonal systems with widespread biological effects) has been demonstrated during spaceflight. The relevance of these alterations to salt and water excretion and to other metabolic alternations remains uncertain and requires further study. Suppression of gonadal hormones including testosterone, an anabolic hormone, at zero-*g* was considered to be a possible, albeit not a prepotent, factor in the bone and muscle loss. The circadian rhythms for testosterone, follicle stimulating hormone, and luteinizing hormone should be examined during future flights.

The panel believes that stress could exercise an important effect on several endocrine and metabolic systems in space. Stress factors include anxiety, overt pressure to perform tasks, peer pressure, space sickness, physical exertion, and crowding. During future flights, such as those contemplated for the Space Shuttle, certain flight personnel (those responsible only for experiments) may be shielded from many of the stresses to which astronauts have been exposed heretofore. Therefore, insights into endocrine and metabolic functions under different conditions of stress may be forthcoming.

Developmental Biology and Genetics

One of the fundamental questions involved in future spaceflights is whether animals born and reared in a gravity-free environment exhibit normal anatomic, physiologic, and behavioral patterns upon return to earth. The panel reviewed the potential effects of zero-*g* on embryogenesis and organogenesis in animals and stressed the need for careful selection of the appropriate species to be studied. It was concluded that the field is in its infancy and that very little is known about these phenomena. Another promising area for investigation will be the influence of zero-*g* on plant physiology, since the cellular mechanisms involved in gravity perception may be similar in all organisms.

The panel believes that there is no fundamental issue or hypothesis regarding the biology of single cells that requires a critical test in space. On the other hand, the hazardous effects of high-atomic-number particles and high-energy radiation, which can penetrate tissue and kill cells, are relevant to the functioning of nonregenerating organs, such as the brain and the retina of the eye. However, the effects of such radiation might be tested in ground-based experiments.

Also the panel addresses issues of more general relevance to space biology. The need to perform high-quality, ground-based experiments whenever possible before embarking on a scientific project in space was stressed. Well-planned studies on gravity receptors should first be performed using the clinostat.* The absence of appropriate controls in previous studies has highlighted the need for the provision of a centrifuge on future flights. The role of stress in animal experiments requires that more attention be paid to preflight preparation of experimental animals.

The Space Shuttle should provide a significant advantage in future experimentation through sequential observation and inflight modification by the attendant scientists. The panel stresses the importance of adequate training of payload specialists in the laboratories of the principal investigators, since some techniques in experimental biology are not standardized, and small misunderstandings about methodology may alter significantly the outcome of an experiment.

Vestibular

The operational problems created by space motion sickness and their implications for the selection of personnel and the planning of flight activities have provided an important stimulus for increasing our understanding of the vestibular function in a weightless environment. There are several theories of space motion sickness, but only short-term solutions have been effective. These include applying techniques used for detecting susceptibility, training for motion sickness avoidance, and methods for amelioration of symptoms.

Research on motion sickness would be of practical importance not only for spaceflight but could also provide insight into the mechanisms of sensorimotor symptoms in general. There is a need to develop animal models for use in the study of motion sickness and to expand research effort concerned with protective adaptations to nauseogenic stimuli in earth-based studies.

Among the approaches to the management of space motion sickness are methods for identifying individual susceptibility and the use of more effective drugs to control the symptoms. Future facilities for vestibular research should incorporate linear acceleration and artificial gravity machines, which could be used for the training and selection of crew members.

*An instrument that simulates, but does not reproduce, zero-g on the ground.

Ecology

This panel considered the theoretical and practical implications of life in a closed environment. New methodologies have to be developed for analyzing a self-sustaining closed ecosystem, since the only known closed ecologic system that is self-regenerating is the earth. In an attempt to define the minimum amounts and kinds of information that will provide an adequate understanding of a closed ecosystem, the panel analyzed simple closure experiments in biology and concluded that it is incorrect to view organisms or ecosystems simply as mechanical or chemical transformers with constant rates. Rather, they are subject to, and adapt to, temporal change so that their behavior can change significantly when external conditions are altered.

In considering the practical problem of developing a closed, self-regenerative system for the support of human beings in space stations, the panel believes that such a system has to focus on redundancy, compartmentalization, and human control. Some major problems involve the use of storage pools for the principal chemicals, the production and accumulation of trace toxins, and the prevention of biologic epidemics. Total energy would not be limiting, since the sun is a powerful source. It was asserted, however, that any experimental model of a closed system that could serve as a forerunner, albeit primitive, of the ultimate space station would in no way resemble a natural earth habitat. Rather the appropriate conceptual picture of a space station is an array of separate compartments for vegetation, animals, and humans and for chemical processes, each with its own optimum light, temperature, and atmospheric requirements but with interconnecting links and storage facilities.

II
PANEL REPORTS

Renal and Electrolyte Panel

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Renal and Electrolyte Physiology

INTRODUCTION

In the 1960's, man demonstrated with remarkable success his ability to withstand the relatively short-term influences of weightlessness during spaceflight in orbit around earth. A uniform and intriguing feature of each mission in the Mercury, Gemini, and Apollo programs in this period was the loss of body weight encountered by each flight crew member, amounting to some 2–3 kg on the average. It is of particular interest that weight loss of this magnitude was evident even in flights of no more than a few hours' duration. The rapidity with which this weight loss occurred can only be explained by acute loss of body fluids, specifically the net loss of sodium salts and water, primarily through the kidneys. The initiating factors responsible for this augmented urinary excretion of body fluids were the subject of much discussion and debate in the pre-Skylab era and led, eventually, to a substantial commitment of the Skylab life-sciences effort to attempt to define the mechanisms and pathways involved.

REVIEW OF SKYLAB DATA

In general, the results obtained in the Skylab studies support the view that entry into the zero-g environment results in a rapid translocation of fluid from the legs into the more cephalad portions of the circulation including the heart and great vessels. On the basis of estimates of the change in the volume of the legs, it would appear that approximately 2 liters of fluid, including both blood and interstitial fluid, are displaced from the legs. This estimate does not include any possible contribution of fluid translocated from the organs lying below the diaphragm.

Excretion of Salt and Water

In response to the redistribution of extracellular fluid, resulting in central volume expansion, there is a relative increase in the urinary excretion of sodium, potassium, calcium, and water as would have been predicted from the results of analogous perturbations in terrestrial experiments. In the first 24 to 48 hours of flight in Skylabs 3 and 4, a negative balance of sodium chloride and water was demonstrated clearly in five of the six crew members. (Because of the heat problems encountered in the first few days of Skylab 2, meaningful analysis of salt and fluid balance was not possible.) In Skylabs 3 and 4, the negative balances, in part the result of decreased salt and water intake and in part the result of increased losses in the urine, account for a loss of approximately 2 kg of weight.*

After the initial loss, which seems to be largely completed in 3 to 4 days, changes in body weight were more gradual, and since the sodium-balance data were closely comparable to preflight values, we interpret the slow weight changes as reflecting changes in tissue mass. In other words, it appears that a steady state of salt and water balance was maintained. Although these subjects had rather high salt intakes, there is no reason to believe that the pattern of response would have been different if intakes were at a more moderate level.

In many ways the immediate postflight recovery period is a mirror image of the early days of flight, i.e., the magnitude of the positive balance of salt and water approximate the negative balance of early weightlessness. This finding strongly supports the view that a steady state of salt and water balance is maintained beyond the first few days of the flight period.

The mechanism of the relative increase in salt and water excretion is not clear. In ground-based studies in man and experimental animals, a number of factors have been invoked as possible contributors to the augmented salt and water excretion that attends expansion and dilution of the central blood volume. These include plasma protein concentration, aldosterone, vasopressin, putative natriuretic hormones, and changes in renal hemodynamics. Which of these variables might be responsible for the early losses of salt and

*Throughout the preflight period, during postflight recovery, and during flight, with the exception of the first few days, salt intake exceeded the measured output by a considerable margin. Presumably, this reflects significant but unmeasured salt losses in sweat. Such losses remain unaccounted for and make interpretation of the balance data difficult, except when there were major deviations from balance, such as occurred in the first few days of flight and during recovery.

water cannot be determined from the experience in Skylab. The readjustment of volume probably occurs within the first few hours of flight, a period when there are many stresses unrelated to volume shifts. The stress factors, *per se*, are known to perturb those variables thought to influence the regulation of salt and water excretion. Unfortunately, it was not possible to obtain measurements of these variables or, in fact, of the rate of salt and water excretion, during this critical period.* On the other hand, when many of these factors were measured on the third day of flight and thereafter, they appeared to be appropriate for the level of salt intake.

It should be noted that aldosterone and renin levels in plasma and urine were extremely low in the preflight period of each Skylab mission, undoubtedly a consequence of the high level of sodium intake. While these hormone levels are reported to have increased by about 100 percent when measured in flight (day 3 and thereafter), the very-low-baseline values indicated that the absolute changes with weightlessness were trivial and, we believe, unlikely to have influenced sodium or potassium excretion appreciably.† For similar reasons, any possible declines in the levels of these hormones in association with the central volume expansion that occurs early in flight would not be expected to alter electrolyte excretion patterns significantly.

Although it has been suggested that in the response to expansion of the central blood volume, suppression of the secretion of vasopressin (antidiuretic hormone) is a key mechanism of volume control, it is noteworthy that in the Skylab situation the high osmolality of the first day's urine (> 1000 m Osm) indicates that vasopressin secretion was high rather than low. This is not surprising since there were several stimuli that are known to stimulate secretion of vasopressin: the tensions associated with the launch, the onset of motion sickness, and the effects of drugs taken in an attempt to minimize the motion sickness. Consequently, the data do not suggest an important role for vasopressin in the control of central volume in this situation, a finding that is not surprising in view of the fact that, in ground-based experiments, administered vasopressin does not prevent the augmentation of salt excretion that follows volume expansion. These findings indicate that, in the long run, it is in the control of salt excretion *per se* that the mechanism for volume regulation in space must be sought.

A question that may be important for more prolonged spaceflight and that is not resolved by the available data is whether control mechanisms restore central volumes and pressures to their normal preflight levels or whether the adjustment is incomplete—resulting in some degree of persistent expansion of

*The necessary collections of urine during the first 5 hours of exposure to zero-g have never been obtained.

†There is further discussion of these changes in Chapter 3.

central volumes and/or increased central vascular pressures. The puffiness of the face and distended neck veins reported by Skylab crew members throughout each flight raise the question of persistent expansion of central volumes; but these findings might be explained by changes other than overexpansion of vascular volume, for example by loss of gravitational molding of the face or increased venous tone. On the other hand, the volume of fluid thought to be translocated into the cephalad portions of the body from the legs can be accounted for by the loss of weight that occurs in the subsequent 1 to 2 days, suggesting that central blood volume is restored to or near preflight levels. Moreover, mobilization of a substantial volume of interstitial fluid, free of red blood cells and low in protein concentration, would, if not excreted, lead to reduced hematocrit and plasma-protein concentrations. That this was not observed suggests that the mobilized interstitial fluid was, indeed, excreted. In fact, the plasma-protein concentration and hematocrit, at the time of first measurements (on flight day 3), were increased approximately 10 percent above preflight levels. This suggests that the bulk of the fluid phase of the blood translocated from the legs was excreted, the unexcreted protein mass and red blood cells accounting for the observed elevations in plasma-protein concentration and hematocrit.

This hemoconcentration was transient in that the concentration of plasma protein and hematocrit returned to preflight levels in subsequent inflight observations. Admittedly, this type of analysis is imprecise at best and does not preclude the presence of some continuing increase in central volume and pressure. Comparison of central venous pressures in the early and late flight period would help to resolve this issue.*

The central vascular congestion that occurred early in flight appeared to produce only minor symptoms, which were not debilitating and did not seem to affect work capacity.†

In contrast to the foregoing sequence, blood and interstitial volume re-enter the legs on return from space, leading to a contraction of central blood volume, which is a potential source of problems, including decrease in blood pressure on assuming the erect posture, fainting, and decreased exercise capacity. These affects appear to have been minimized by the use of lower-body *g*-suits for the first few days after recovery. It should be recognized, however, that the use of the *g*-suit might delay readaptation to the earth's gravity after re-entry. Relatively rapid re-expansion of extracellular fluid volume by the administration of approximately 2 liters of isotonic Ringer's solution intravenously might accelerate the process of physiologic re-adaptation.

*A detailed discussion of this subject is included in Chapter 2.

†The possible contribution of cephalad congestion to the motion sickness that occurs in this phase of flight is discussed in the report of the Vestibular Panel (Chapter 5).

Excretion of Other Electrolytes

POTASSIUM

During the first 2 days of flight, there was a slight negative potassium balance associated with the salt loss induced by expansion of central volume. Thereafter, there was a small but continued loss of potassium as urinary excretion exceeded intake. However, the latter loss was in proportion to the negative nitrogen balance, suggesting that it was the consequence of shrinkage of muscle mass rather than depletion of the potassium content of living cells. In support of this view, the increased excretion of creatinine provides evidence of loss of muscle, while the constancy of the plasma-potassium concentration argues against significant potassium depletion.*

As noted above, changes in the concentration of aldosterone in plasma and urine are unlikely to have played an important role in the modest losses of potassium.

CALCIUM

As detailed in Chapter 3, excretion of calcium in the urine exceeded preflight values and urinary plus fecal calcium losses exceeded calcium intake throughout flight. These changes appear to be the consequence of mobilization of calcium from the skeleton. Associated with this mobilization of calcium, there was an increase of approximately 0.5 mg/dl in the concentration of calcium in plasma. It is not known whether the increment in plasma calcium was predominantly in the bound, complexed, or ionized fractions of the total calcium concentration. Although the increase in the calcium concentration in plasma suggests that there was an increase in the amount of calcium in the glomerular filtrate, it is likely that the increase in calcium excretion was attributable primarily to decreased reabsorption by the tubules. The mechanism of this presumed reduction in reabsorption of calcium by the renal tubules is not apparent. Among the theoretical possibilities are a decrease in the concentration of parathyroid hormone in the circulation, sustained metabolic acidosis, or abnormalities in the synthesis by the kidney of 1,25-dihydroxy vitamin D_3. Although no reduction of parathyroid hormone levels in plasma was detected by the immunoassay method used, the nonspecific nature of the method makes it impossible to exclude a decrease in the concentration of biologically active material. Furthermore, although there were

*It has been suspected that abnormalities of heart rhythm observed in Apollo 15 might have been the result of abnormalities of the (unmeasured) concentration of potassium in plasma. Neither the results in subsequent Apollo flights nor in Skylab offer any confirmation of this suspicion. In Skylab, the concentration of potassium in plasma remained entirely normal.

no in-flight measurements of acid-base status, there is no *a priori* reason to suspect that there was significant metabolic acidosis. In support of this position is the fact that immediate postflight samples of blood had normal concentrations of plasma bicarbonate; moreover, the normal concentrations of sodium, potassium, and chloride in the plasma of samples obtained in flight argue against a significant abnormality of acid-base status. However, the unlikely possibility of a significant increase in unmeasured organic anions leading to a metabolic acidosis without an increase in chloride concentration cannot be excluded on the basis of available data. Hence, it would be desirable to attempt to measure the concentration of bicarbonate in some of the frozen, stored plasma samples that were obtained in the Skylab flights. If, after such measurements, a true reduction of plasma bicarbonate is suspected,* evaluation of acid-base status in Shuttle flights would seem warranted. Finally, a role of 1,25-dihydroxy vitamin D_3 in the persistent elevation in calcium excretion has not been excluded.

SUMMARY

The Skylab experience suggests that the acute changes in vascular volume are reasonably well tolerated for up to 84 days. The observed changes in renal function appear to be due almost entirely to increases in central blood volume and are acute, transient, and, reasoning from terrestrial experience, physiologically appropriate. There is nothing to suggest that abnormalities in renal function (including glomerular filtration rate) or in the regulation of salt and water balance will arise in more prolonged spaceflights. However, a note of caution is warranted because of a concern that a continued high rate of calcium excretion might lead to significant damage to the kidneys either through calcification of the kidneys or the formation of calcium-containing kidney stones.

SUGGESTIONS FOR THE FUTURE

In considering further studies that might profitably be pursued, it is important to separate those items that might be important for future more-

*Since it is possible that much of the CO_2 has been lost from these samples, it would be important to measure the bicarbonate concentrations in samples stored frozen for a correspondingly long period such as those from ground-based controls and those with known concentrations of bicarbonate obtained immediately after recovery. If these measurements suggest significant storage-related losses of CO_2, it still might be possible to get valid estimates by re-equilibrating the plasma with a gas mixture containing 5 percent CO_2.

prolonged spaceflight from those that might help to clarify important physiologic mechanisms operating on earth, as well as in space, by exploiting the unique aspect of the gravity-free environment. To deal first with the latter: We have said that the increase in salt excretion in response to the expansion (and dilution) of the central blood volume was predictable. This should not be interpreted as meaning that the mechanism is understood. Although the elucidation of this mechanism would constitute a major contribution to physiology and medicine, it is our unanimous opinion that the necessary limitations imposed by spaceflight make that situation unsuitable for the studies that are likely to clarify this important physiologic mechanism. Sufficient approximation of the fluid shifts involved in spaceflight can be attained in ground-based studies to make it possible to carry out any study that might be contemplated for spaceflight, but with much more latitude for manipulation and measurement on the ground.

Accordingly, our limited recommendations relate specifically to measures that might improve man's ability to function in spaceflight and that might help to assure his safety in more prolonged weightlessness. In this regard, there are several unresolved questions:

1. Is there a persistent expansion of the volume of blood in the central circulation and with it increased central pressures that might eventually lead to impaired heart function? This question is dealt with in depth by the Cardiovascular Panel (Chapter 2). Although we place the likelihood of such increased pressures at a much lower value than does the Cardiovascular Panel, we agree that the currently available data do not provide the basis for deciding which view is correct. If more prolonged spaceflight is contemplated, the question should be resolved by inflight measurements of central venous pressures and cardiac size and, if feasible, central blood volume and intracardiac pressures. These measurements should be made after the initial diuresis and periodically throughout the remainder of the flight if the values remain elevated.

2. Is immersion in water an adequate model for studying the redistribution of fluid that occurs in weightlessness? The data available to date indicate that there are many similarities. If the correspondence of the two conditions could be established, the physiologic behavior of individuals in spaceflight might be made more predictable. Accordingly, we recommend that individuals who are to fly in space be the subjects of immersion studies in which the same measurements are made as are subsequently to be made in spaceflight, e.g., changes in the volume of limbs and central blood vessels and fluid and salt excretion. Such preflight immersion tests might help in identifying individuals whose cardiovascular systems would not tolerate or whose renal systems might not respond appropriately to the acute redistribution of blood volume.

3. Does central vascular congestion contribute to motion sickness? This possibility should be evaluated in ground-based immersion studies (see report of Vestibular Panel, Chapter 5). If these studies indicate that congestion does contribute to the vestibular disturbance, the possibility of ameliorating the central venous congestion should be explored. One possibility would be to have the subjects wear a lower-body *g*-suit for 2 to 3 days prior to flight. This would result in central redistribution of blood volume, which should lead to renal compensation prior to entering space and might reduce the early space sickness.

4. Although there can be no doubt that the increased excretion of calcium is the consequence of mobilization of bone salts, might it be possible to divert a larger fraction of the excreted calcium to the feces without substantially increasing the concentration of calcium in the plasma? The only serious concern over the continuing normal function of the kidneys in spaceflight relates to the sustained increase in calcium excretion, which is known to carry the hazard of calcium deposition in the kidney and urinary passages with deleterious effects on function. At the same time, decreases in urinary excretion should not be induced at the expense of a substantial increase in the concentration of calcium in plasma. It is possible that the very high salt intake that has been the rule among members of the flight crews has favored increased excretion of calcium in the urine, and the effect at zero-*g* of a lower salt intake on calcium excretion in the urine should be examined.

CONCLUDING COMMENTS

The anticipated problems of prolonged spaceflight are largely outside our area of immediate concern. However, because they may ultimately impinge on the function of the kidneys and on regulation of fluid balance and because we have given considerable thought to them, we believe that it is appropriate to state our views. The results of the Skylab experience indicate that the weightless state certainly creates a serious problem in the loss of bone and muscle mass and that it may create abnormalities of the volumes and pressures in the heart and great vessels that might, in longer flights or in less physically adaptable individuals, lead to irreversible damage to the cardiovascular system.

The data obtained in Skylab clearly show that there is a progressive and unrelenting decalcification of bone as a consequence of the removal of gravitational stress. Although there is no evidence that significant structural weakness of bones has been induced in the very small group of individuals who have been studied and in the relatively short periods of weightlessness to which they have been subjected, continued losses of calcium at the rates observed would certainly lead, in appreciably longer spaceflights, to changes that would have serious consequences on return to the earth's gravitation.

Of more immediate concern are the consequences of the mobilization of calcium that has occurred in those flights already accomplished. Continued high rates of excretion of calcium in the urine are known to be associated with deposition of calcium in the kidney and with the formation of kidney stones. These not only are serious problems in themselves, but they may lead to serious deterioration of renal function. It is possible that one might find safe biologic means to stabilize the bones and to prevent the mobilization of calcium from them, but we are not optimistic about this possibility. This possibility could be explored, but the necessary studies would be a long-term undertaking, and there is a serious likelihood that they would prove fruitless. Unfortunately, too, the definitive test of their effectiveness would require long-term spaceflight since there is no adequate ground-based model to replace it.

The loss of muscle mass could also be a distressing consequence of long-term spaceflight, although less serious than that of bone loss, since, as far as we know, the effects are limited to the weakness of muscles themselves. However, it is clear that the vigorous exercise in which the Skylab astronauts engaged prevented neither the muscle wasting nor the decalcification of bone. How less athletic and vigorous individuals, less inclined or willing to follow the exercise program that the Skylab participants undertook, will fare remains to be seen.

We are less concerned with the potential cardiovascular problems. First, as indicated above, we are not certain that they exist, although we believe that, as a prelude to longer flights, the necessary measurements should be made. Second, if they do exist, we are more confident that, by manipulation of salt intake and with drugs that increase salt excretion, it will prove possible to bring central pressures down to satisfactory levels. (The propensity of such drugs to raise the calcium concentration in plasma by interfering with calcium excretion could introduce new problems.)

Taking into consideration all the problems that remain to be solved, the uncertainty that satisfactory solutions can be found, and the long time that is likely to pass before it is clear whether such satisfactory solutions can be found, it seems to us that the best course to take would be one that obviates the problem by eliminating the weightless state in situations in which really prolonged stays in space are projected. Thus, if serious consideration is given to the establishment of permanent manned space stations, every effort should be made to provide a simulated gravitation field. We are not sufficiently informed as to whether some fraction of 1 *g* would suffice, and this question should be explored. However, we are sufficiently concerned about man's ability to adapt satisfactorily to prolonged weightlessness to urge that, despite the anticipated difficulty and expense, every effort be made to provide for gravitational stress in any structure intended for long-term human habitation.

Cardiovascular Panel

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2
Cardiovascular Research

INTRODUCTION

The gravitational force of our planet is the only environmental factor that has remained constant in the course of man's evolutionary development. It has shaped his body as well as his locomotive pattern. A major building element that man has used in architecture is also found in his own body structure: the column. Two columns, the legs, elevate the eyes roughly 6 feet above the ground and give the human body the appearance of some kind of "Gothic" structure (Figure 2.1). Those columns also make it possible to walk. However, this particular structure has been designed for earthbound use only, and, under conditions of weightlessness, it appears as awkward as a Gothic cathedral launched into space. Moreover, creatures destined by nature to float in a quasi-weightless environment, such as plankton, are quaintly similar in body shape to man's latest architectural achievement: the satellite (Figure 2.2). It seems safe to predict that if man remains in space for enough generations, he will undergo significant changes in his fundamental anatomy aimed at reducing his "Gothic building element." It is fascinating to reflect that the prototype of this evolutionary change was detected as soon as it was looked for: the immediate and persistent loss of bone and muscle mass, occurring predominantly in the legs (that have suddenly become useless), in association with circulatory changes initiated by a major shift of fluid out of the legs. In observing these responses to zero-*g*, functional elements of the human body may be unmasked that would otherwise remain forever undetected as long as man remained rooted to his normal 1-*g* environment.

At the onset of manned space exploration two fundamental questions were asked: (a) Will the circulatory system function in space in a way that will maintain life? (b) What mechanisms will be involved in this success or failure? The answer to the first question is now known to be "yes," at least for a period of up to 84 days. In the longest of Skylab missions, the astronauts exhibited no obvious functional abnormalities of the circulatory system. However, a deconditioning of the circulation was seen after re-entry which lasted about 50 hours. The second question remains for the most part unanswered. Definitive studies in the future should help to replace speculation with a better understanding of the control of the circulation in general, and in particular, of its control in the space environment.

Among the observations in Skylab,[1] one was of key importance and relevance. Reliable anthropometric measurements demonstrated that up to 2 liters of blood and interstitial fluid are displaced from the lower extremities toward the cephalad region of the body. It can readily be assumed that the major portion of this volume entered and distended the intrathoracic circulatory organs including the heart chambers.

The dramatic cephalad redistribution of fluid during spaceflight raises the possibility that an important basic physiologic mechanism, which may not be readily apparent in ground-based studies, becomes unmasked in the setting of

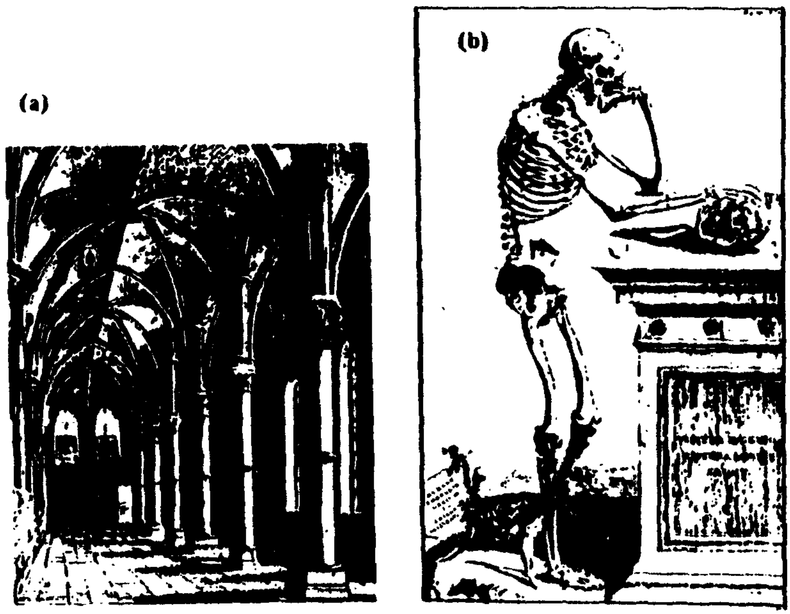

FIGURE 2.1 Similarity between (a) Gothic architecture and (b) human skeleton.

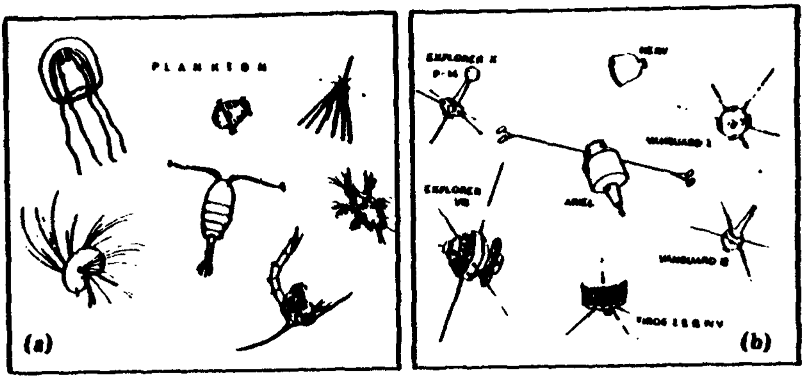

FIGURE 2.2 Similarity between "floating" creatures such as plankton (a) and satellites designed to function under conditions of weightlessness (b).

zero-g. If so, definition of the mechanism could enhance our understanding of the regulation of the circulation in health and in disease. Of equal importance is the fact that engorgement of the central circulation directly affects cardiac dynamics, reflexly influences hemodynamics, and also influences the patterns of salt and water excretion by the kidneys.[2] Considerable emphasis in this chapter, therefore, is directed to the impact of the cephalad redistribution of body fluids that accompanies the translocation from 1-*g* to zero-*g*.

THE HEADWARD MIGRATION OF BODY FLUID

Early evidence from the Apollo flights[3] suggested that manned spaceflight is associated with a decrease in mean calf girth of approximately 3 percent. More recent data from the Skylab flights[1] confirm and extend these findings, documenting in an unequivocal manner that an average of 1.8 to 2.2 liters of fluid are lost from the lower extremities. This decrement was first demonstrated on day 4. However, earlier measurements were not made, and it is not only conceivable, but likely, that this alteration may have occurred within the initial 24 hours of flight. The rapidity of onset of the changes and their rapid reversal following return from flight underscore the likelihood that they are due to fluid shifts rather than to a loss of lower limb mass *per se*. Such an interpretation receives support from the following observations: (a) the subjects experienced head fullness and nasal stuffiness; (b) photographs obtained during flight documented facial plethora and distention of jugular and scalp veins and veins of the temple and forehead; (c) hand and forearm veins also were described as filled and distended throughout flight in some of the astronauts.

Unfortunately, measurements of central venous pressure have never been obtained in flight; in-flight measurements of cardiac size and the presence or absence of pulmonary congestion also are unavailable. Hence, despite the indirect evidence cited above, any precise conclusions about either the degree of initial central hypervolemia or the changes in central volume that occur with time must remain speculative. It is important to note, however, that if central venous congestion of substantial magnitude were to persist throughout the flight, exposure to zero-*g* would induce cardiovascular and hemodynamic abnormalities, which are closely comparable with those seen in patients with congestive heart failure.

As discussed in detail in Chapter 1, the translocation of fluid from the lower extremities into the upper portions of the body, and presumably into the intrathoracic circulation, initiates a net loss of salt and water from the body, which presumably is compensatory in nature. It is our view, and one that is amenable to measurement, that even in short-duration flights, the natriuresis and diuresis fail to restore central volume to normal. Hence, central hypervolemia, pulmonary congestion, and increase in heart size would persist. We believe that the loss of salt and water, whether complete or incomplete, is due to the activity of the control mechanisms regulating extracellular fluid volume. The stimulus to the natriuresis and diuresis, in our view, most likely relates to activation of mechanoreceptors in the heart and the adjacent veins, and any of the neurohumoral factors that are known to influence salt and water excretion by the kidney could mediate the natriuresis and diuresis. Among these are aldosterone, catecholamines, natriuretic factor(s), and antidiuretic hormone.

SIMULATION OF ZERO-*g* ON EARTH

Some insight into the reaction of the human body to weightlessness may be obtained from data obtained from earthbound simulation experiments utilizing bedrest* and water immersion.

Bedrest

Since man typically spends approximately two thirds of his existence in the upright position, the erect posture may be assumed to represent the normal control condition. When erect, hydrostatic pressure leads to translocation of blood to and expansion of the vascular bed in the dependent regions of the body. Because of the attendant pooling of blood, proper filling of the heart

*The results of some relevant bedrest studies have recently been summarized, and the data are available from NASA.[4]

requires 400 to 500 ml of blood more in the upright position than in the recumbent position. Conversely, with a change from the upright posture to recumbency, approximately 400 to 500 ml of blood are translocated into the intrathoracic vasculature. This translocation would result in a hyperdynamic circulation, which would constitute an unsteady state. A reflex reduction of heart rate and peripheral vasodilatation prevent acute hypertension. With prolongation of the bedrest, the total blood volume is reduced, mainly by virtue of the occurrence of a natriuresis and diuresis. Once the 400 or 500 ml has been lost, a new steady state is achieved that is appropriate to the recumbent posture.

Water Immersion to the Neck

With head-out water immersion, approximately 700 ml of blood is translocated from the lower extremities into the thorax and a natriuresis and diuresis follow. However, this loss of body fluid does not relieve the central engorgement, because the central venous pressure is determined by the water level in the immersion tank. While this technique is useful to study fundamental processes of volume control and may simulate the early hours of weightlessness, it probably does not simulate prolonged weightlessness in terms of volume control. The apparent persistence of cephalad engorgement of the astronauts, after the initial diuresis, is not only consistent with the greater displacement of fluid volume at zero-*g* than that with water immersion but may indicate a less-effective renal response. A summary of the results obtained during immersion experiments is given in Appendix 2.C.

FACTORS INVOLVED IN THE INDUCTION AND MAINTENANCE OF THE REDISTRIBUTION OF BODY FLUIDS

Recent studies[5] have shown that the interstitial tissue compliance may influence the distribution of fluid between the intravascular and extravascular compartments. Furthermore, it has been suggested that the compliance of the interstitial space can be modulated by a substance secreted by the kidneys when the organism is in negative water balance.[6]

Applying these concepts, one might speculate on the existence of factors controlling the compliance of the interstitial space along the body axis in the gravitational field. A low compliance below heart level would only allow small amounts of fluid entry into the interstitial space. Above heart level such an edema-preventing factor does not appear to be necessary on earth since the venous pressure is close to zero, thus favoring inward filtration of extracellular (i.e., interstitial) fluid. In space, however, a pressure close to central venous pressure prevails throughout the entire postcapillary circulation including that in the head and neck (as evidenced by the distended neck veins of the astronauts). The change in pressure profile upon entry into space, in association with the active control of interstitial compliance, could lead to mobilization of fluid from the interstitial compartment of the legs (resulting in "bird" legs) and an increased outward filtration in the head region (resulting in "puffy faces" and eyelid edema). In the head region, the level of counterpressure to which the interstitial space is subjected is apparently insufficient to oppose outward filtration. In the postflight period, some crew members have had pretibial edema, which persisted for 2-3 weeks. This can be taken as further indication of a disturbed mechanism controlling fluid distribution. Other possibilities that cannot be excluded are an alteration of the precapillary-postcapillary resistance ratio due to myogenic autoregulation, a resetting of the neurohormonal vasomotor control mechanisms, or an alteration of the lymphatic drainage. It appears at present that regional tissue compliances can be assessed in humans,[7] but the evaluation of the other possibilities are more likely to require animal experiments.

HEMODYNAMICS CONSEQUENCES OF THE FLUID SHIFT

Although little is known about hemodynamic changes in space[1,3] some inferences can be obtained from terrestrial studies. As noted above, head-out water immersion and the transition from the upright to the supine position result in increases of central blood volume on the order of 700 and 400 ml, respectively. The correspondent increases of central venous pressure (right atrial filling pressure) and pulmonary pressure are about 15-18 mm Hg during immersion and 2-4 mm Hg during recumbency. Evidently, the level of central pressure during water immersion is directly dependent on the hydrostatic pressure exerted by the water, i.e., on the hydrostatic pressure difference between the right atrium and the water at the level of the right atrium. It is noteworthy that water immersion is not associated consistently with distention of the neck veins, as occurs during spaceflight. In the supine posture, the neck veins are distended only when they are at approximately the same level as the right atrium during extreme recumbency. The increases in stroke volume and resting cardiac output are very similar in immersion and recumbency (approximately 30-40 percent). The hemodynamic response to exercise in the recumbent position is virtually identical to that in the sitting posture: cardiac output increases in direct proportion to the increase in oxygen uptake because of an increase in heart rate, while right and left ventricular filling pressure show only insignificant or minor increments. Stroke volume increases modestly. The hemodynamic response to exercise during immersion in terms of cardiopulmonary pressures has not been studied.

During prolonged bedrest the changes in the circulatory system include a reduction of plasma volume and decreased orthostatic tolerance and aerobic capacity. No countermeasures have been found that consistently prevent the decrease of physical work capacity. Similar changes have been shown to occur in the weightless state. We believe that the central cardiovascular changes during weightlessness may affect pulmonary function. While the only respiratory parameter measured thus far in space is the vital capacity (there was a 10 percent decrease) other changes have been documented during simulated weightlessness. During water immersion (Appendix 2.C) only moderate (10 percent) reductions of vital and total lung capacities occurred, but there were increases of the closing volume on the order of 50 percent. These changes could be explained in part by a cephalad shift of the diaphragm. They also could reflect engorgement of the pulmonary vascular system. During water immersion there is a decrease in arterial oxygen pressure and an equivalent increase in the alveolar–arterial oxygen pressure difference. Both changes presumably reflect interference with pulmonary gas exchange. From the hemodynamic profile of the two simulation models, we believe that neither can be considered satisfactory in terms of reproducing the hemodynamic changes that we anticipate will be found to occur in true weightlessness. As a matter of fact, it is probably illogical to rely too heavily on any simulation model until precise information is available on the hemodynamic response that actually does occur during weightlessness.

Nevertheless, the considerable rise in central venous and pulmonary artery pressures (15–18 mm Hg) observed during immersion does arouse some concern about the same phenomenon occurring at zero-*g*. Left ventricular filling pressures of this magnitude ordinarily are encountered only in the presence of acute or chronic left ventricular failure. Although many observations, in particular those relating to the maintenance of excellent physical work capacity throughout flight, suggest that ventricular filling pressures are not elevated excessively at zero-*g*, no relevant measurements have yet been made. If elevated left ventricular pressures do persist, it is conceivable that long-term exposure to a zero-*g* environment could induce major deterioration of cardiac function.

Thus, two important questions concerning central hemodynamics require answers:

1. Is the central venous pressure elevated, and, if so, to what extent and for how long?

2. Are cardiopulmonary pressures during prolonged exposure to zero-*g* maintained at a level that could have pathological consequences?

These questions and those raised in previous paragraphs can only be answered by long-term observations in a properly equipped cardiopulmonary space laboratory.

Such a laboratory must support human studies using subjects specifically selected for this purpose. Dr. Lambertsen, at the conclusion of the 1974 Skylab Life Sciences Symposium[3] stated:

It seems now that a good deal of attention from here on is going to be required to take the excellent observations made in the program to date and modify the experimental procedures drastically in ways that are controllable. . . . In other words, we now need professional subjects in addition to the pilot-commander and other responsible individuals in the spacecraft system. . . . I think that we now have to set up the kind of long-term laboratory in space in which such professional subjects are, in fact, considered not as astronauts but as subjects, with physically competent individuals serving as transport crew. . . ."

This statement appears, at present, as up-to-date as it was in 1974.

EXTENDED CONSIDERATIONS

The experimental approach outlined above must be expanded and supplemented by additional studies, primarily on animals. A major reason is that the most dramatic and significant changes produced by spaceflight occur during the transitions into and out of weightlessness. Because of the operational constraints of those critical periods (up to 24 hours after entry and during the 24 hours preceding reentry), measurements in humans have been extremely difficult, if not impossible, to obtain.

Animal Studies

To fill the gaps of knowledge on the magnitude and time course of the rapid adaptations, the unanesthetized, chronically instrumented animal can be highly useful. Both normal and diseased animal models are indicated. The closer the physique of the animal species employed resembles that of man, the better will be the experimental design.

The highest priority measurements in normal animals include

1. Cardiac output, aortic pressure, and atrial and ventricular pressures and volumes;
2. Pulmonary volumes, pressures, and flows;
3. Flow distribution to various organs and the effectiveness of its control (i.e., brain, heart, kidney, bone, and skeletal muscle); and
4. Biomechanical, histologic, and histochemical assays after staged sacrifice.

Similar measurements are indicated in models with experimentally induced pathologic states such as hypertensive vascular disease and coronary arterial flow restriction. Histologic findings in rats in the course of Russian experiments and autopsy findings in the Russian cosmonauts have raised the possibility that pathologic changes in the myocardium and/or the coronary vessels may be induced, accelerated, or unmasked during exposure to the zero-*g* environment. Before man can be committed to long-term sojourns in space, investigations aimed at definitely establishing the role of zero-*g* exposure in this context also appear important.

Optimal data-processing and mathematical-modeling techniques are an integral part of the approach to dealing with the complexities of circulatory control under the conditions created by the spaceflight sequence.

Inflight Artificial Gravity

The implications of introducing artificial gravity include not only providing a means of counteracting possible undesirable circulatory effects of weightlessness but also providing a mechanism for detailed evaluation of regulatory functions. Because of the fact that man is not upright continuously on earth, periodic acceleration in a small oscillating or rotational device might be effective in counteracting any adverse consequences of weightlessness. Additionally, the responses to selected driving waveforms of established periodicities could provide insight into the regulatory capability and range of the intact system.

Physical Exercise in Space

Though many observations suggest that physical training during spaceflight might be a valuable countermeasure for deconditioning, the precise role of physical exercise and the type of exercise needed have to be established by systematic, sequential evaluations of aerobic (maximal O_2 uptake) and anaerobic (lactate tolerance) capacity and of muscle strength. In order to assess better the adaptation of the skeletal muscle both to gravity *per se* and to exercise during weightlessness, these studies should be complemented by an analysis of muscle enzyme patterns and muscle fiber distribution using muscle biopsy. Muscle biopsy has been used extensively during recent years for the evaluation of the effect of physical exercise in health and disease.[8]

Possible Medical Benefits

Estimating direct medical benefits is difficult and speculative at this time. Undoubtedly, fabrication of dedicated inflight laboratories may lead to the development and improvement of cardiovascular investigative techniques and technology. However, it must be emphasized that present knowledge does not suggest that space is an environment offering specific advantages for any form of specific medical treatment or patient care.

Transition from intrauterine to extrauterine life at birth represents a dramatic and unique adaptive process, which involves within a short period of time the onset of the respiratory function and a profound remodeling of the circulation with redistribution of blood flow. It is completely unknown if the gravitational field is an essential or even indispensable factor for these adaptations. It is conceivable that studying the course of neonatal cardiorespiratory adaptation in appropriate animal species at zero-*g* could yield unexpected insights into the mechanisms of adaptation and of their failures. The latter could include specific congenital cardiac malformations such as patent ductus arteriosus.

SUMMARY AND CONCLUSIONS

The experience hitherto gained from manned spaceflight demonstrates that the cardiovascular system can adapt promptly to weightlessness and that man can maintain an excellent functional capacity in space for prolonged periods of time. However, an impressive body of data indicates that sudden exposure to zero-*g* is associated with a rapid shift of a considerable amount of interstitial fluid and blood from the lower toward the cephalad parts of the body. Most of the translocated fluid is accommodated in the intrathoracic compartment, distending its vascular structures and presumably inducing significant changes in central hemodynamics. The increase of the intrathoracic blood volume is apparently "interpreted" by the body as a "total body" intravascular volume expansion and elicits compensatory mechanisms (i.e., natriuresis and diuresis), which reduce total blood volume. The lack of any impairment in inflight physical work (aerobic) capacity indicates that the contracted blood volume is an appropriate adaptation to the zero-*g* environment. However, this adaptation becomes inappropriate upon return to normal gravity. Postflight circulatory studies demonstrate decreased orthostatic tolerance, decreased physical work capacity, and lowered exercise stroke volume and cardiac output in the sitting position.

All of these postflight phenomena are consistent with a state of relative hypovolemia. Changes in vascular (venous) compliance are also likely to occur during spaceflight; hence, there are additional adaptive changes that may affect cardiovascular control mechanisms.

Any recommendation as to future in-space investigation should obviously be directed to increasing our understanding of cardiorespiratory changes induced by weightlessness. Although ground-based simulation models must be fully exploited, some of the essential information requires the use of a true zero-*g* environment. Ultimately, the data could not only enhance our understanding of normal, physiologic adaptive mechanisms, but they could yield new insights into the understanding of disease states on earth.

From our analysis, we wish to propose a series of studies relating to the cardiorespiratory system. These are listed below according to priority and feasibility.

Recommendations

1. *Short-term exposure (one day to three weeks)*: Human.

Measurement of cardiac dimensions (rest).

Determination of plasma volume and plasma levels of hormones contributing to volume control (ADH, renin, aldosterone, catecholamines, and diuretic and natriuretic factors).

Measurement of central venous, pulmonary artery, and systemic pressures (rest and exercise).

Measurement of stroke volume and cardiac output (rest and exercise).

Measurement of lung volumes (vital capacity, residual volume, closing volume) (rest).

Measurement of pulmonary diffusing capacity (rest and near maximal exercise).

2. *Long-term exposure*: Human.

Sequential measurements (monthly) of above-mentioned parameters.

Evaluation of physical exercise programs in terms of aerobic and anaerobic capacities complemented by muscle biopsy studies before and immediately after spaceflight.

3. *Studies of the time course of adaptation during entry to zero-g and reentry to 1-g:* Animal.

Hemodynamics (vascular pressures, cardiac output, flow distribution) and respiration.

Further studies should await the results of the foregoing experiments.

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APPENDIX 2.A: SKYLAB INFLIGHT EXPERIMENTS: CARDIORESPIRATORY SYSTEM

Resting Conditions	*Inflight*	*Postflight*
Heart rate	0	+
V_{O_2}, V_{CO_2}, systalic blood pressure	0	0
V_E	(+)	(+)
Diastolic blood pressure	-	0
Lung volumes: vital capacity	-10%	0
ECG/VCG:	PR+, QRS max+, VPB (stress)	0
Exercise (25, 50, 75% of V_{O_2} max)		
Heart rate	0	+
V_{O_2}/heart rate	0	(-)
W_{160}	0	-
V_{O_2} max (estimated)	0	(-)
Systolic blood pressure	0	-
Diastolic blood pressure	-	0
ECG/VCG	0	0
LBNP response		
Orthostatic tolerance	-	-
Heart rate	+	+
Pulse pressure (systolic-diastolic BP)	-	-
Calf volume	++	+
Blood pooling after leg muscle pumping under LBNP	+	0
Peripheral circulation (legs)		
Muscle blood flow	+	0
Venous compliance	+	0

Abbreviations: ECG, electrocardiography; VCG, vectorcardiography; PR, ECG PR interval; QRS max, maximum QRS vector; VPB, ventricular premature beats; LBNP, lower-body negative pressure.

Symbols: +, increase; – decrease; 0, no change (relative to preflight values.)

APPENDIX 2.B: SKYLAB PREFLIGHT AND POSTFLIGHT EXPERIMENTS: CARDIORESPIRATORY SYSTEM

Exercise hemodynamics	
Heart rate	+
Mean arterial pressure	0
Stroke volume	-50%
Cardiac output	-30%
Total peripheral resistance	+
Cardiac size	(-)
Echocardiography	
LVEDV (estimated)	-
LVESV (estimated)	0
Stroke volume (estimated)	-
Left ventricular free-wall thickness (estimated)	0
Stroke volume/LVEDV (under LBNP)	0
Cardiac electromechanical properties	
Electromechanical systole ($Q - S_2$)	0
Ejection time, ET (end QRS - end S_2)	-
Pre-ejection period, PEP: ($Q - S_2$) - ET	+
PEP/ET	+
First sound amplitude	(-)
Static and dynamic lung volumes	
Vital capacity, residual volume, total lung capacity, forced vital capacity, forced expiratory volume per second, closing volume	0

Abbreviations: LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LBNP, lower-body negative pressure; S_2, second sound.

Symbols: +, increase; -, decrease; 0, no change (postflight compared with preflight).

Note: Data from Reference 9.

APPENDIX 2.C: EFFECTS OF HEAD-OUT WATER IMMERSION

HEMODYNAMICS	
Central blood volume	+0.7 l
Heart volume	+180 ml
Right atrial pressure (CVP)	+18 mm Hg
Oesophageal (pleural) pressure	+5 mm Hg
Right atrial transmural pressure	+13 mm Hg
Cardiac output	+1.8 liters/min (32%)
Stroke volume	+26 ml (35%)
Mean systemic blood pressure	+10 mm Hg (11%)
Total peripheral resistance	-30%
Peripheral venous tone	-30%
Mean pulmonary blood pressure	+17 mm Hg
Mean pulmonary transmural pressure	+12 mm Hg
Leg muscle blood flow, rest	+130%
RESPIRATION	
Lung volumes	
Vital capacity, total lung capacity	-10%
Functional residual capacity	-36 to -43%
Residual volume, RV	-9%
Expiratory reserve volume	-71%
Closing volume, CV	+41%
Closing volume/vital capacity	+56%
Closing capacity (CV + RV)	0
Gas exchange	
V_D/V_T	0
$Pa_{O_2} (F_I = 0.2)$	-10 mm Hg, -7 mm Hg
$(A - a)DO_2$	+9 mm Hg
$Pa_{O_2} (F_I = 1.0)$	0
Ventilation/perfusion equality (^{133}Xe)	+
Pulminary-capillary blood flow	+20%
D_L/V_A	+37%
KIDNEY AND HORMONES	
Renal response	
C_{In} (glomerular filtration rate)*	0
C_{PAH} (effective renal plasma flow)*	0
Filtration ratio	0

*C, clearance.

Diuresis	++
C_{H_2O}	++
Urine osmolarity	--
Sodium (Na) excretion	+++
Potassium (K) excretion	++
Bicarbonate excretion	+(peak, 500 ml)
Plasma volume	-
ADH, Renin, Aldosterone	
Antidiuretic hormone	-(-50%)
Plasma renin activity	-(-60%)
Plasma aldosterone	-(-60%)
Renal prostaglandins	+100%

Note: Data from Reference 9.

Endocrinology Panel

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3
Endocrinology

BONE AND MINERAL METABOLISM

Overview

Progressive loss of skeletal mass is one of the major hazards of prolonged spaceflight. Parallel studies carried out in Skylab and with normal subjects at bedrest on earth have indicated that negative calcium balance persists throughout prolonged periods of weightlessness or immobilization. The available data give some indication of the magnitude of skeletal loss and describe some observations concerning possible cellular and hormonal mechanisms involved. However, the most fundamental questions concerning the mechanisms and consequence of bone loss in space have not been answered to date. Definitive mechanistic studies are essential if prolonged spaceflight is contemplated; moreover, these will help in understanding the mechanisms by which skeletal mass is controlled and, thus, in the understanding and treatment of metabolic bone disease on earth.

In this report the current knowledge obtained from spaceflight and terrestrial studies of bedrest is reviewed. The important methods that have been applied to this problem and that could be applied in the future are critically evaluated, and the specific opportunities that future spaceflight and terrestrial research can provide are described. Specific recommendations in this area include experiments designed to determine (1) the relative contribution of changes in bone formation and bone resorption to the loss of skeletal mass; (2) the major hormonal factors that may contribute to such changes; and (3) techniques, including therapeutic modalities, that might be useful in preventing or limiting excessive skeletal loss in prolonged spaceflight. Recommendations are based on the use of existing methods and obviously will be expanded and altered as new methods become available.

Review of Accumulated Data

Studies on skeletal loss during spaceflight in man. The major source of information on bone metabolism in weightless individuals is from data obtained during the three manned Skylab missions of 28, 59, and 84 days, respectively. In addition, in earlier Gemini, Apollo, and Soyuz flights some data were obtained on calcium metabolism in men, and animal data have been obtained more recently in some of the Cosmos missions. The methods used for studying the skeleton in man included calcium balance studies and assessment of changes in bone mass using both single photon transmission measurements with a rectilinear scanner and x-ray film densitometry. There was a rapid increase in urinary calcium excretion, which began soon after entry into a zero-g environment and which persisted throughout the spaceflight. On the longest Skylab mission, the increased rate of calcium excretion was accompanied by a progressive decrease in net intestinal calcium absorption and an attendant rise in fecal calcium loss. Thus, the data favor the view that throughout the periods of weightlessness the subjects remained in a state of negative calcium balance. On the basis of these results, it has been estimated that six months of weightlessness would result in a loss of approximately 2.5 to 3 percent of total body calcium.

Early studies using x-ray densitometry documented significant mineral losses in both the upper and lower extremity in flights of 4 to 14 days. In later flights the more sensitive method of photon absorptiometry using a monoenergetic isotopic photon source was employed. By performing area scans, it was shown that the bone mineral was lost from the lower extremities (os calcis) but not from the upper extremities (radius and ulna). The same observation has been made in subjects studied during prolonged bedrest. Of considerable interest and importance is the fact that the degree of bone loss from the os calcis could be correlated with the degree of negative calcium balance. Calcium losses were accompanied by progressive losses of nitrogen, phosphate, potassium, and muscle mass. In relation to possible methods of avoiding skeletal wastage, it is important to note that in both the Skylab flights and earlier Gemini flights a variety of exercise regimens was tested and none was able to reverse calcium or nitrogen loss, although partial effects were noted in some individuals. The potential value of such regimens require further study (see below).

Bedrest studies have shown changes in calcium balance and skeletal mass similar to those found in space. The loss of calcium and bone persisted in bedrest experiments ranging up to 36 weeks in duration. The bone mineral loss was again more prominent in the lower than in the upper extremities; short-term changes in axial mineralization, where important changes probably take place, could not be evaluated with available methods. One difference between bedrest and the Skylab flight was that there was a relatively greater loss of calcium in immobilization, but a relatively greater loss of nitrogen occurs in space. For example, the negative calcium balance in Skylab averaged slightly less than 100 mg per day, whereas, in parallel immobilization studies (i.e., bedrest), the calcium loss was approximately 154 mg per day. On the other hand, nitrogen loss persisted throughout spaceflight, reaching values as high as 4.5 g per day, while during bedrest, values of only 1 g per day were reported.

The os calcis mineral changes during bedrest studies were quite variable and have not shown a consistent relation to the degree of negative calcium balance. Part of this discrepancy was reconciled when two factors were tested for their ability to predict susceptibility of the calcaneus bone to mineral loss during bedrest: (1) the initial mineral content of the calcaneus and (2) the initial bone turnover rate as estimated by urinary hydroxyproline excretion rates. Thus, in subjects with a high initial os calcis mineral content and a low hydroxyproline excretion, there is a lower rate of os calcis mineral loss during bedrest than in subjects with the opposite control (i.e., baseline) value. Based on this observation, the ratio of initial os calcis mineral content to control urinary hydroxyproline excretion per gram of creatinine was used in an effort to predict the expected mineral loss in individual subjects exposed to varying periods of bedrest. The results obatined from the nine Skylab crewmen were found to fall within 2 standard deviations of the bedrest-derived mineral-loss profiles. Thus, this measure may be used as a discriminant for long-term spaceflights. Additional studies have raised the possibility that there may be ethnic differences in the susceptability to mineral loss.

Calcium kinetic studies have been done on immobilized subjects but not during spaceflight. These, coupled with balance studies, have been used to make estimates of the rates of bone resorption and formation. Such estimates indicate that both resorption and formation increase in bedrest and that the skeletal loss must, therefore, be ascribed to a disproportionately greater increase in bone resorption. The only data that might bear upon this question for man in spaceflight are from autopsy specimens of bones obtained from the three Soviet cosmonauts who died after a 21-day flight. The bone sections showed "a good number of unusually wide osteocytic lacunae." There is evidence, although there is no universal agreement, that wide osteocytic lacunae are a reflection of increased bone resorption. In the studies cited, control observations were inadequate.

Animal studies in space have suggested a somewhat different mechanism for bone changes. Wistar rats flown on Cosmos 605 showed "osteoporosis of the metaphysis with decrease in the amount of primary spongiosa in the vicinity of the epiphyseal plates." These changes were interpreted as being due to decreased bone growth. More recently, on Cosmos 782, periosteal bone formation was found to decrease by an average of 40 percent during flight when analyzed using tetracycline labeling techniques in rats. Following the flight, bone formation rate returned to normal. While these results are striking, they do not necessarily represent the effects of weightlessness, since effects of flight stress, changes in food intake, or behavior could also influence bone formation and were not fully controlled.

Biochemical studies that have been done to confirm bone loss include measurements of the urinary excretion of bone collagen matrix degradation products. These have been limited and are somewhat conflicting. One report indicates that both free and peptide-bound urinary hydroxyproline and hydroxylysine glycosides showed no significant changes during Skylab. Using the same methods, a marked increase was observed in three quadriplegic subjects on earth. Of course, the quadriplegic individuals had severe immobilization, associated with breakdown not only of bone but of skin peptides, and the source of the urinary collagen produced was not clear. On the other hand, mean values for hydroxyproline excretion recently calculated from specific analysis of the urine of the Skylab 4 astronauts (C. S. Leach, Lyndon B. Johnson Space Center, Houston, Texas, personal communication) indicated an increase of about 50 percent during flight, which would be consistent with a parallel loss of matrix components as well as mineral from the skeleton. These studies have not been fully controlled for gelatin and meat intake (both sources of hydroxyproline); moreover, there were wide variations during the control period so that further studies are obviously needed. Measurements of urinary hydroxyproline excretion in bedrest studies have clearly indicated an increase that is parallel to the loss of mineral.

Endocrine studies in spaceflight and immobilization are relatively few, and the data are in considerable conflict. Part of this may be due to methodologic problems, which are discussed below. The hormones to be considered might be divided into two groups. The first group includes the calcium regulating hormones, parathyroid hormone (PTH), calcitonin (CT), and the active metabolites of Vitamin D. PTH is known to stimulate bone resorption, and calcitonin will inhibit it. Bone remodeling requires the presence of both PTH and thyroid hormone. Other hormones may also be required. Vitamin D metabolites also stimulate bone resorption but have a potent effect on enhancing gastrointestinal absorption of calcium and may affect phosphate absorption. PTH also has a major action on the kidney to decrease the tubular reabsorption of phosphate and increase the tubular reabsorption of calcium.

The second group of hormones are those that have general effects on body metabolism but that also affect the skeleton. Glucocorticoids are known to inhibit bone growth, and during stress or during endogenous or exogenous glucocorticoid excess, bone growth is arrested and marked osteopenia may develop. Thyroid hormones are known to accelerate bone turnover and specifically to stimulate bone resorption. There is recent evidence that those hormones that are trophic for growth in other body systems, such as growth hormone through its intermediary somatomedin, and insulin are also able to stimulate the growth of the skeleton directly or indirectly.

PTH values have been reported both to increase slightly and to decrease during Skylab flights, while bedrest increases immunoreactive PTH in man. A study of immobilized monkeys also showed an increase in circulating immunoreactive PTH. One would have predicted that PTH levels should fall during immobilization or weightlessness because of the suppressive effects of hypercalcemia. Thus, it is extremely important to resolve these paradoxical and discrepant data. The validity and specificity of PTH immunoassays are under active investigation in many laboratories. Increase in thyroid hormones and cortisol have been reported in Skylab studies and at bedrest on earth. A decrease in insulin was reported in the Skylab studies. These changes are discussed elsewhere in this report.

Therapeutic approaches other than exercise have not yet been evaluated in spaceflight. However, preliminary to possible studies in space, a number of therapeutic trials have been carried out on subjects immobilized for prolonged periods. A variety of physical techniques were attempted at bedrest, including longitudinal compression of the body as well as impact loading. Although the effect of impact loading appeared somewhat beneficial, the accumulated data are inconsistent in this respect. Supplementation of the diet with calcium and phosphate has been attempted. In subjects in which the calcium intake was increased from 1 to 2.3 g per day and phosphate from 1.7 to 3 g per day, the calcium as well as phosphorus balances were significantly less negative. Supplementation of the diet with phosphate alone abolished the usual hypercalciuria but had no effect on the degree of negative calcium balance.

Synthetic salmon calcitonin has also been evaluated as an inhibitor of bone resorption and had no protective effect. A diphosphonate (ethylene hydroxydiphosphonate or EHDP), which is known to block both the formation and the dissolution of bone crystals and to inhibit bone resorption, was administered at the time immobilization was initiated. It produced an initial increase in hydroxyproline excretion and no effect on calcium balance. The increase in bone accretion rate that usually occurred at bedrest was blocked, and serum phosphate concentration was elevated. The effects on phosphate and bone formation were sustained, but there was a subsequent fall in hydroxyproline excretion, and, late in the study, bone resorption rates and negative mineral balances appeared to be reduced. On the basis of these late effects, a study is currently being carried out in which the diphosphonates are being started prior to the immobilization. It should be noted, however, that prolonged use of diphosphonates in children with metastatic calcifications and in adults with Paget's disease has resulted in osteomalacia or rickets. This is probably the combined result of impaired activation of vitamin D and direct effects on bone mineralization of the drug. Moreover, the attendant hyperphosphatemia may prove hazardous in immobilization because of the predisposition to hypercalciuria.

Requirements and Opportunities

In order to develop a better understanding of the effects of spaceflight on the skeleton and to utilize that information maximally for a better understanding of skeletal function and disease on earth, a number of steps should be taken.

1. The most important of these is to attempt to determine the mechanism by which skeletal mass is lost in spaceflight and during immobilization. If the mechanisms are the same under the two circumstances, confirmation of the usefulness of the immobilization model will be provided. If they are different, the information obtained from the immobilization model will still be useful, since this factor is clearly important in clinical osteopenia on earth.

2. A second major opportunity will be to assess the role of hormonal factors on changes in bone formation and/or resorption and on the resultant net loss of bone mass. The hormone studies should include measurements not only of the major calcium regulating hormones but those that are important in systemic metabolism generally. Nonhormonal studies might include not only the ions but unusual factors such as prostaglandins, osteoclastic activating factors (OAF), and serum bone collagen stimulating factors mentioned above.

3. A third opportunity would be to assess further possible disabling consequences of skeletal loss in spaceflight or during immobilization. This information will be extremely important in assessing the feasibility of prolonged spaceflight. Such studies will have to be carried out in relation to studies of muscular function, which are obviously interrelated. Musculoskeletal function in turn may have to be examined in the light of changes in cerebral function, particularly the vestibular apparatus.

4. The fourth area of opportunity would be to use both the spaceflight and immobilization models to assess current methods for the prevention and treatment of bone loss. This would include use of the spaceflight model to assess the role of different *g* forces in preventing loss.

5. The fifth opportunity would be to develop better methods for skeletal research and to assess current methods through the use of the spaceflight and immobilization models.

In the following paragraphs each of these opportunities will be considered. Some specific hypothesis that might be tested will be presented. But this can represent only a selective approach to the large number of problems that might be considered in the future.

Mechanism of bone loss. The cellular mechanism of bone loss during weightlessness or immobilization presumably is related to the fact that the skeleton normally develops and remodels in response to gravitational and muscular stress. When these influences disappear, skeletal physiology is markedly altered. It is not known whether the normal adjustments to gravitational and muscular stress are made primarily by changes in the activity of osteoblasts that form bone, or osteoclasts that resorb it, or by modulation of both cell types. It seems likely that both cell types will be involved. In view of the conflicts in the results obtained by kinetic and balance methods in the bedrest model and in the morphologic study in space using rats, we have insufficient information to develop a working hypothesis. The initial studies must also be guided by what is feasible methodologically. Using relatively short periods of weightlessness or bedrest it should be possible to determine effects on cellular morphology of bone and bone formation rate. If osteoclastic activity and bone formation rate are well maintained in weightless or immobilized humans, this will conform the kinetic studies implicating increased bone resorption as the primary mechanism and indicate a major difference from the rat model. The implications of such a finding for subsequent hormonal and therapeutic approaches will be numerous, and the results would greatly alter the sequence of studies in other areas. If, on the other hand, a substantial inhibition of bone formation is found both in weightlessness and at bedrest, then this would bring into question the kinetic data previously obtained and also affect hormonal and therapeutic approaches in the future. A final possibility is that bone formation will decrease in the weightless state but not at bedrest. Such a result would, unfortunately, make the bedrest model no longer tenable for studies of prevention or therapy of bone loss in space.

This analysis presupposes that the primary abnormality is in bone itself and not the result of some changes in calcium metabolism in other systems. The findings in Skylab that hypercalciuria persisted throughout the flight while fecal calcium losses increased progressively can be used to support this view, since such changes would be expected if the movement of calcium from bone to blood were increased. The alternative possibility, i.e., a primary defect in calcium transport in the intestine or kidney during weightlessness, should not be completely dismissed. This possibility can be investigated by the hormone and kinetic measurements recommended in the next section.

Hormonal and nonhormonal factors. Although the hypothesis that skeletal loss is directly due to a gravitational force on the skeleton appears to be the most reasonable, an additional permissive or regulatory role of hormonal factors on this process cannot be excluded. To this end, studies on the biological activities of PTH, vitamin D, calcitonin, insulin, somatomedin cortisol, and other as yet unidentified serum factors may be necessary. One of the most important measurements that is needed in assessing the hormonal response during skeletal loss is the assessment of ionized calcium. A small number of total calcium measurements obtained during the Skylab missions indicate an increase of total calcium by 0.4 to 0.5 mg/dl. With no change in total protein or albumin, this finding is consistent with an increase in ionized calcium. Increments in a nonionic ultrafilterable calcium binding complex, which may result from accelerated bone or muscle metabolism, has not been ruled out.

A remote possibility, which should be tested, is that some degree of chronic acidosis is responsible for mineral loss. There is no reason to suspect this from preliminary data in Skylab or at bedrest, but it can be easily ruled out by appropriate studies of pH, blood gases, and bicarbonate using inflight measurements. Since these measurements will also be important for assessment of cardiovascular and respiratory function, they seem quite justifiable.

Consequences of bone loss. The major areas of concern are (1) the time required for recovery of lost bone after return to gravity or activity and the influence of slow recovery on musculoskeletal function; (2) the possibility of irreversible bone loss, particularly of trabecular bone; (3) the possible toxic effects of calcium and phosphate released from bone on soft tissues, particularly the kidney; and (4) the functional hazard of a diminished skeletal mass and the potential for fractures in response to impact loading and tortional stress.

Major skeletal losses are likely to occur only after prolonged periods of weightlessness or bedrest. Results of ongoing research projects will be relevant to these questions.

The possibility that prolonged spaceflight could lead to renal stone formation must also be recognized. It could be assessed to some extent in shorter spaceflights by determining whether the urine shows an increase in preformed crystals, a tendency to persistent acidity or alkalinity, a change in its ability to inhibit or enhance crystal growth, or some change in the content of stone-forming components other than calcium (e.g., oxalate, uric acid, crystine).

Therapy or prevention of bone loss. Data obtained on the mechanism of bone loss may influence the direction of therapeutic and preventive measures in the future. At present, one of the most important therapeutic approaches available is the use of various weight-bearing exercise or artifical-gravity regimens that specifically counteract the loss of gravitational and muscular stress, believed to be responsible for bone loss in space or during bedrest. In this area, the initial experiments on artificial-gravity regimens must be carried out on animals by centrifugation in space and comparison with control animals maintained in the same capsule but without gravity. In such animal studies, it may be possible to determine not only whether restoration of gravity through centrifugation has an effect on skeletal mass but also the amount or duration of gravitational stress required. Obviously, the simplest way of dealing with skeletal loss in space would be to restore earth gravity. This has great technical limitations, and any partial gravitational influence that is effective might be much more practicable. Repeated short periods in a gravitational field or a low-*g* force would be much easier to maintain in space than a continuous 1-*g* state.

Whatever the outcome of studies of partial gravitational force, additional studies on the prevention of bone loss by nutritional or pharmacological means will be worthwhile, not only because they may ameliorate skeletal loss during long spaceflight, but because they could provide new insights into the therapy of metabolic bone diseases on earth. If the major mechanism for bone loss in both spaceflight and immobilization is increased bone resorption, then studies aimed at inhibiting bone resorption should have highest priority. Studies using diphosphonates are currently being performed; and, by manipulation of dose and the type of drug, it may be possible to develop an effective inhibitor of bone resorption that can be used for prolonged periods without undue toxicity. Current studies in man and animals indicate that by using lower doses of a diphosphonate, EHDP or by using a different compound, dichloromethyline-diphosphonate, it is possible to avoid osteomalacia or rickets that is usually encountered with high doses of EHDP.

If decreased bone formation is the major mechanism by which skeletal mass is lost in space, then therapy may be difficult if not impossible. There are no known agents that reliably stimulate physiologic bone formation. Fluoride has been shown to stimulate osteoblastic activity, but the bone formed may not be localized to areas of physiologic need. Insulin stimulates bone collogen synthesis but is not readily manipulated. It would be worthwhile to look for compounds that stimulate bone matrix formation and mineralization not only for spaceflight but for the treatment of metabolic bone disease, and current ground-based studies on prostanglandin, somatomedin, and other serum factors may provide new approaches to this problem.

Evaluation and development of methods. The development of better methods of evaluation of skeletal function and metabolism is clearly necessary for the ultimate solution of the problem of bone loss in space and should be supported by NASA. Much of this development can be carried out in ground-based experiments. A number of approaches exist, but only a few will be mentioned here. As suggested above, the development of better methods for the analysis of bone mass using whole-body dual-photon-transmission scanning and computerized transaxial tomography would be useful. The ability to assess bone resorption quantitatively by measurement of a specific bone collagen degradation product in urine would be of enormous advantage. Better understanding of the local humoral mechanisms by which bone cell function is modulated obviously would help in designing future studies. The use of bone biopsies for *in vitro* studies of bone and bone-cell metabolism and assays of serum factors influencing bone growth are among the many approaches that might be useful. Finally, as better methods for assessing bone turnover and bone blood flow become available, they may find a role in the efforts to explain the effects of weightlessness on the skeleton.

General Requirements

There are a number of general requirements that must be fulfilled if we are to take advantage of the opportunities for new information listed above. In order to assess the mechanism of bone loss in space and at bedrest, to study its humoral concommitants, to develop new methodology, and to evaluate new therapeutic techniques, new approaches in experimental design will be required. Collaboration between several individuals and laboratories will become mandatory. Because there is conflict concerning interpretation and technique for many of the methods, more than one established active worker in the field should be consulted before deciding on any given procedure. Some of the methods will cause some discomfort to the subjects, yet it is hard to see how any real insight into the mechanisms of bone loss can be obtained without bone biopsies. Since stress-related changes are probably of primary importance, these would have to be sought in weight-bearing bones, and the medical and ethical justification for such procedures would have to be addressed. Multiple assays, continuous-blood-withdrawal technique, and multiple venipunctures will be involved. Subjects must be able to take part in the experiment without interruption or disruption. Hence, the use of active stressed astronauts with excessive scheduled responsibilities must be avoided. The activities of human subjects must be carefully controlled, although they could function as experimenters in the laboratory, performing scheduled procedures and analyses. Most of the studies listed above require the use of human subjects. Animals do offer the advantage of making more tissue available for study and can be studied in larger numbers, but they do not provide good balance data in flight, have limited blood volumes, and are not true bipeds. This means that the number of subjects will be limited to four to seven in experiments using the Space Shuttle. However, results obtained during immobilization and Skylab suggest that a series of experiments with three subjects per experiment can produce useful and meaningful data.

The only animal studies in space that we currently recommend are those that test the ability of graded or discontinuous "*g*-forces" to reverse bone changes produced by zero-*g*. These should be carried out on animals that are under continuous observation, and the Space Shuttle would be appropriate for such investigation.

Specific Recommendations

1. A series of experiments should be designed using the Space Shuttle to assess the mechanism of bone loss during weightlessness. These experiments should be carried out in parallel with experiments on the effects of immobilization at bedrest in similar subjects. Calcium balance, isotopic kinetic studies, appropriate hormonal measurements, and possibly bone biopsies after multiple tetracycline labeling should be obtained in all subjects. These experiments should be carried out for the longest feasible time of spaceflight. In initial Space Shuttle experiments this may be only one month or less, but if longer times become feasible, they should be used.
2. Animal studies should be performed in space to evaluate the effect of varying "*g*-forces" on bone.
3. Ground-based research should be continued on the therapy and prevention of bone loss, on the analysis of its consequences, and on new methods for assessing both the function and regulation of the skeleton. This research should include studies on specific prevention of bone loss in immobilization using EHDP (with emphasis on the potential hazards of inducing osteomalacia); development of quantitative and sensitive methods for assessing mineral loss in segmental areas of the skeleton and methods for measuring bone resorption and bone-cell behavior in humans; evaluation of varied dietary regimens with Ca:P ratios equal to or greater than one on the rate of bone loss in flight; and the establishment of exercise programs designed primarily to maintain the integrity of bone.

MUSCLE-METABOLIC

Overview

A consistent finding in spaceflight has been increased protein catabolism including muscle breakdown. The data include a persistent rise in urinary nitrogen (averaging 4.5 g per day) and urinary amino acids and a 35 percent increase in 3-methylhistidine in the urine. Because these changes did not occur under terrestrial conditions, it is reasonable to attribute them to the space environment. The extent to which these changes were due to zero-*g* or to other stress reactions attendant to spaceflight have not been determined. It is noteworthy that the negative nitrogen balance persisted through the 84-day Skylab 4 flight and was not prevented by an increasingly vigorous exercise program. These observations cause concern that muscle wasting on prolonged spaceflights might be extreme and limit effective astronaut performance. There is an obvious need to understand the mechanism of development of accelerated muscle breakdown in space and develop measures for its prevention or amelioration.

Review of Current Knowledge

The mechanism by which physical activity maintains muscle mass and functional capacity is incompletely known. Cardiac muscle responds to an added workload by hypertrophy and hyperplasia. This is associated with increases in DNA and RNA synthesis. In skeletal muscle, maintenance of innervation is essential. There is evidence that myotrophic factor is released at the motor end-plate. The absence of such a factor may be responsible for the atrophy that rapidly follows denervation.

Hormonal factors contribute to the maintenance of muscular tissue. Androgens, specifically testosterone, exert a major myotrophic effect. They are responsible for the sex differences in muscle mass and strength. Pituitary growth hormone has a diphasic effect on skeletal muscle. In hypopituitarism, muscular development is impaired and strength is decreased. These changes in the hypopituitary patient are rapidly corrected by growth hormone administration. Muscular strength may be increased early in clinical conditions associated with increased growth hormone (GH) secretion. When GH secretion is excessive for many years, muscular strength actually decreases—a true acromegalic myopathy.

Cortisol excess is a potent cause of muscular atrophy in man. Experiemental evidence suggests that cortisol-induced myopathy may be the result of inhibition of muscle protein synthesis rather than stimulation of proteolysis.

With respect to muscle metabolism, spaceflight appears to be analogous to the fasting state in which muscle protein is broken down to its constituent amino acids. The cathepsins involved in this process remain to be identified but may be cytoplasmic rather than lysosomal. Knowledge in the regulation of these cathepsins is still limited. Enzymatic reactions convert many of the amino acids to alanine and glutamine prior to release from muscle. It is the glutamine and alanine that are preferentially removed from blood by the liver for glyconeogenesis. The fat of amino acids in the liver is determined by cortisol, insulin, and glucagon.

Requirements and Opportunities

Characterization of protein metabolism in space. In addition to the measurements of urinary nitrogen, amino acids, and 3-methylhistidine already performed, it would be critical to study the level of individual amino acids in the plasma to determine whether the fasting pattern is similar to or different from that which occurs on earth. In addition to static measurements of the concentration of these amino acids in plasma, it would be important to gain information concerning their turnover. Measurements of hepatic extraction of these amino acids would not be ethically permissible or technically feasible in space, but studies of the flux of these amino acids and their appearance in glucose can now be conducted with stable isotopes (carbon-13 and deuterium) using gas chromatography and mass spectroscopic methods.

Parallel studies of glucose metabolism should also be performed to determine whether the mild tendency for low fasting plasma sugars and low plasma insulin concentration noted during immobilization and weightlessness are the result of decreased hepatic glucose release or increased peripheral utilization. If it could be shown that decreased hepatic glucose release occurred despite increased availability of alanine, glutamine, and other precursors, a defect in gluconeogenesis could be suspected.

The studies mentioned above should be compared with studies on earth of ambulatory subjects and subjects confined to prolonged bedrest.

Mechanisms of protein catabolism. (a) Influence of gravity: It is unclear whether other mammals incur the same degree of muscle atrophy as man does in space. It would be important to conduct experiments in space with rats and other small animals that are able to exercise in order to determine whether an animal model for human muscle atrophy in space could be developed. If the model could be established, it would be possible to use the gravitational centrifuge in space to determine whether muscular atrophy could be prevented by normal or fractional gravitational force.

It is of primary importance to establish whether absence of gravitational stress is the main cause of muscle atrophy during spaceflight. If it is, further sophisticated studies (outlined below) would probably be unwarranted. If, however, muscular atrophy cannot be prevented by provision of a gravitational force and a multifractional process appears likely, a wider range of studies will become necessary.

(b) The role of hormones in the development of the negative nitrogen balance in space requires further study. Preliminary measurements in Skylab indicated that the 8:00 A.M. plasma growth hormone levels were modestly elevated in space. Because growth hormone is secreted in discrete pulses at different times of the day, depending on food, physical activity, sleep, stress, and other stimuli, single measurements at an arbitrary time period provide little information concerning total growth hormone secretion. In order to characterize growth hormone secretion, it is necessary either to have a continuous venous blood aspiration or to have frequent sampling by withdrawal of small blood samples at frequent intervals, for instance, every 2 to 3 hours. Both of these methods would require subjects dedicated to clinical research with no other tests on experimental days.

It is now widely held that at least some of the growth stimulation and anabolic effects of growth hormone are not directly exerted by the hormone itself but by secondary hormonal mediators, the somatomedins. The evidence that somatomedins, presumably synthesized in the liver, affect cartilage and fibroblasts is convincing. There is also some experimental evidence that these tissue growth hormones affect muscle and possibly bone metabolism. For this reason, it would be desirable in the evaluation of anabolic hormones to have measurements of somatomedins. Bioassays have limitations in precision and in specificity, but radioreceptor and radioimmioassay methods should be operational and practical by the time Space Shuttle flights dedicated to biomedical research are operating.

Insulin is an anabolic hormone that deserves greater attention in space. Skylab measurements suggest a decrease in fasting levels. This finding obviously provides a very incomplete picture of total insulin secretion. More complete characterization could be obtained by insulin measurements on the continuous or intermittent samplings techniques mentioned earlier for growth hormone. An additional technique of evaluation of total insulin secretion is provided by determination of urinary C peptide (C peptide is the connecting peptide that is cleaved from proinsulin to yield insulin). This peptide is released in stoichiometric amounts with insulin as the beta granule is extruded from the beta cell of the pancreas. Fortunately, this peptide has a relatively long plasma half-life and appears in the urine in substantial quantities. Measurements of urinary C peptide could provide a measurement of total pancreatic production of insulin in space.

While the actions of the glucagon are complex, this hormone does promote hepatic gluconeogenesis from amino acids as well as from glycogenolysis. Measurements of this hormone when correlated with plasma glucose and insulin concentrations permit characterization of the hormonal regulation of hepatic carbohydrate metabolism. Plasma glucagon measurements require that blood be collected in the presence of a proteolytic enzyme inhibitor, Trasylol, and the employment of an antiserum with high specificity for pancreatic glucagon.

Prevention of muscular atrophy. It is urgent to consider measures that will prevent muscular atrophy from occurring in spaceflights. While the evidence for the occurrence of protein loss of muscle has largely been biochemical, sophisticated measures of muscle performance should be applied. While this panel is not expert in this area, electromyographic, biochemical measures of muscle efficiency (oxygen requirement and lactate production during defined exercise) and measurements of contractal strength and endurance should be considered to identify and quantitate defects in muscle function acquired in spaceflights.

A study should be made of the optimal exercise program that would minimize muscular nitrogen loss. While the astronauts on the Skylab program engaged in an increasingly active program of exercise, the type of exercise and the duration of exercise was largely self-selective. Unfortunately, this program was not effective in preventing the nitrogen loss or muscle wasting in space. Expert muscle physiologists and psychiatrists should be consulted to devise a more effective program of exercise that might be instituted in an experimental protocol to determine objectively its effectiveness.

The diet consumed by the astronauts in Skylab contained, on the average, 85 g of protein per day. There is also some reason to believe that the caloric intake was insufficient for the vigorous activities of the astronauts. It has been observed that a high nitrogen intake provided by amino acids is effective in hyperalimentation programs in achieving positive nitrogen balance in certain clinical conditions of protein wastage. Therefore, we recommend that a study be conducted comparing the effectiveness of a diet containing a substantial increase in its protein content (e.g., about 130 g per day) with the one ingested on previous Skylab flights.

If the trials of extended exercise and increased dietary protein prove ineffective in restoring nitrogen balance, hormonal therapy should be considered. The most promising agents to be considered would be testosterone and pituitary growth hormone. The use of testosterone hormone to increase muscular strength in athletes is common knowledge. A critical trial of this agent in prolonged spaceflight would be justified. For flights of several months, spermatogenesis would return promptly after cessation of therapy. More prolonged administration of the hormone will cause more concern. Any trial of testosterone would require monitoring of sperm count.

The use of pituitary growth hormone to maintain muscular performance is less promising for practical and theoretical reasons. First, the supply of this hormone is limited, and diversion of the available hormone would deprive needy hypopituitary patients. Second, growth hormone not only stimulates muscle but also has anti-insulin effects and might lead to acromegaly. Nevertheless, if the problem of nitrogen loss continues to be unsolved in space and synthetic or other new supplies of growth hormone become available, an experimental trial of this hormone should be considered.

Recommendations

A program should be instituted to study the pathogenesis and control of the muscular atrophy and its attendant negative nitrogen balance that occur in space. This program should include basic studies of muscle physiology and biochemistry both in space and land. The Space Shuttle should be employed for clinical studies of amino acid and nitrogen metabolism, as well as for studies of muscle function. It should also be used to evaluate exercise, dietary, and hormonal therapeutic measures.

ENDOCRINE

Data collected during bedrest studies and Skylab missions reveal certain homeostatic derangements, which, if substantiated, could prove of biological significance for chronically immobilized subjects and subjects in a hypogravity environment.

Renin–Angiotension–Aldosterone System (R-A-A-S)

Critique of current state of knowledge and results from bedrest studies and Skylab. The R-A-A-S and the pituitary-adrenal axis show increased activity during weightlessness, which may influence the many metabolic and fluid alterations that are observed during spaceflight. While the hormonal data obtained during immobilization do not correspond completely to all the Skylab observations, there are sufficient provocative findings to suggest that the adrenal cortex is activated during the weightless state.

The negative sodium balance that occurs during early orbital flight (1 to 3 days) is also observed in almost identical temporal relationship during bedrest studies. Similar shifts in sodium balance also occurred during water immersion. During this early period, increases in central blood volume occur mainly because of translocation of fluid from the lower extremities, resulting in increased cardiac output. The proposed series of homeostatic events that follow include:

1. Reflex peripheral vasodilatation,
2. Suppression of the R-A-A-S,
3. Suppression of antidiuretic hormone (ADH),
4. Increased secretion of humoral natriuretic substances,
5. In some astronauts, reduced thirst (water intake).

These events establish a new steady state of reduced extracellular fluid, which is maintained throughout spaceflight. The confirmation of certain of these proposed hormonal events is limited by the difficulty in obtaining samples of blood at critical times for the measurements of cortisol, ADH, aldosterone, and renin.

Transient suppression of aldosterone very early in flight could conceivably be a significant determinant of the natriuresis, and this should be evaluated in more detail. Interpretation may indeed be difficult because of the stress and activity attendant upon lift-off, orbital insertion, and early space activities. Studies made during bedrest, when stress and activity are considerably less, may be better for obtaining these early measurements.

After the initial one to three days of flight, hormonal information is adequate for interpretation.

Urinary aldosterone and 17-hydoxycorticosterioid levels are normal in most bedrest studies. A recent study documented slight but significant increases in both urinary and plasma aldosterone concentration by the third day of bedrest. This same study also documented an increase of the 8 A.M. plasma renin activity (PRA) by day three as well as increases of the integrated nocturnal (midnight to 9 A.M.) PRA levels by day three. Plasma cortisol levels and its urinary metabolites were normal.

The infrequent inflight plasma aldosterone levels are minimally elevated by day three based on a single 7 to 8 A.M. blood sample. Urinary aldosterone levels during the flight vary from day to day, but the mean value is significantly increased above preflight values. No sustained increases of renin levels were documented by (infrequent) morning blood samples. However, urinary free cortisol was increased and, in common with aldosterone patterns, showed variability from day to day. While the limited morning samples of plasma cortisol were normal, increased cortisol secretion and higher integrated cortisol levels probably existed throughout the day. Urinary 17-ketosteroids were clearly elevated, and fractionation showed the components to be primarily of adrenal origin. Urinary 17-hydroxycorticosteroids were normal, but inflight specimens showed a shift from tetrahydrocortisone to tetratrydrocortisol, which again could be interpreted as resulting from the altered metabolism due to stress and/or influence of mild thyroid excess

Urinary norepinephrine and epinephrine inflight were surprisingly similar to preflight values, despite evidence of an adrenal stress response as documented by elevations of urinary free cortisol and 17-ketosteroids. The hormonal secretion patterns are consistent with a mild chronic adrenal hypersecretion with intermittent pulses of ACTH release. This intermittent secretion of ACTH, in contrast to sustained secretion, would produce the simultaneous secretion of both cortisol and aldosterone in the face of normal renin levels.

The enormous activity required to operate Skylab and the effort expended during exercises and performance of a variety of experiments are indeed sufficient to modify patterns of hormonal secretion, specifically, pituitary and adrenal secretion. The generalized increase of the adrenal steroids makes it difficult to attribute increased aldosterone secretion to renin alone. That such a role may exist after orbital insertion can be suspected by the recent observations from bedrest studies in which both aldosterone production and renin levels are significantly greater than control by day three.

The adaptation of hormonal systems to a reduced but stable extracellular fluid, after the initial natriuresis, may be necessary to maintain it unchanged during the rest of the flight. Hyperaldosteronism may exist in both weightlessness (in the absence of stress) and during a prolonged bedrest study. While reduction in volume could be the trigger for the increases in the R-A-A-S, one cannot exclude other factors such as beta-adrenergic activity.

Opportunities and recommendations–general. The abberations in adrenal secretion need further and more accurate documentation.* Stress, if possible, must be reduced to further understand the contribution of a presumably activated R-A-A-S.

Opportunities and recommendations–specific.

1. It is important to characterize circadian patterns for ACTH, cortisol, renin, aldosterone, and catecholamines during preflight and periodically during flight. Concurrent with these studies assessment of central blood volume during early and prolonged flights are needed.

2. Parallel documentation of the hormonal events of the first and subsequent days of bedrest is needed. There is a continuing need to develop more information from bedrest studies. The circadian rhythm of hormones in recumbency after prolonged bedrest is unknown. Comparison of similarly obtained hormonal data from well-motivated inflight experimental subjects versus active working crew may be eventually necessary to define the stress phenomena.

3. The hormonal control or modulation of the extracellular fluid should be further evaluated by strategies directed at interruption of the R-A-A-S at specific sites and at critical times with pharmacological agents.

These studies should first be applied to subjects during bedrest by pretreatment with agents such as propanolal, saralasin, and converting enzyme inhibitor. Propanalol would block beta adrenergic activity, saralasin blocks the angiotension II receptor, and converting enzyme inhibits the conversion of angiotension I to angiotension II. During the same time period, The ACTH–

*It should be pointed out that this conclusion is at variance with the view of the Renal and Electrolyte Panel, which considers the small absolute changes in aldosterone secretion to be of less significance.

cortisol axis can be tested acutely by ACTH stimulation and/or dexamethazone suppression before and during bedrest immobilization procedures.

Pituitary Thyroid Function

Thyroid hormone excess, as in the disease thyrotoxicosis is known to cause protein wasting and skeletal demineralization under terrestrial conditions. Thyroid hormone excess is also known to cause a shortening of Achilles reflex time, findings that have been observed in astronauts tested upon their return from space missions. These actions of thyroid hormone (which duplicate several of the important metabolic complications of spaceflight) merit an interest in pituitary-thyroid function even though there is no *a priori* reason to suppose that this system would be affected by extraterrestrial residence.

Limited data collected in the Skylab program in nine crewmen provide suggestive evidence that a mild degree of pituitary-thyroid hyperfunction may occur at some time in spaceflight. Before flight, plasma thyroxine (T4) was 7.0 ± 1.0; they did not return to these levels until 11 days postflight. The increase in T4 was accompanied by significant increases in plasma TSH, thus indicating that thyroid activation had occurred through pituitary activation. Russian studies are quoted as confirming occurrence of high free T4 on re-entry.

In light of current knowledge of pituitary control, increased TSH secretion suggests a change in the secretion of the hypothalamic hormone, TRH. Elevations of T4 levels cannot be attributed to altered concentrations of thyroid binding protein because the T3 uptake test remained relatively constant throughout.

Before accepting that thyroid hyperfunction does, in fact, occur during spaceflight, several major reservations must be considered. First, no data are available *during* flight. It is conceivable that the elevated TSH-T4 values are a response to re-entry and that thyroid hormone may be depressed during space flight and that a "rebound" effect is being observed. Second, data are not available on plasma T3 concentration, an even more valuable measure of thyroid hyperfunction. Finally, there are not data on plasma reverse T3 (rT3), which is an indicator of the peripheral degradation of hormone. Even if a degree of thyroid hyperfunction did occur, there are insufficient data to conclude that it would in fact influence protein or bone metabolism under conditions of spaceflight.

Studies of stress in man under terrestrial conditions provide little guidance in this area. Most workers report that physical stress lowers plasma TSH and T4, and that starvation or low-carbohydrate diets lower T3 without lowering T4, but one or two reports suggest that psychological stress may increase plasma T4. The stress effects of the spaceflight experience are at present completely unknown.

Recommendations

1. Measurements should be made of T_3, T_4, and reverse T_3 (rT_3) on specimens obtained during Skylab 2, 3, and 4.

2. For future Space Shuttle flights, detailed analysis of plasma T_3, T_4, TSH, rT_3 (and diurnal patterns), and T_3 uptake should be considered and prospectively planned.

3. Measurements should be made of basal metabolic rates during Shuttle flights utilizing the calorimetric method (i.e., spacesuit heat exchange or oxygen consumption under basal conditions).

Gonadal Hormones and Prolactin

A characteristic response to physical stress in the human is depression of sexual function. In women, this often results in anovulation and amenorrhea, whereas effects in the male have not been well characterized. The most complete study of combined physical and psychological stress in men is that in which a group was followed through Officer Candidates School. Plasma testosterone, an indicator of pituitary-gonadal function, was low when compared with posttraining blood specimens in all but one man, indicating suppressed function. Since testosterone is an anabolic hormone, comparable changes occurring during the stressful environments of spaceflight could conceivably contribute to the well-documented bone and muscle loss as well as to decreased libido during long flights. On-site interview with one astronaut revealed no obvious changes in libido during the 85-day Skylab 4 mission. Apparently, the astronauts were capable of erection and ejaculation.

Data already available are insufficient to judge the effects of spaceflight on testosterone secretion. In three Skylab 4 subjects, urinary preflight testosterone was reported as 66.4, 58.8, and 55.3 μg/day. Mean values for inflight days 1–28 were 124.1, 114.6 and 79.8 μg, respectively. Comparable mean data for inflight days 29–56 were 83.4, 88.4, and 62.2 μg, respectively. On the other hand, plasma testosterone levels in the same subjects (Skylab 2, 3, and 4) measured mainly at 7 A.M. and immediately prior to and following the termination of flight showed a trend toward lower values after the mission. Moreover, the role of altered sexual activity prior to and during spaceflight as a possible determinant of testosterone secretion must be considered in light of currently available data, which suggests that orgasm leads to increased plasma testosterone. The possible usefulness of anabolic steroids in muscle and bone function should also be considered.

Data regarding the effect of bedrest, immobilization, or weightlessness on gonadal function in the female are unavailable. Alterations in the cyclic secretion of FSH and LH with abnormal estrogen and progesterone production could also conceivably occur during immobilization or in weightlessness. Changes in aldosterone secretory patterns, already observed for males in Skylab missions, could modify the electrolyte-water economy in menstruating women, since aldosterone is normally lower in the follicular phase and higher in the luteal phase of the menstrual cycle.

The ability to measure blood prolactin reproducibly with a sensitive radioimmunoassay represents a technical advance achieved since the completion of the Skylab missions. This hormone has only one established function in humans, namely, the stimulation of lactation. Some workers claim that prolactin also influences water and electrolyte balance and stimulates the bioactivation of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol, which could be a factor in influencing calcium metabolism. Under normal environmental conditions, prolactin manifests a circadian secretory rhythm; the telologic significance of this in nonlactating males is still unknown. Prolactin secretion is also increased by physical and emotional stress.

Nothing is known about the effects of either immobilization or weightlessness on prolactin secretory patterns. It could prove to become a sensitive hormonal indicator of stress in both immobilization and weightlessness.

Recommendations

1. More complete analysis is needed of plasma levels of prolactin, FSH, LH, and testosterone, for which specimens may already be available.

2. For future inflight studies, circadian patterns for testosterone, FSH, and LH should be obtained. This is of special significance if plans are under way to include females in the astronaut corps.

3. Detailed analysis is needed of prolactin, estradiol, progesterone, FSH, LH, and aldosterone secretory patterns in both men and women during bed-rest immobilization.

The Role of Stress in Endocrine-Metabolic Response

General concerns. A number of stress factors besides weightlessness, vibration, and radiation impinge upon the astronauts and may influence endocrine and metabolic changes. These include overt or inapparent anxiety elements related to safety and novelty, pressures to perform tasks (mission control), peer pressures, self-determined goals, space sickness (which interferes with work efficiency in this highly motivated group), physical exertion (especially extravehicular), and possibly crowding. All of the above have been shown in various ground-based studies to be stressful to at least some individuals.

Elevated urinary excretion of free cortisol probably reflects several of the above stressful factors. The elevated cortisol secretion may contribute to the nitrogen and bone wastage.

Recommendations

1. It is recommended that astronauts have detailed psychological evaluation directed to the evaluation of their individual patterns of endocrine response. Possible techniques include diary entries, psychiatric debriefing, or even a psychiatrist onboard during spaceflight.

2. Payload personnel who are shielded from some of the kinds of psychological pressures affecting the astronauts should be included in future flight schedules.

3. Detailed stress evaluation in ground-based studies is required to test these various elements of response, including psychological evaluation. Novel relaxation techniques such as biofeedback and group therapy may be appropriate.

Genetics and Developmental Biology Panel

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Genetics and Developmental Biology

OVERVIEW

The development of spaceflight offers a unique opportunity to investigate fundamental problems of cellular and organismic biology for which the absence of gravity may be a crucial variable, as well as to discover the limits of human adaptation to weightlessness. The most useful experiments would be those that illuminate our understanding of basic biological processes both on earth and in space. If a long-term goal is to colonize space, it will be of fundamental importance to learn something of the variability of biological and human responses to zero-*g*.

While the panel considers that investigations directed toward these ends might be performed profitably both in space and on the ground, the following experiments, designed to test specific hypotheses, would appear to be particularly promising and should be performed at an early opportunity.

1. As has been noted by a previous panel, "... a study that would have great biological significance is one in which experimental animals would be reared from conception to maturation in a zero-*g* environment."[1]

These experiments would shed direct light on the importance of gravity-sensitive receptors in the fertilization and embryological development of animals and would, in addition, provide an answer to the important question of whether animals reared in a gravity-free environment exhibit normal anatomical, physiological, and behavioral patterns on return to earth. We urge that such experiments be undertaken.

2. High-energy particles of high atomic number (HZE radiation) are, like weightlessness, a unique feature of the space environment. The precise effect of HZE particles on the brain, eye, and other anatomical structures is unknown.[1,2] The availability of a ground-based accelerator capable of producing HZE particles now permits the design of precisely ordered experiments. Such experiments should be supported.

3. Since gravity reception and response is a well-known phenomenon in plant physiology,[3] this area should continue to be supported. Present evidence indicates that ground-based studies are likely to be as informative as experiments inflight.

We would like to reaffirm the position taken by several previous study groups that not only is it unnecessary to repeat all possible biological experiments in space, but every effort should be made to ensure that experiments of the highest scientific quality are carried out and that they are controlled with the same rigor as would be demanded in experiments conducted on earth.[1,2] We would like to emphasize, in particular, the following general principles:

(a) It would be difficult to overemphasize the need to perform high-quality ground-based experiments before embarking on a scientific project on the Space Shuttle. Such experiments may frequently eliminate the need for experiments in space.

(b) Although the value of the clinostat has been criticized as an approach to near weightlessness because it equalizes the gravity vector rather than removing it, all experiments on plants in which gravity receptors are being investigated should first be performed with extensive, well-planned experiments on the clinostat.

(c) In previous Skylab experiments, interpretation of the results has been confounded, *inter alia*, by the absence of appropriate controls. The need for a centrifuge on future flights is of the highest priority. For many experiments conducted on cells as well as for those on small animals, such as mice, a small centrifuge would be sufficient. For experiments designed to investigate weightlessness on larger animals a large centrifuge might be required. However, engineering problems associated with the construction and installation of a large centrifuge should not inhibit the development of small compact centrifuges without which all gravitational experiments in the life sciences are uninterpretable.

(d) Efforts should be made to minimize stress on experimental animals, in view of the well-known effects of stress on, for example, reproductive performance in mice and other mammals. For this reason, high-quality animal facilities should be provided at or near the site of launch. Particularly for mammals, a preflight preparation period of several weeks may be required, as well as a postflight assessment period and facilities for ground-based controls.

(e) The Space Shuttle will permit scientists to be in attendance during the conduct of an entire experiment in space. This is a significant advantage for it permits sequential observations and experimental modifications to be made that will greatly expand the range and sophistication of biological experiments that can be carried out.

(f) It is particularly important in those cases in which the payload specialist accompanying an experiment into space is not the principal investigator that the payload specialist spend an appropriate training period in the principal investigator's laboratory. We make this suggestion because the tools and techniques of experimental biology are not well standardized and because small misunderstandings in methodologies may significantly alter the outcome of an experiment.

(g) Spaceflights of prolonged duration are of crucial importance if full gestation of a variety of animals is to be observed in a gravity-free environment. In view of the possible importance of gravitational effects during gametogenesis on subsequent development, it will be necessary to make observations on more than one generation. Similarly, experiments on plants should include observations over several life cycles.

REVIEW OF EXISTING KNOWLEDGE

The genetic effects of radiation in space have been the subject of extensive study, and no significant synergism between radiation and spaceflight has been observed. Similarly, there have been no convincing indications that spaceflight causes significant detectable abnormalities in single cells.[1,2] On the other hand, plant responses to gravity are well known and have been extensively studied. In general, results obtained from experiments conducted in space have confirmed ground-based experiments.[3,4] In the field of animal development, few conclusive results have been obtained.

Previous studies[1,2] have examined the existing knowledge, but it should be noted that there are at present no critical and well-documented reviews of the results obtained.

REQUIREMENTS AND OPPORTUNITIES

Developmental Biology

ANIMAL

The Panel was unanimously of the opinion that high priority should be given to the question of whether vertebrates, and mammals in particular, can undergo normal embryonic and postnatal development in space. Normal development in conditions of weightlessness has been reported for plants, drosophila, and some other invertebrates.[1,2] Similar but more extensive studies on vertebrates are now required, both in order to uncover any possible causal role of gravity in the differentiation of form or function and to throw light on the various physiological problems raised by manned flight. Information on whether a complete life-cycle can occur in space would also have obvious implications for the feasibility of eventual colonization of space.

Early stages of development (embryogenesis). In the last 10 years, rapid strides have been made in studying the very early stages of mammalian development, from fertilization up to the beginning of organogenesis (7 to 10 days in mouse and man). *In vitro* culture techniques have made a substantial contribution to our knowledge of the factors underlying development during this period. However, there are several critical developmental processes for which the underlying mechanisms are still largely or wholly obscure and that might depend at least in part on gravity. In particular, it would be valuable to know to what extent weightlessness would disrupt fertilization, cleavage, and primary-axis formation.

Frog eggs, which contain a large amount of heavy yolk, are highly sensitive to gravity up to the time of the first cleavage division. As yet, we do not know what determines the plane of the first cleavage division in the mammalian egg. Although such eggs are relatively small and "non-yolky," the hypothesis that gravity plays a part is worth testing. Studies on cleavage in zero-*g* would bear on the question of whether mitosis and cell division are to any extent disturbed by weightlessness. The formation of the blastocyst cavity occurs eccentrically; the relation of this to gravity is again not known. At this stage, the mammalian embryo is still radially symmetrical; it is not until a few days after implantation that bilateral symmetry develops, and the embryo acquires polarity. Although it is basic to the whole of subsequent development, we are still totally ignorant of the mechanisms underlying this process of axis formation. Gravity provides a possible directional stimulus; the extent to which it is implicated in axis formation can only be tested in a zero-*g* environment.

Fertilization and cleavage in conditions of weightlessness could be investigated both *in vivo*, in appropriately mated animals, and *in vitro*, where the rate and pattern of cleavage could be continuously monitored by time-lapse cinemicrography. Primary-axis formation would need to be studied *in vivo*, with the embryos removed from the uterus and fixed for subsequent histological examination at different stages of development.

Later stages of development (organogenesis). Evidence suggests that, for each organ system, there is a critical period during which development can be disrupted by relatively small environmental insults. Men exposed to prolonged weightlessness have shown vestibular problems, loss of bone calcium, and decrease in plasma volume and red-cell mass. Adult monkeys subjected to prolonged inactivity in casts have shown even more striking changes, including cessation of osteogenesis, loss of muscle mass, and degeneration and fibrosis of skeletal and perhaps cardiac muscle.[5] Gravity-deprivation might have a still more marked and more permanent effect if exerted during critical periods of development, just as sensory systems (receptors and their neural connections) are known to develop abnormally in animals raised in the absence of sensory input (e.g., visual systems of animals raised in darkness). If animals were to develop in space from conception to maturation, or even if pregnant females could be maintained in a weightless environment for the duration of the appropriate critical periods, the following questions could be investigated.

(a) If the animal is exposed to zero-*g* at the time of development of the vestibular apparatus, will the morphology of the vestibular apparatus be affected? Even if the morphology is undisturbed, will postnatal function be preserved? Is there an analogy with the child with strabismus, who uses only one eye and, in consequence, loses the vision of the unused eye?

It seems probable that the integration of vestibular and other neurological functions important for balance continues well into postnatal life. If weightlessness is shown to affect the development of balance mechanisms, the hypothesis of critical periods in development could be tested by exposing animals to zero-*g* for various periods during postnatal life.

(b) If the animal is exposed to weightlessness during the development of the cerebellum, the effects of gravity as a stimulus to normal morphological and functional development could again be tested. Will such an animal subsequently show abnormalities in involuntary body movements? Some additional information might be derived by exposing mice with genetically determined defects in cerebellar morphology or function to zero-*g*.

(c) If the animal is exposed to weightlessness during prenatal and/or early postnatal life, will autonomic functions related to gravity perception, such as peripheral blood pressure control, develop normally?

(d) If the animal is exposed to zero-*g* during the initial period of osteogenesis, will bone formation occur? Will the balance between osteoblasts and osteoclasts be normal? Will bone morphology be normal? Will postnatal bone formation take place normally in the absence of weight bearing, or will it be deformed by muscle pull in the absence of gravity? The effect of weight-bearing on the conformation of the skeletal system is well known; for example, in animals and human beings with rickets, the processes of healing and the residual deformities are thought to be reflections of the effects of weight and muscle pull on softened but still growing bones. However, the extent of the contribution of each force, whether in normal or rachitic bones, remains unclear. One possible way of partitioning the two elements, muscle pull and weight bearing, would be to expose rachitic animals to zero-*g* for a period, followed by treatment for the rachitic condition. Upon return to gravity, the deformities seen would be attributable to muscle pull.

(e) If an animal is exposed to zero-*g* at the time of development of the heart, will the cardiac syncytium form and function normally? If the animal is exposed to zero-*g* at the time of initial hemopoiesis, will the red-cell mass in the embryo or young adult be significantly decreased? Will the plasma volume be affected? Will the body distribution of fluids be abnormal?

Choice of species and genetic variability. The choice of species for particular developmental studies will need to be considered carefully. For studies of early embryogenesis, and for general teratological studies in the prenatal period, the mouse is the species of choice, both because of its small size and because of the large amount of embryological and genetic data available. For vestibular studies, in which testing of reflexes and electrophysiological investigations after return to earth would be important, golden hamsters or guinea pigs, or even cats, would be preferable. In any small animal, parturition and early postnatal care is likely to present grave problems in the animal-holding units as envisaged at present; until these problems can be overcome, studies on postnatal development, including behavioral development in relation to vestibular function, would be better carried out on pigeons or chicks. Further experiments should also be considered on fish, in view of the suggestive results on locomotor orientation obtained previously, and on frogs, in which gravitational forces prior to the first cleavage division are known to exert a powerful determining influence on development.

Experiments on lower organisms could also be envisaged for which gravitational forces are known to play a determining role in development. For example, in cellular slime molds where the stimuli involved in cellular aggregation have been extensively studied, the subsequent upward migration of cells to form the stalk and fruiting body appears to be a response to light and potentially to gravity and should be investigated.

Within a species, consideration should be given to the genetic constitution of the strains used. If no effects of weightlessness on development are seen initially, the sensitivity of various organs to this stress could be enhanced by using appropriate mutant strains; these might be particularly suitable for a study of the role of gravitational force in palatal closure. For example, strains of inbred mice are known that produce offspring with a 15–20 percent incidence of clefts of the hard palate. The frequency of malformation can be increased by administering doses of cortisone to the pregnant female that have little or no effect on nonsusceptible strains. If inbred animals prove unsuitable for use in space, because of their reduced viability and fertility, or lack of maternal vigor in tending the young, F_1 hybrid animals showing the trait in question could be substituted.

Some *Drosophila* strains are known to show geotaxic effects, in that they fly up or down when confined in an appropriate chamber, rather than laterally.[6] To test whether this is a response to gravity, the flies could be bred under conditions of *zero-g*, and the behavior of mature flies observed after return to earth. If the effect is dependent on the development of some gravity-sensitive mechanisms in the central nervous system that arise in response to gravity, the response of the mature flies in the chamber should be obliterated.

PLANTS

Plants offer, perhaps, the most promising area yet identified for the study of gravity perception and response. Tropic responses to gravity are well known; it also seems that gravitational forces may play a part in lignification. Since at the cellular level the mechanisms involved in gravity perception may be similar in all organisms, the investigation of gravity responses in plants should be a priority area for NASA.

A particularly important question, which so far is still entirely unanswered, is the initial establishment of polarity in a plant cell. Since this is presumably a developmental process, studies involving at least one life cycle may be required.

To date, the consensus of opinion seems to be that plant experiments in space add little to earth-based studies. The results of plant investigations in Biosatellite confirmed but did not extend the results of clinostat experiments on earth[3,4]; it therefore seems that although the environment afforded by a clinostat is essentially different from that of weightlessness, plant cells may not be capable of perceiving the difference. We recommend that, until a strong case for the necessity of experiments inflight has been made, support should be concentrated on ground-based studies.

Cell Biology

Experiments thus far carried out in space indicate that *zero-g* has little or no effect on most simple cell functions such as DNA replication or content, spindle formation, cell division, cell mobility, organelle movement, and cell morphology. Thus, with the exception of problems in developmental biology specified elsewhere in this report the Panel found it difficult to identify specific areas in cellular or molecular biology where the effects of examination of *zero-g* seemed of immediate importance.

This is not to say that we believe that gravity has no effect on simple cells.

In the case of plants, it is evident that the geotropic responses of the organism are mediated by gravitational effects on the distribution of subcellular organelles, presumably starch grains. The mechanisms by which organelle redistribution influence hormonal balance, membrane potentials, water flux, and direction of cell growth are, as yet, unresolved questions of fundamental importance. These problems can profitably be further explored on earth. Virtually every group that has examined the potential utility of using zero-*g* as a probe for gravitational effects on plant cells has come to this conclusion. We have seen no new evidence nor heard compelling arguments that lead us to a different conclusion.

In the case of animal cells, the studies of Montgomery *et al.* on Skylab,[7] and those of the Russians on Kosmos,[8] have identified no significant effects of weightlessness on cells grown in culture. While it can be argued that more detailed studies in space of the distribution of cytoskeletal elements (actin, myosin, tropomyosin, alpha-actin, tubulin, 100-Å-diameter filaments) and organelle and plasma membrane movement might reveal undiscovered effects, we believe that new and compelling experimental evidence or theoretical arguments must be forthcoming to justify such experiments. On the other hand, we see no objection to the performance of such experiments as by-products of other higher-priority projects, provided that these by-product experiments are adequately controlled.

The separation of molecules, organelles, and cells by electrophoresis under conditions of zero-*g* has been proposed and even attempted.[9] We view this as a methodology in search of a problem and unlikely to be of practical importance at present.

In summary, we see no fundamental issue or hypothesis regarding the biology of single cells that requires a critical test in space at this time. Cellular and molecular biology can best be employed as tools to dissect the effects of weightlessness on the whole organism. However, an expansion in ground-based research would be expected to lead to a better conceptual and experimental framework for the understanding of the effects of weightlessness on cells and organelles undertaken by original and competent investigators in this area.

Genetics and Radiobiology

Genetics. In the past, NASA has carried out an extensive series of experiments on the genetic effects of radiation in the space environment. These experiments, which were carried out in the Gemini flights and in Biosatellite II,[10] were reviewed thoroughly by another summer study.[1] The conclusion reached by the study was that there were no repeatable statistically significant results indicating a synergism between radiation and spaceflight. Thus, the NASA program answered the worrisome possibility that radiation in space presented an untoward hazard to manned spaceflight.

Whenever well-defined genetic endpoints were studied, the results in both controls and the irradiated series were the same in space as on the ground. The experiments were broad and included experiments on chromosomes in human blood cells, *Neurospora*, *Drosophila*, *Habrobracon*, and *Tradescantia*. Thus, it appears that the Spacelab environment would not seem to offer any special opportunity for genetic studies—a conclusion reached by the 1973 study on scientific uses of the Space Shuttle.[2]

Within the biosatellite program, however, some aspects of the flight profile did induce genetic and cytological effects. Thus, vibration induced some translocations in *Drosophila* sperm and sex-linked recessive lethals in *Habrobracon*. Furthermore, disturbed mitoses and nondisjunction were found in experiments with *Tradescantia*, *Drosophila*, and *Habrobracon*. Such effects, however, were by no means universal in that many of the systems flown on Biosatellite II failed to show them. Although the evidence is good that such effects of the spaceflight environment (including vibration and atmospheric factors in the spacecraft) are real, the Santa Cruz study (*Space Biology*, National Academy of Sciences, Washington, D.C., 1970) concluded that "the difficulty and complexity involved in isolating the variables and in repeating, directing and quantifying the stimuli are so great that we believe that this line of study should not be pursued further in space flight experiments until its complexities have been thoroughly studied in earth laboratories."

The advent of the spacelab in which man can tend his experiments and in which a centrifuge can be placed to provide a 1-*g* onboard control, now allows the experiments and the controls to come from organisms that have had identical exposure to other spaceflight factors. This might now provide the opportunity to study the previously noted perturbations of cell division.

Radiobiology. The ambient radiation in space consists almost entirely of electrons and protons. The radiobiological effects of such particles are very well understood, and the hazard from such particles can be predicted from physical dose measurements, which should be made.

In addition to the electrons and protons mentioned above, a relatively small number of galactic particles of high atomic number, *Z*, and high energy, *E* (HZE particles) are present in space. The *Z* number extends from $Z = 18$ (argon) to $Z = 90$. These highly energetic particles can penetrate tissue and kill cells traversed by the core of the particle track. This core has a diameter of 10-50 Å and contains at least half of the energy lost by the particle. Thus, HZE particles can act as microneedles killing a one-cell-thick cylinder of cells. In regenerating tissues, this should present no hazard, but in non-regenerating tissues such as the brain or the retina of the eye, extended exposure could lead to the loss of function.

We endorse the recommendations of previous study groups that ground-based studies on the effects of HZE particles are important, so that better estimates can be made of the hazards, as well as to gain fundamental information about the radiobiological effect, of such particles. The studies already begun should be continued and extended. It should be emphasized that these experiments must be carried out with accelerators capable of delivering known numbers of particles to specific cells or tissues, rather than being carried out in space where one can only accumulate rare events random both in time and tissue location.

RECOMMENDATIONS AND SUMMARY

General

GROUND-BASED EXPERIMENTS

A mandatory prerequisite for all experiments that are to be conducted in space is the careful performance of extensive ground-based research related to the project under consideration.

PROVISION OF A GRAVITATIONAL FIELD IN THE SPACECRAFT

In all experiments in space in which the experiment or hypothesis is designed to evaluate the effects of zero-*g*, control experiments must be performed on a centrifuge capable of providing a varying *g*-force within the spacecraft, in addition to appropriate ground-based controls.

Specific

GROUND-BASED EXPERIMENTS

There are a number of specific areas in which because of already-observed abnormalities in space, ground-based experiments are urgently needed.

1. The normal development of bone, particularly at the cellular level, is still poorly understood. In view of the striking decalcification that has been demonstrated in man exposed to a zero-*g* environment, sophisticated ground-based studies are needed.

2. Similarly, the changes in muscles that have been reported to occur in weightlessness suggest that more research on muscle turnover and cellular degradation of muscle protein should be supported.

3. Although it is evident that there are certain problems regarding the development of plants at zero-*g* that would be important to investigate both from the viewpoint of basic biology and the colonization of space, extensive experiments should be performed on the ground, e.g., on the clinostat before experiments are conducted in space.

4. The precise effects of HZE particles on the brain, eye, and other anatomical structures should continue to be investigated using the ground-based accelerator.

EXPERIMENTS IN SPACE

1. High priority should be given to those experiments designed to answer the question of whether vertebrates, and mammals in particular, can undergo normal embryogenesis and postnatal development in space. These studies are not only important from the viewpoint of basic biology but are crucial to any discussion regarding the possible colonization of space.

2. It is not, in general, recommended that additional studies in radiobiology, genetics, or cell biology be performed in space at this time.

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Vestibular Research Panel

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5
Vestibular Research

OVERVIEW

The function of the vestibular system during exposure to weightlessness was once again thrust into the forefront of biomedical interest in space by the occurrence of space motion sickness in the Apollo missions and by the even more frequent occurrences during the Skylab flights. These events are consistent with the reports of vertigo, nausea, and disorientation coming from the Soviet manned-flight experience. As we enter the Space Shuttle era, with the promise of launching of large numbers of scientists and others without extensive piloting background into short-duration spaceflights, the question of prevention and treatment of space motion sickness has become of paramount importance. Furthermore, the phenomenon of vestibular adaptation to extended periods of weightlessness has emerged as one of considerable interest, both from the point of view of human performance in long-duration space missions and as a question of fundamental interest in sensory biology. A considerable research effort will be required to solve both the short-term operational problems implied by space motion sickness and readaptation following return to a gravity environment and to develop meaningful spaceflight experiments to investigate the phenomenon of adaptation to the weightless environment.

The vestibular problems associated with spaceflight are considered in the context of four related topics: (1) *Operational problems* are associated with human performance in space. The problem of space motion sickness in the early Shuttle era includes selection of personnel, training regimens, and inflight prevention and treatment. (2) *Supporting motion sickness research* is required to provide the background for further advances in understanding and management of space motion sickness. The panel evaluated the various explanations for space motion sickness and outlined experimental programs designed to reveal the underlying mechanisms, with contributions from the disciplines of physiology, pharmacology, and psychology. Consideration was given to the possibility of meaningful, limited experimentation on astronaut-subjects who could fly the OFT* missions to help evaluate some of the more immediate objectives concerning selection, habituation, training, and treatment of space motion sickness. (3) *Basic vestibular research* deals with an orderly program of human and animal experiments, both on the ground and in space, designed to advance our basic knowledge of the vestibular system, including adaptation to the zero-*g* environment: (a) extending the human behavioral response measures of otolith function and motion sickness susceptibility planned for early Spacelabs to further human and animal behavioral experiments, (b) ground-based research programs on the underlying pathways of otolith information processing, and (c) inflight neurophysiological experiments designed to reveal the basis of vestibular adaptation to weightlessness. (4) *Major facilities for inflight experiments* are considered as well as the requirements for special ground-based supporting facilties. Furthermore, the question of the relationship between vestibular problems and the use of artificial gravity for long-duration spaceflight is considered, and suggestions are made for appropriate research that could be conducted in the Shuttle era.

REVIEW OF CURRENT KNOWLEDGE

Following the Gemini and Mercury programs, which were apparently free of any severe motion sickness problems, symptoms of motion sickness appeared frequently during Apollo and Skylab. Before proceeding to a discussion of the most important characteristics of the motion sickness problem in space and the underlying biological questions, it is well to define some terms. A review of the space motion sickness problem that adequately summarizes the major characteristics and the sensory conflict theory was recently presented by Benson.[1] He wrote, "Motion sickness may be defined as a condition, characterized primarily by nausea, vomiting, pallor and cold sweating, that occurs when man is exposed to certain real or apparent motion stimuli.[2] The malady has long been recognized as the unfortunate consequence of exposure to unfamiliar motion, in particular the motion associated with various modes of transportation (e.g., seasickness, airsickness), though with the advent of manned space flight, it became apparent that the unfamiliar environment of an orbiting vehicle could, under certain conditions, also induce symptoms like those of motion sickness."

*Orbital Flight Test, early test flights of the Shuttle.

It is apparently not the weightless condition *per se* that causes the space motion sickness but rather the tendency of astronauts to make frequent large head and body movements, which are possible in the larger spacecraft. Reducing head movements tends to eliminate the symptoms. Head movements with eyes open are the most disturbing. Considerable differences exist among individuals with respect to their susceptibility to space motion sickness. However, this susceptibility has not been successfully predicted on the basis of air sickness or ground sickness susceptibility or on the basis of tests involving semicircular canal function in the absence of vision.

The symptoms of space motion sickness usually appear shortly after active movements begin in weightlessness and last for at least three days, with possible performance detriments and lingering symptoms continuing over nearly a week. Following adaptation, the symptoms usually disappear, although in at least one instance an astronaut induced nausea by head movements on day 10 of his weightlessness exposure, and drowsiness and lethargy ("sopite syndrome") may persist even longer.[3] Antimotion sickness drugs have a clear beneficial effect, but there are major individual differences in drug effectiveness, side effects, and preference. Training programs based on habituation to a variety of unusual motions have not yet been shown to have any protective value. The Soviet cosmonauts have experienced significant motion sickness problems (approximately 50 percent of the cosmonauts suffered symptoms) despite the vigorous preflight vestibular habituation program that they undergo. Postflight postural difficulties and sensations of disorientation upon head movements, especially with eyes closed, have also been reported. The duration of the difficulty in re-adaptation to the 1-*g* environment appears to be related to the duration of the zero-*g* exposure.

Benson concluded his summary of space motion sickness characteristics with a statement with which the panel is in complete accord[1]: "The features of the sensory and autonomic disturbances that have come to be called space sickness are thus very similar to those produced by certain motion stimuli in a terrestrial environment. Although similarity does not prove that the causal mechanisms of space sickness are necessarily the same as those of motion sickness, in the absence of evidence to the contrary, parsimony dictates that space sickness must be considered as just another form of motion sickness." The existing theories given serious consideration for explaining space or motion sickness are reviewed in Appendix 5.A.

Of the experiments attempting to quantify vestibular behavior in weightlessness, the most directly applicable are those of Graybiel *et al.*, carried out during the M131 series on Skylab.[4] They demonstrated the ability of astronauts to make almost unlimited numbers of cross-coupled angular acceleration head movements while rotating within the spacecraft, without reporting any signs of motion sickness. Furthermore, there was some evidence of a carryover of this tolerance to postflight tests. Similar stimuli carried out in preflight tests on the ground produced symptoms. Although the inflight tolerance of such head movements could be associated with the lack of any conflicting static gravitational cue to the otolith organs in space, this does not explain the carryover of immunity to the postflight conditions. Such an observation is more consistent with the development of a generalized visual-vestibular adaptation in space, involving a sensory rearrangement in which otolith information is somehow disregarded relative to visual and semicircular canal signals. Such a tentative explanation must, of course, be tested quantitatively, first by human and animal behavioral experiments and later through neurophysiological investigations. Other observations of relevance from the manned space program include an apparent loss of sense of awareness of body position in relationship to fixed objects in the spacecraft and the need for strong visual vertical references to help to ascertain the apparently necessary presence of a phantom "down." Some tests conducted during short-duration parabolic flights yield information that is presumably relevant to the illusions in weightlessness and to the genesis of space motion sickness. The Panel supports the continued use of such flights in the investigation of space motion sickness etiology and prevention.

The animal experimental data obtained in orbital flight are sketchy and contain some contradictory evidence. Nevertheless, they lend support to a notion of adaptation of the graviceptor system in weightlessness and suggest that further behavioral and neurophysiological work in this area will be of value. In particular, the Skylab observations of fish looping after long-term weightlessness, and the development of differences between fish that hatched in space and those brought into space fully developed are suggestive of adaptation processes that may bear some similarity to those apparent in humans.[5] Neurophysiological measures of frog otolith afferent activity in OFO-1,* although limited and containing other environmental disturbances, nevertheless suggest the possibility of adaptive behavior that can be investigated at the single-unit level.

REQUIREMENTS AND OPPORTUNITIES

Operational Problems (Short-Term Solutions to Support of Man in Space)

SELECTION TESTS

The U.S. experience of manned spaceflight has indicated that none of the ground-based measures of motion sickness susceptibility yet tested have been particularly useful in predicting an individual's likelihood of experiencing motion sickness. Although one might conclude from this that space motion

*Orbiting Frog Otolith experiment conducted by NASA in 1970.[6]

sickness is a completely distinct entity, and that susceptibility cannot be predicted in an individual from measures of liability to earth-based forms of motion sickness, this conclusion does not seem to be warranted, because earth-based preflight testing of motion sickness susceptibility was not systematically performed on all 44 astronauts who have flown to date. In fact, there are strong evidential and theoretical grounds for assuming that space motion sickness is merely another variant of terrestrial motion sickness, and one would expect some degree of correlation between susceptibility on earth and susceptibility in the space environment. It is reasonable to expect that those few persons who show truly exquisite sensitivity to several types of motion sickness on earth, and who exhibit no adaptation, would show a similar sensitivity to the space environment. Beyond these few persons, however, reasonable estimates of susceptibility cannot now be made. Additional research on motion sickness susceptibility is required before selection criteria are established, which exclude other than the exquisitely sensitive individuals described above.

TRAINING FOR MOTION SICKNESS AVOIDANCE

The Panel agreed that there were three viable training approaches aimed at minimizing the risk of space motion sickness:

Pre-adaptation training. Ground-based training through controlled exposures to parabolic and/or roller-coaster flight maneuvers designed to achieve some degree of pre-adaptation to the nauseogenic properties of orbital flight.

Symptom management. Ground-based, preflight training (supported by laboratory research) directed at improving the critical detection and management of symptomatology.

Inflight adaptation schedules. Training designed to accelerate the acquisition of productive adaptation.

Of these three, the most promising was thought to be inflight adaptation scheduling, since this was a concept that was firmly grounded on theory, research data, and inflight observations, particularly cosmonauts[7] on Soyuz 14 and Salyut 3. Thus far, moderate and nonsystematic pre-adaptation training has not been shown to be effective, since previous responses to parabolic flight did not appear to afford subsequent protection, nor to be predictive of orbital susceptibility. It is far from certain whether 20- to 40-second parabolic flight maneuvers actually reproduce the nauseogenic components of orbital flight. Nevertheless, in the absence of any evidence to suggest that exposure to a wide variety of other acceleration and rearranging conditions affords any protection against space motion sickness, parabolic or roller-coaster flights with controlled head movements represent our best earth-based model. Furthermore, there are theoretical grounds for hoping that adaptation to these ground-based maneuvers may transfer in some degree to the weightless environment. This is an empirical question that could be tested on the OFT astronaut passengers.

The three training programs are outlined in more detail below:

Pre-adaptation training. For this program to succeed, it should involve stimuli that approximate, as closely as possible, the stimuli of orbital flight conditions. The two most likely situations are parabolic flights with controlled multidirectional head and body movements and roller-coaster maneuvers with similar movements. Head movements superimposed upon rotation were not thought to be useful for pre-adaptation training. Once the stimuli suggested earlier for astronaut selection have been tried on a sufficient number of space travelers, the stimuli that most closely predict susceptibility to space motion sickness might be assessed for pre-adaptation training. It seems likely, however, that several hours of training per day over a period of many weeks would be required to acquire a transferable adaptation.

Inflight adaptation schedules. It is believed that we could exercise control over the nauseogenic stimulus by controlling head and body movement. In this context, we need answers to the following questions:

1. Are some movements (such as head pitch or roll away from the subjective vertical) more provocative of sickness than others?

2. How does rate and extent of movement influence provocation? When these questions are answered, it should be possible to prescribe the optimum locomotary mode for the early stages of flight.

An investigation should be made of the utility of mechanical head restraint devices, as well as head movement feedback signals, to assist the astronaut in avoiding nauseogenic head and body movements in flight prior to adaptation to zero-*g*. In addition, inflight adaptation might be enhanced through personalized visual field control where one can manipulate the presence or absence of visual references, the extent of the visual field, and the nature of the visual field, including earth reference or internal visual–vertical cues. Astronauts' reports indicate an increased dependence on visual cues as the adaptation process proceeds.

Experiments would involve the evaluation of inflight adaptation schedules in which a combination of positional and visual factors were systematically studied.

A further investigation should be undertaken to determine how drugs can best be used to promote adaptation.

Symptom management. There appears to be a critical point in the development of motion sickness symptomatology beyond which removal of the nauseogenic stimulus does not always bring about rapid recovery. Before this point is reached, removal of the stimulus usually results in rapid recovery, but individuals differ in the stimulation required to reach this critical point.

Since severe motion sickness markedly interferes with the adaptation process, it is important that all inflight personnel be trained to detect their own critical points through exposure to a variety of ground-based provocation studies.

In addition, a number of symptom management techniques should be evaluated experimentally, both inflight and in ground-based laboratories. Inflight techniques include (a) use of appropriate locomotor strategies; (b) visual reference lines to define verticals; (c) use of work places designed to promote swivel, rather than nodding, head movements; (d) drugs administered either intramuscularly or transdermally; and (e) use of passively applied tactile cues aligned with the visual vertical.

Ground-based preflight techniques to be evaluated include the relations between past exposure and levels of motion sickness, and further exploration of biofeedback techniques. Establishment of an agreed upon terminology would greatly assist the communication of subjective aspects of the sickness during crew debriefing.

Supporting Motion Sickness Research

THEORIES FOR MOTION SICKNESS

An understanding of the mechanisms underlying space motion sickness may provide important guidelines for the selection of personnel, preflight training regimens, and inflight prevention and treatment. The problem is also of theoretical interest, since it raises questions concerning the operation of sensorimotor systems in unusual environments as well as the adaptation to such environments. In Appendix 5.A, the major theories for space motion sickness are evaluated with the aim of defining areas where further research is needed. These include the sensory conflict theory, various hypotheses for otolith dysfunction or alteration in semicircular canal response, and possible influences of body fluid redistribution on the central nervous system or vestibular organs.

CENTRAL MOTION SICKNESS MECHANISMS

One weakness in understanding motion sickness is the lack of information about the underlying pathways in the central nervous system. Basic neurophysiological research is, therefore, needed to identify these pathways so that they can be studied under a variety of conditions and so that they can provide an additional test system for development and testing of antimotion sickness drugs. Known areas in the brain stem that are involved in vomiting should be further identified. These areas, inputs to them, and their projections should be characterized anatomically and physiologically. Studies of inputs to the areas should emphasize those from visual and vestibular systems. Subsequently, there should be repetition and extension of experiments showing that stimulation of areas in the vestibulo-cerebellum causes vomiting. This should be followed by systematic study of visual–vestibular interactions in cerebellar areas so identified; these experiments should prove particularly interesting because the cerebellum has been suggested as a locus where sensory mismatch takes place. Further experiments on neural organization would be based on the results of the above studies.

Once the appropriate areas of the brain stem and cerebellum are identified, the behavior of neurons in these areas can be monitored under various conditions, for example, development of motion sickness and exposure to zero-g. Then, pharmacological studies in these areas become possible.

INDIVIDUAL DIFFERENCES IN MOTION-SICKNESS SUSCEPTIBILITY

U.S. and Soviet efforts to develop predictive models for space-sickness susceptibility are justified because of the utility of such models in crew selection and training and as a contribution to the understanding of motion sickness on earth. However, existing efforts to predict susceptibility on the basis of studies of responses of small populations of astronauts to Coriolis head movements[4] or by eliciting a history of previous susceptibility have been unsuccessful. Although there has been a suggestion[8] that previous spaceflight appears to confer some immunity on subsequent missions, this observation is of little value in the selection and training of new astronauts. Ground-based motion sickness studies indicate that there are wide and relatively consistent differences in individual susceptibility to a given type of nauseogenic stimulus. While some individuals appear particularly susceptible to certain kinds of stimuli, the degree of individual liability is, within broad limits, predictable from one provocative situation to another.[2]

It seems likely that individual predilection to space sickness in orbit can be similarly predicted if proper account is taken of those intrinsic and extrinsic characteristics that determine susceptibility in the individual. We suggest that further research be broader in scope and not focus on one single measure of susceptibility. Rather, the effects of exposure history and intrinsic factors such as age, gender, adaptability, retentivity of adaptation, and sensory modality preference on individual susceptibility should be determined across a wide range of provocative circumstances, and their predictive value assessed for a large population of subjects. Useful provocative stimuli include (1) head movements in parabolic and roller-coaster flight, (2) visual–vestibular conflict producing situations including rollvection and linearvection, (3) simple swing motion, (4) off-vertical rotation, (5) linear oscillation, (6) administration of heavy water, (7) oscillatory rotation combined with visual search, and (8) centrifuge exposure involving different orientations relative to acceleration direction. The model resulting from such a study could then be used with a greater degree of confidence in predicting flight crew susceptibility and could be further refined by retrospective analysis.

BASIC INVESTIGATION OF PHARMACOLOGY OF ANTIMOTION-SICKNESS DRUGS

Antimotion-sickness drugs currently in use have proved to be helpful but not fully adequate. The mechanisms of action and the central sites of action are essentially unknown, but certain generalities are widely accepted. Effective drugs have anticholinergic, adrenergic, antihistaminic, or tranquilizing properties, but most drugs with only one or two of these properties are not effective, and the specific property of a drug that makes it effective against motion sickness is not known.

Clearly, the development of more adequate antimotion-sickness drugs would be valuable for use on earth as well as for supplementing the physiological adaptation to motion sickness in space.

Each individual has his own best antimotion sickness drug.[9] For purposes of spaceflight, the identification of additional drugs that are of approximately the same value as the scopolamine–dexadrine and promethazine–ephedrine combinations would allow space travelers a wider choice, with better protection (and fewer side effects) in some individuals. The route of delivery, metabolism, and time course of action of such drugs should also be investigated.

In the longer term, to develop antimotion-sickness drugs, structure–activity relationships of known effective drugs should be investigated in animal models and in tests of human motion sickness. Standard screening for new drugs should also be done. Understanding could be advanced by investigation of both antimotion- and promotion-sickness drugs, since the involvement of the chemoreceptor emetic trigger zone seems to be important.

As new central areas involved in motion sickness are discovered, the neurochemical activites of motion sickness can be revealed and further pharmacological progress can be expected.

ANIMAL MODELS OF MOTION-SICKNESS RESEARCH

Several experimental paradigms using animals have been proposed to model human motion sickness, but none of these is reliable for studying all aspects of human motion sickness, and no model currently available is reliable for selecting antimotion-sickness drugs.

The most commonly used animal model is the vomiting response to motion (usually swinging motion) in dogs. Unfortunately, this model does not indicate any protective effect for scopolamine,[10] one of the very best antimotion-sickness drugs. Since a reliable experimental model for screening drugs could dramatically increase the rate of advance of antimotion-sickness pharmacology, it is worthwhile attempting to modify this model to make it effective. It is possible that the model would show a protective effect of scopolamine if different stimuli (for example, linear accelerations or moving visual fields) were used. Of course, *any* successful modification of the model would be welcomed.

PERCEPTUAL ADAPTATION RESEARCH

Outlined below is a program of ground-based research designed to extend our basic knowledge of the mechanisms of protective adaptation to motion sickness. This program is predicated on the assumption that the processes of adaptation to the conditions of orbital flight are essentially the same as those observed in relation to earth-based nauseogenic circumstances such as the Slow Rotation Room.

There is some evidence to indicate that prolonged exposure to cross-coupled accelerations does not result in the dramatic aftereffects normally observed on cessation of the briefer exposures.[2] An important question, therefore, is: Does overadaptation lead to a diminution of aftereffect phenomena? Answers to this question are likely to have a close bearing on recommendations regarding extra inflight adaptation procedures to minimize aftereffects on return to earth.

Other basic questions relevant to our understanding of protective adaptation are the following:

1. To what extent is the rate of adaptation influenced by the discrepancy present in any one sensory channel, and the number of discrepant channels?
2. How does the protective adaptation decay as a function of the number of prior exposures to the adapting stimulus?
3. To what extent (if any) is active movement superior to passive movement in the acquisition of protective adaptation?
4. What are the factors that promote the generalization of protective adaptation to stimulus conditions other than those conferred by the initial adapting stimulus?
5. Is there a stable and enduring feature of the individual that we can term "adaptability"? To what extent can measures of adaptability in one condition of sensory rearrangement predict rates of adaptation to qualitatively different

kinds of rearrangements? To what extent do measures of initial adaptability predict the extent to which protection is retained over longer periods of time (the individual factor of "retentivity")?

6. What are the physiological and psychological correlates of adaptability and retentivity?

7. Are the mechanisms of adaptation observed in visual-vestibular conflicts (with head fixed) the same as those observed to be nauseogenic involving head movements (for example, cross-coupled accelerations in a rotating device)?

The results of these ground-based experiments should lead to recommendations for scheduling inflight adaptability tests, beginning as early as OFT. In turn, each flight should also help to validate the suggestions of these ground-based findings.

Basic Vestibular Research Relating to Weightlessness

HUMAN BEHAVIORAL TESTS RELATING TO ZERO-g ORIENTATION AND ADAPTATION

The inflight motion sickness and orientation experiences reviewed earlier suggest some form of spatial sense adaptation over the course of the weightless experience. A viable hypothesis is that quasi-static orientation cues became based more on visual than on otolith signals and that this adaptation carried over to postflight posture control.

Human research on space sickness should be systematically conducted on a sufficiently large subject population to assure scientific validity. Inflight experiments, of the type scheduled for two subjects on Spacelab 1, should be extended on further Spacelab missions. The tests should specifically use a controllable linear acceleration device to study otolith-dependent responses inflight at various stages of adaptation. Promising measures include perception of linear acceleration, oculogravic illusion, dynamic eye deviation and counterrolling, postural responses to artificial falls, the latency and strength of visually induced roll, and the Hoffman reflex (indicating spinal excitability). In addition, current plans call for a standardized measure of susceptibility to motion sickness during linear oscillation. Further work to help to clarify the semicircular canal and otolith-related inputs to this adaptation should extend these tests to a larger number of subjects and augment them with more specific canal tests such as rotation or heavy-water stimuli. It is essential that preflight and immediate as well as continuing postflight tests of ocular deviation and postural control be conducted to assess the re-adaptation phenomenon. These would appear to be desirable tests to begin with the OFT flights.

Ample evidence from Skylab experiments in man suggests certain sensor-motor coordination disabilities in space. These disabilities, which are indicated by a reduced awareness of position, may be due to either a lack of necessary sensory cues or, more interestingly, a central behavioral state in which the existing cues are not effectively converted into motor commands. Initial Spacelab experiments should be expanded to explore the mechanisms underlying these deficits.

BASIC VESTIBULAR RESEARCH USING ANIMALS: GENERAL CONSIDERATIONS

Because the vestibular system is the sensory system most affected by spaceflight, the availability of the zero-*g* environment presents unique opportunities for its study. Specifically, it is of great interest to determine how vestibular pathways respond initially on exposure to zero-*g* and what compensatory changes take place as exposure is prolonged. Experimentation on animal models should lead to understanding of the basic neurophysiological processes that underlie the vestibular responses of man on earth and in zero-*g*.

On the basis of information currently available from spaceflights, we assume that central otolith pathways will show compensatory changes in zero-*g*, and emphasis should be placed on their study. Experiments should begin with behavioral studies on animal models. Several criteria bear on choosing an animal suitable for behavioral and neurophysiological vestibular experiments in space. These include knowledge of the behavioral repertoire and of the morphology and physiology of its peripheral and central substrates. Other important factors are comparability with man and whether use of the animal is practical in view of operational constraints. Not even the most promising animal will meet all criteria, and compromises will be necessary. Possible models are the cat, or another mammal, and the frog. The cat has the advantage of being closer to man and of having well-developed and well-studied postural reflexes. There is extensive, although incomplete, knowledge of the neurophysiological basis of these reflexes. Experiments on mammals in space may be difficult, however, and the frog may be a considerably more practical preparation. There is knowledge of its less-varied postural repertoire, and neurophysiological data are accumulating. An important drawback of the frog is that many aspects of the organization of central nervous structures relating to the vestibular system differ from those in mammals.[11]

It should become clear during behavioral experiments whether the cat, or another mammal, such as a small primate, is suitable for experiments in space. Whichever preparation is chosen it should be used for both behavioral and neurophysiological studies.

BEHAVIORAL TESTS RELATING TO ZERO-*g* ADAPTATION IN ANIMALS

Experiments on mammals should be similar to those planned for Spacelab I on the effects of linear acceleration on man. Identified otolith reflexes to linear acceleration that are available for study include ocular counterrolling, response of postural muscles including neck muscles, and the so-called drop reflexes. Work on nonmammalian vertebrates, especially body orientation in the frog and looping in the fish, would also be instructive. The results of behavioral studies on man and animals will provide guidelines for subsequent neurophysiological experiments on adaptation to zero-*g*. Again, such studies are of a basic nature and will require a number of years to complete. A series of ground-baseline experiments is sketched in Appendix 5.B.

PHYSIOLOGICAL EXPERIMENTS IN SPACE

Experience with early Spacelabs should indicate whether mammalian preparations are suitable for neurophysiological experiments in space and, indeed, whether constraints on the experimenter make any manned electrophysiological experiments practical. In this section we suggest a variety of experiments that involve exposure to zero-*g*, including some that do not depend on manned experiments.

To begin with, one or more types of small vertebrates, preferably including a small mammal such as the guinea pig, should be sent into space for the purpose of morphological assessment of changes in the labyrinth, particularly the otoliths, as a result of exposure to zero-*g*.

Inflight studies of otolith afferent fibers should be continued, with manned experiments emphasizing data acquisition from a large population. The frog is probably a suitable preparation for this purpose. Extensive earth-based knowledge is needed for comparison. This may become available by the time the experiment can be carried out because this is an active field of investigation.

Studies of compensatory changes in central otolith pathways could first be performed on earth during the period of recovery from adaptation to zero-*g*. Such experiments should be performed promptly on the same animals used for behavioral studies, with protocols similar to those used in background studies. The same animals should also be used for morphological studies.

A potentially useful preparation for investigating central otolith pathways in space is the chronically prepared mammal. Necessary preparation for stimulation of the vestibular nerve and for recording from the vestibular nuclei would be performed on the ground. The animal could then be studied in the alert or anesthetized state, with results compared with those from a similar preparation on the ground. This approach eliminates inflight surgery and makes possible recording from many neurons at different stages of the flight. The behavior of second-order otolith neurons to a range of variety of natural stimuli would be studied. Investigation of interaction with visual stimuli is also important. If these experiments are successful, they can then be extended to higher-order otolith neurons. The value of the experiments will be enhanced by recording simultaneously from more than one neuron. This is made possible by computer programs for nerve-spike wave-shape discrimination. If alert mammalian preparations are suitable for inflight studies, it becomes of great interest to monitor the behavior of neurons in areas related to motion sickness and vomiting at various stages of flight.

As alternative preparation, if manned experiments on the central nervous system are possible, but the mammal proves impractical, is the acutely prepared frog.

Given current technology, inflight neurophysiological experiments require an experimentally skilled neurophysiologist who is familiar with single-unit recording and can deal with the many problems that arise in maintaining animal preparations. The complexity of even the simplest experiments implies that they should first be tried in simulated flights.

Facilities for Vestibular Research and Artificial Gravity Investigation

FACILITIES FOR ORBITAL RESEARCH

Based on the scientific conclusions reached by this study, a NASA investment in developing the capability to expose human and animal subjects to linear accelerations of arbitrary waveform appears justified. Since such accelerations must be created without causing significant perturbations in the orbit of the spacecraft, the use of several separate devices is required. The necessary accelerations can probably be achieved using a linear acceleration sled and a 1-*g* onboard animal centrifuge for delivering static forces. The space sled acceleration facility being developed by the European Space Agency seems to represent a reasonable concept, provided that design compromises are not made that limit its utility as a general research facility. Low vibration levels, flexibility of control, rotation capability of the space sled chair, and a facility for mounting animals in any desired orientation are desirable. In addition, consideration should also be given to controlled thrust or rotation of the entire spacecraft so that subjects can be exposed to extremely low-frequency linear accelerations.

All linear acceleration facilities should be equipped with suitable displays for the generation of angular and linear visual motion cues in order to assist in the manipulation of combined visual–vestibular sensory inputs.

In addition to this equipment for natural stimulation, there must be state-of-the-art neurophysiological recording and stimulating equipment centered around computer-based stimulus control and data acquisition.

GROUND-BASED SUPPORT FACILITIES

For purposes of both basic research and flight crew training, onboard acceleration facilities should be duplicated on the ground and located at a facility that will permit convenient testing of crews immediately before and after orbital flight. In view of our recommendations for preflight training, NASA should maintain several aircraft for zero-g research and training using 20–40 second parabolic and roller-coaster trajectories. At least one of these aircraft should have an experimental bay sufficiently large to permit practice by astronauts of head and body locomotion strategies and be equipped with functioning versions of the space sled and centrifuge. Consideration should be given to the possible advantages of equipping this aircraft with an automatic flight-control system capable of flying more accurate zero-g trajectories than can be currently achieved with manual techniques. T-38 aircraft can probably be used for preflight adaptation purposes by both the Shuttle flight crews and passengers, provided the emphasis is placed on maneuvers creating periods of weightlessness rather than merely aerobatic flight.

ARTIFICIAL GRAVITY

Background. The notion of producing artificial gravity by centripetal acceleration in a rotating spacecraft was considered extensively in the early days of manned spaceflight when it was of serious concern whether humans would find even short-duration weightlessness tolerable. With the successful experiences of the American and Soviet flights, however, and the apparently successful physiological adaptation, interest in this topic waned. The essential constraints on spacecraft *g*-level radius and angular rotation rate were considered in the original calculations of the Von Braun torus.[1,2] Consideration of the engineering details and physiological implications of artificial gravity was the topic of an AIAA symposium in 1972, at which time it was the consensus that such measures would not be needed. The reason for a current revival of interest in artificial gravity, however, reflects its possible need both for some suggested new projects such as space colonization or space industry and for the habitability requirements associated with long-duration manned explorations in which the physiological requirements referred to elsewhere in the report might require artificial gravity.

Vestibular constraints on artificial gravity requirements. Those elements that are of particular relevance to spatial orientation are the *g*-level, radius, and angular velocity. It is clear that if otolith cues are to continue to be of use for spatial orientation, then some minimum *g*-level is required, of a magnitude as yet undetermined. The 1/6-*g* level at the lunar surface is sufficient for this purpose, at least for several days. The angular velocity of the artificial gravity situation will determine the cross-coupled angular accelerations when individuals make head movements having a component of angular velocity normal to the spacecraft rotational axis. Similarly, linear velocity in any direction other than along the rotation axis will result in Coriolis forces, which require adaptation. Furthermore, if a nonrotating hub is to be used, particular attention must be paid to the problem of transition between the artificial *g* rim, with its associated Coriolis and cross-coupled angular acceleration forces, and the zero-*g* hub. In this regard, it might be considered as a long-term project to adapt space travelers to zero-*g* by the use of limited-duration exposures in the hub, while returning the trainees to rest periods under the 1-*g*, head-fixed conditions of the rim.

Shuttle era artificial gravity demonstration. If serious consideration is to be given to the use of artificial gravity in the future NASA manned space programs, some effort should be devoted to the possibility of demonstration of such concepts and testing of the physiological responses to artificial gravity by use of rotating vehicles or structures that might be constructed in earth orbit during the Shuttle era.

RECOMMENDATIONS

We recommend:

1. Support of a substantial integrated long-term program of research concerning vestibular and related spatial sensors, and adaptation to weightlessness. The program should cover ground-based background and inflight experiments on human otolith-related behavioral responses, animal behavior, and animal physiology. We support development of versatile and controllable acceleration devices for Spacelab, including a 1-*g* animal centrifuge. An expanded effort is required to solve the space motion sickness problem.

2. Research on the basic mechanisms of motion sickness in general and space motion sickness in particular including (a) testing of the theories of sensory conflict, otolith dysfunction, and fluid shift; (b) determination of the central pathways involved and the pharmacology of antimotion-sickness drugs; and (c) development of an appropriate animal model for testing purposes.

3. Study and implementation of techniques for astronaut selection and training based on sensory conflict situations. Retrospective review of training experience and space motion sickness instances.

4. Use of the OFT flights for testing the training effectiveness and inflight management of motion sickness, including head and body movement regimens and drug assessments, as well as selection criteria.

5. Further development of antimotion-sickness drugs and delivery systems for treatment, as well as prevention of motion sickness in space and on earth.

6. Demonstration of artificial gravity concepts and tests of habitability and physiological responses by use of a rotating vehicle in the Shuttle era.

7. Planning of a developmental biology experimental program to investigate the role of gravity in the development of graviceptor system and postural reflexes. (Discussed in the section on developmental biology.)

8. Training of all crew members in the recognition and standard reporting of symptoms of lethargy, as well as more conventional motion-sickness symptoms.

APPENDIX 5.A: THEORIES FOR MOTION SICKNESS

Sensory Conflict Theory

The "sensory conflict" hypothesis is today the most generally accepted theory for space motion sickness. According to this theory, motion-sickness symptoms result when unfamiliar (in the context of previous experience) or unexpected combinations of sensory signals are sent to the central nervous system. For example, information on the direction and magnitude of the net gravito-inertial force is available to the central nervous system from the otolith organs. Under conditions of weightlessness, the pattern of activity in otolith afferents does not correspond to that associated with any static orientation or activity on earth. It is clearly desirable that the sensory conflict theory be further tested and elaborated by carefully controlled ground and flight experiments using active and passive head and body movements. Available versions of the theory must be couched in terms of testable quantitative models, which can be used to define critical experiments and thereby be rigorously evaluated.

Other Theories for Space Sickness

Several other mechanisms have been suggested that could contribute to sensory conflict in weightlessness and thus cause motion sickness. These include otolith dysfunction or alteration in semicircular canal response. It has been suggested[13,14] that body fluid shifts resulting from weightlessness might create vestibular abnormality or somehow produce space-sickness symptoms via a direct effect on the central nervous system in the absence of sensory conflict. On earth, pathology of the vestibular system often causes vertigo and motion sickness in patients. It is not inconceivable that exposure to weightlessness might directly cause some change in the peripheral end organs, such as alteration in the rate of formation or resorption of otoconia, or alterations in sensory transduction or encoding. Direct experimental evidence for the existence of such changes has been scanty. Frog otolith activity monitored during orbital flight has revealed changes in background discharge and response dynamics. However, the total number of units studied to date is small, and it is difficult to attribute the observed changes specifically to the weightless condition.

In orbital flight, in the absence of gravity, body fluids shift from the extremities to the head and thorax, producing discomforting sensations of fullness in the head, and nasal congestion, neck vein distention, and facial edema. Increased venous pressure resulting from this redistribution might conceivably have a direct affect via the cerebrospinal fluid on the regulation of the labyrinthine fluids or the blood supply to the labyrinth.

Other mechanisms have been postulated that would result in a change in the nature of the sensory information produced by the vestibular organs, aside from those involving fluid shift. For example, it has been suggested[15] that bilateral inequality in the size of the otolithic masses could be of significance in the weightless environment. Also, there is some evidence in experimental preparations suggesting that the semicircular canals may normally be sensitive to gravito-inertial linear acceleration, and hence their response characteristics would be functionally altered in a weightless environment. Evidence that these effects are of physiological significance is not strong, however. In our view, it is unlikely that they represent significant primary or secondary causes of space motion sickness.

It has also been suggested[14] that perhaps space-sickness symptoms result from direct effects of body-fluid redistribution on the central nervous system in a manner essentially unconnected with the creation of sensory conflict. In our view, however, the notion that fluid shifts are directly involved in producing space-sickness symptoms via either central or peripheral mechanisms seems unlikely for several reasons. First, such a hypothesis does not provide a ready explanation for the major etiological role apparently played by astronaut head and body movements. Also, with the possible exception of one Russian study using head-down tilted bedrest,[16] other experimental and pathological conditions leading to fluid shift are not known to produce symptoms of space sickness or vestibular dysfunction. Finally, if end organ function was altered, concomitant changes in auditory function might also be expected to occur but have not been reported.

On the basis of available evidence, fluid-shift effects cannot yet be ruled out as a secondary cause of space sickness, although the hypothesis that such effects play a major etiological role seems unlikely. Before further work is done on the possible mechanisms of such an effect, a limited NASA effort seems justified to obtain a better description of body-fluid redistribution and associated cardiovascular effects inflight and to determine whether vestibular dysfunction and/or motion sickness results during ground-based simulations of body-fluid shift.

APPENDIX 5.B: BACKGROUND INVESTIGATIONS ON EARTH-ANIMAL STUDIES

Background animal studies of otolith pathways are required:

1. There must be systematic localization of second-order otolith neurons by anatomical methods. Second-order neurons are identified by their response to whole nerve stimulation and as otolith neurons by their response to linear acceleration and by their location in areas of the vestibular nuclei where otolith afferents have been shown to terminate. Both utricular and saccular second-order neurons should be identified.
2. There should be a study of the physiological organization of otolith pathways within the vestibular nuclei.
3. Standard information on the behavior of second-order otolith neurons is needed. For example, response dynamics and directional selectivity should be studied. In addition, the responses of the same neurons to static tilts and to angular accelerations should be characterized.
4. Interaction of vestibular with other inputs, particularly visual, should be studied at identified second-order neurons.
5. Because it is not possible to explain vestibular reflexes solely in terms of the activity of second-order neurons, the above studies (3 and 4) must be repeated with otolith neurons at further stages of behaviorally relevant pathways. These include vestibulospinal and vestibulo-ocular pathways, as well as pathways to higher levels of the nervous system.

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Ecology Panel

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6
Ecology

INTRODUCTION

As a preface to the analysis by this panel, some ecological principles that are clearly understood should be laid down. When any population of organisms, including man, is very small in relation to the available resources, it is relatively easy to maintain and no great manipulations are required. Under such conditions, any population will impinge relatively little on cyclical processes occurring in the world, some of which may be biological, while others are purely physical and chemical.

A population of African elephants leaves its droppings behind and can anticipate that before it returns to that same place these droppings would have been recycled by an army of beetles and flies and worms into mineral materials. In turn, the minerals would have entered plants or be ready to enter plants. In any case, they would no longer be there as droppings. When it is small enough, the elephant population can rely on natural recycling. Using the elephant as an arbitrarily chosen example, there is reason to believe that under natural conditions (i.e., prior to the occurrence of railways) the elephants' annual migration pattern in Africa was typically of several hundred miles. During the course of this migration the elephants were feeding on plants that were becoming ripe or coming into an appropriate edible stage at each step of the way, leaving behind the half-digested material but not returning to the same feeding ground more than once a year. Therefore, approximately 10 months were available for the regeneration process to occur behind them before they returned. It seems that each of the kinds of plants eaten on this migration differ somewhat in nutritive quality and that the process of developing a balanced diet involved a time scale on the order of a year.[1] By contrast, as the available space per elephant contracts, eventually a point is reached at which there is no possibility of physical health (quite aside from psychological health) without human manipulations. That is, a clever manager of elephants can maintain elephants in good condition in a small enclosure. This means he must provide food of an appropriately balanced sort, he must clean up wastes, he must do for the elephant the job that the natural world did in the wild. Since a manager's activities must replace natural cycles, he imposes a burden on the world not obvious from within the enclosure itself. He takes food from an external system and returns wastes to that system for degradation. The elephant seems confined but, in fact, exploits indirectly a large system through the active intervention of the manager.

In fact, it is possible to assert tentatively that the only ecological system that is certainly self-generating is the earth itself. This regeneration depends on a free flow of materials throughout the system and on the presence of large quantitative buffers. To the degree that the size of these buffers, as for example, the total amount of bicarbonate in the ocean, is reduced, the rate at which materials flow through ecological systems must be correspondingly increased or the systems have to be altered either quantitatively or qualitatively. Thus, it follows that if we want to maintain a spatially small ecological system in a "natural" state, we must manipulate the flows of energy and material through the space in which the system exists, so as to mimic the types of flows that would have occurred had the enclosure not been present. As enclosed ecological systems become smaller they can only be maintained in a natural-appearing state by more intensive management and manipulation. The nature of the management and manipulation required is not completely obvious for any ecological system.

It is, therefore, a question of fundamental, scientific interest to set up actual enclosures, observe the pattern of ecological decay in these enclosures, and, concurrently, attempt to ascertain what procedures would be required on a management level to prevent this type of decay. Technical problems associated with maintaining a continuing life-support system in space would represent an extreme example of the closure of an ecological system.

There is a converse to this problem, namely, that to the degree that the number of organisms in an ecological enclosure of any given size is caused to increase, that enclosure becomes effectively smaller. We can imagine a sufficiently dense population of humans and the organisms associated with humans on the earth that will tax the regenerative properties that have so far permitted essential ecological steady states. By increasing one or more kinds of populations excessively, we can make the fact that the globe is finite become dangerously apparent.

The theoretical problem then is the development of a theory of ecological closure and its consequences with particular applicability to the maintenance of very small ecological systems. By seriously focusing on closure itself as a problem, we found ourselves dealing with problems that had, to our knowledge, not been carefully elucidated in existing ecological thought.

Specifically, there is an implicit destructiveness in the complete analysis of an ecological system. That is, if we want to know what organisms exist in a forest and how they are interacting with each other, and we want to know this in some complete way, we would have to identify the kinds of organisms present using normal taxonomic procedures, and we would have to count the number of each kind. For each distinguishable type of organism, we would have to know how much that organism contributes to the flux of energy and chemical materials through that ecosystem. By the time we accomplished this task, we probably would no longer have a forest. Further, we would have to present our results in some form that would probably be a rather extensive interaction matrix, whose elements would be functionally interdependent, involving all the thousand or even ten thousand species present in a small forest.[2] In short, the complete description of an ecological community is quite likely to destroy that community and to be as complex and as difficult to understand as the community itself.

We have, therefore, addressed ourselves to the theoretical question: What is the minimal amount and kind of information that is required from an ecological system that will still permit us to get an adequate understanding of how that system is likely to be affected by being closed off from surrounding systems? This is discussed in this chapter.

We believe that our attempt to answer this question has been in large part successful, since organisms in an ecological system are the end result of a long evolutionary history, so that the presence or absence of a particular kind of organism in a particular place transmits to the observer a great deal of information about the events occurring at that place. The reasonably formal development of a community description or ecosystem description based on an identification of the kinds of organisms in an area and a small number of quantitative measurements of abundance and of physical parameters represents an addition to ecological theory. It also admits of the formulation of certain predictions about the properties of ecological closure, and it is hoped that these predictions, if verified in the actual experiments that we describe, would facilitate the management of a broad diversity of types of ecological systems.

It should be indicated here that hitherto there has been a general emphasis in ecological analysis on the purely quantitative aspects,[3] and there has been a tendency to denigrate or ignore the species identities, the so-called species list, thereby not using the information available in the evolutionary history of each kind of organism. This has resulted in ambiguity of conclusions. While we have not completely eliminated this ambiguity, we have, we think, made some progress. In the process, we have been forced to examine carefully some of the ways that ecology differs from other disciplines.

A HISTORY OF CLOSURE EXPERIMENTS

Many ecological experiments have involved closure of one sort or another, although generally they have not been designed to test the effects of closure. The light and dark bottles used in oceanographic and limnological studies of primary production represent the smallest enclosures and the most complete degree of closure except for the explicit studies on closure done by Maguire (Appendix 6.A). In light- and dark-bottle experiments, closure was regarded a nuisance, and every attempt was made to complete the experiments before the effects of closure, referred to as the "bottle effect," became manifest. Effects that were disturbing to the previous investigators are precisely the kinds of effects of closure that we find of greatest interest.[4,5]

The bottle effect has two very separate components: one is the effect of closure, which we have discussed, and the other is the effect of addition of new characteristics to the system. For example, in a bottle there is a glass substrate on which chemical absorption and additional bacterial growth occur. This demonstrates that the process of closure not only prevents exchanges but may intrude on the system in other ways. In many nutritional studies in lakes, the bottle effect has been minimized by either decreasing the degree of closure or increasing the size of the enclosed space. Decreasing the degree of closure involves leaving the containers open to the atmosphere above or to the lake water or both. Increasing the size of enclosures had been effected over a wide range from using larger and larger bottles, to using large plastic bags, to simply partitioning a lake itself.

In studies involving enclosures, it is found that biological changes occur in all containers, whether or not these were considered as controlled containers. That is, the fact of enclosure always has a biological effect. Often the rate of such changes is inversely proportional to enclosure size.

All the results are consistent with previous assertions about the general effects of closure. The stress imposed on an ecosystem by closure accounts for certain observed and predictable changes: (1) more "sensitive" species disappear, (2) dominance of species shifts toward less "sensitive" species, and (3) consequently species diversity decreases. Frequently the new state resembles smaller natural restricted environments.

Similar phenomena have been found in exclosure studies, that is, systems designed to keep certain organisms out of a closed area. In addition, certain terrestrial situations, including agricultural lands and greenhouses, approximate exclosures and enclosures of a sort. These typically involve management procedures and, therefore, will be discussed in another context. In addition to the enclosures that have resulted from experimental manipulation, there are natural experiments, for example, islands of an enormous range of sizes and enormous range of degrees of isolation.[6] Additionally there are isolated lakes, ponds, tarns, and rills.[7]

Occasionally, management procedures and manipulations have also been made on these systems. Furthermore, there are extensive natural history studies on the colonization of new bodies of water or land or bodies of land that have been denuded of pre-existent biota.[8] These give background information relevant to the construction of closed ecosystems.

The above material supports our initial contention that the general effects of enclosure are significant. This has been confirmed in an unsystematic way for field and experimental circumstances. Microbiological examples could have been given, ranging from the Winogradski cylinder through enrichment studies, isolation studies, and pure culture studies.[9]

A SIMPLE CLOSURE EXPERIMENT

A general experimental approach to the problem of closure will be discussed below, but here a particular experimental approach to what might be called the ecology of failure will be outlined. The general tactic is to enclose a part of a system and observe how the system fails, deduce why the system failed, then modify conditions appropriately and experiment again. By executing a series of such experiments, one can learn a great deal about the mechanisms that result in the failure of a system. Because each of these mechanisms is closely related to a functioning mechanism of the whole ecosystem from which the part was extracted, one can learn a considerable amount about the functioning of the entire system.

Processes may be affected by closure and may, in turn, result in considerable change in the community after closure. For example, nutrient cycling may be interfered with or interrupted. This could lead to the starvation of a number of the species as the nutrients they require are locked up in unavailable pools. However, it is possible that disturbance of the nutrient cycle will result in hyperconcentration or toxic pools.

Also, the direct biological effects of competition and predation may operate within the closed confines of the small communities to change, perhaps considerably, the structure and properties of those communities. Finally, it is possible that the population sizes of some species will become small enough to change drastically interaction patterns and result in the elimination of these species from this system. Under these circumstances, it is predictable that the curve showing diminution of the number of enclosures containing the affected species will have an exponential decline.

The processes listed and their interactions may respond differently as experimental conditions are changed. One can produce a table of expected results to suggest what ecological theory predicts in terms of community change and community longevity as a function of these various experimental treatments.

Such an experiment was performed by Maguire[10] and is described in detail in Appendix 6.A. In essence, three different communities of organisms derived from a waste sterilization pond, an aquarium community, and an ephemeral pond were enclosed in volumetric flasks of different sizes containing different levels of nutrients. In certain flasks the addition of glass tubes (refuges) added to the physical complexity of the system. The rate and pattern of disappearance of different organisms was studied over a period of more than a year, and observations on the influence of sample size, nutrient levels, and the presence or absence of refuges were recorded.

The observed variation of these closed communities has provided for a considerable increase of our understanding of the dynamics that follow closure, and of how these dynamics may be affected by size, physical heterogeneity, food level of the enclosure, as well as of the nature of the ecosystem from which the closure was made. In addition these observations are valuable in examining the processes that normally operate in those ecosystems. This quick and simple experiment, therefore, has proved to be very productive.

ANTECEDENTS OF THE ANALYTIC THEORY

As indicated in the Introduction, a complete description of an ecosystem is as complex and difficult to understand as the ecosystem itself. This has been apparent in the history of ecology, and a series of theoretical procedures have been used to circumvent this problem. In order to rationalize our choice of descriptive criteria, it is necessary to examine briefly some of the earlier formulations and indicate why we have accepted parts of them and rejected other parts of them.

Because ecosystems have varied over evolutionary time and because the physical environment varies, organisms have adapted to such changes and require temporal variability to complete their life cycle. For example, some seeds will not germinate unless there are temporal variations in temperature and in moisture. Some plants will not flower unless there are variations in day length, and some population phenomena will not be observed without occasional and comparatively unpredictable disturbances.[11]

It might be thought that physiological measures are directly applicable to ecological situations. It is found, however, that the circumstances under which organisms will grow and reproduce most rapidly in the laboratory do not correspond to the circumstances in which they are normally found in nature.[12] This implies that physiological constants such as maximal growth rate or maximal reproductive rates may be ecologically irrelevant in many circumstances.

This and other evidence suggests that organisms do not behave so as to maximize their productivity or abundance, but to persist.[13] This is another reason to reject a measure of productivity or measures of ecological efficiency as primary measures for an ecosystem. From this it follows that one cannot predict from a species role in the cycling of elements what the species' needs are.

It is generally the case that organisms under various kinds of stress respond not only by changing their rate of reaction to the world but also by changing the modality of reaction, in the sense of playing a trick on the world or finding a meta-solution to a problem—analogous to terminating a chess game by tossing the board over. There are many examples; consider that many bacteria will use available nitrogen if it is present but in its absence become fixers of nitrogen from the air.[14] Brown hydra in competition with green hydra will, in the presence of abundant food, eat their competitors, and in the absence of abundant food, will float away to some new location leaving the area to the green hydra alone.[15]

There are also many cases in which organisms adapt their existing behaviors to new situations in rather surprising ways, as in the classical example of the opening of milk bottles and drinking of cream by the great tit (*Parvus major*).[16]

Therefore, even if one found a rate measure describing the behavior of a group of organisms, it would almost certainly be subject to qualitative change under appropriate circumstances or may be made completely inappropriate under some circumstances. Prediction of the behavior of populations in ecosystems by simple equations is extremely limited, and the limits must be acknowledged.

A complete productivity analysis requires knowing the abundance and age and physiological rates of each kind of organism of each species. Population censuses are almost never complete. For example, even elephants, the largest of land animals, have not been counted successfully to an accuracy of more than 20 percent. Soil organisms can only be censused by complete destruction—washing them out of the soil and completely destroying the soil community. Plant roots have to be dug out of the ground. Few even try to sample fungi in a quantitative way.

The measurement of physiological rates poses further problems. Such rates can be measured for individual organisms, but these measurements are usually done under laboratory conditions that introduce artifacts. Furthermore, expanding from the physiological rate of individuals to the physiological rate for a population introduces sampling errors that are increased with the physiological diversity of the population.

We have rejected complete and direct measures of ecosystems on the grounds that they are destructive. We also believe that it is necessary to explain our apparent rejection of certain indirect measures such as ordination and diversity indices. In general, these are indirect in some sense. Commonly, they contain assumptions relating to the importance of factors that may not necessarily be related to those that are truly significant to organisms in ecosystems.

Diversity indices do not take account of qualitative differences between ecological systems in the sense that two communities can have the same diversity indices and may even respond to perturbations with similar changes in diversity indices without having any species in common.

The most powerful of the modern ordination procedures, cluster analysis, provides a statistical taxonomy. As powerful as it is, the results of cluster analysis are materially improved if the identity of all species is known. In that sense, a species list is a primary measurement.

In summary, one cannot view organisms or ecosystems as mechanical or chemical transformers with constant rates. Instead, organisms and ecosystems are subject to and adapted to temporal changes of several different periods, and organisms can change their behavior significantly when external conditions are altered. Therefore, many of the standard measures used in the past to analyze ecosystems are inappropriate. Thus, we find ourselves in the situation where a complete description of an ecosystem is not possible and past measures seem inadequate. With this background, we have chosen a new measure and a new method of analysis, which is described in the next section.

A NEW DESCRIPTOR FOR ECOLOGICAL SYSTEMS

One of the long-standing problems of ecological theory is the formulation of a measure or descriptor that is both theoretically meaningful and experimentally possible. The problem arises primarily from two sources. First, because of the large number of variables necessary for a complete description of an ecosystem, and the high degree of interrelatedness of its components, an exact mathematical description would require the construction of an enormously large system of coupled nonlinear differential equations. Furthermore, even assuming such a construction, the resulting system would be beyond analytical solution. Second, if the variables are the number or mass of each species in the system as well as a number of physical and chemical parameters, then, as previously mentioned, the experimental determination of the state of a system or subsystem would involve a sufficiently large perturbation so as to destroy the material of interest and to render the study of its time course impossible. This constitutes an ecological uncertainty principle.

Nevertheless, ecologists are able to gain considerable insight and a certain measure of predictability about ecosystems, which indicates the existence of some subtle generalizations and postulates that get around the problem of complexity. Specifically, ecologists are able to infer from only a species list of a specific ecosystem many of the properties of that system. We propose a measure, *D*, in which the ecosystem is defined by its species list and its state defined by the state of a small number of factors. The detailed reasoning that underlies this statement is included in Appendix 6.B.

Closed Ecosystems

At present, all ecosystems are open to the flow of energy and matter. The only closed system that we recognize is the global ecosystem, which is open to the flow of energy but essentially closed to the flow of matter. The concepts of space travel and space colonization force a consideration of closed ecosystems. As we have said, the concept of closure, which has been used sparingly in ecology, may prove to be a surprisingly useful tool in the study of natural ecosystems. Before developing this further, we define the varieties of closure:

1. *Adiabatic isolation.* This is pure thermodynamic closure in which a system is closed to the flow of matter and energy. Adiabatically isolated ecosystems will of necessity die out.
2. *Closed to the flow of matter.* The system is surrounded by walls that are impermeable to matter, but energy may enter and leave the system. The term "closed system" is used in thermodynamics to describe entities with this characteristic.
3. *Biologically closed.* Matter and energy may enter and leave the system, but living organisms (viruses included) may not pass the isolating barriers.

In general, closure may be varied by surrounding the systems with selected barriers and specifying the selectivity. For example, one might surround the system with a barrier with 1-μm-radius pores. It would then be open to bacteria, viruses, rickettsia, and mycoplasma but closed to other organisms. Thus, any closure is a limiting case of restricted flow of energy or matter. A class of experiments in which a uniform ecosystem is divided by various barriers is considered in Appendix 6.C.

A GENERIC EXPERIMENT

The above discussion suggests that a general experimental study of ecosystem closure will be worthwhile. In such experiments, *determining* the minimum size of a closure that will maintain the ecosystem and observing the descriptor, D, are among the factors of interest.

The idea of these experiments is straightforward: pick a convenient ecosystem, make an initial measure of D (the descriptor discussed in Appendix 6.B) that is biologically and chemically complete. Close *S* sets of *n* replicates of the systems, where the sets differ in the size of enclosure only. Once closure is completed, permit the systems to maintain themselves: that is, do not attempt to manage the systems. Follow D over some time period.

More explicitly, we envisage that in initial experiments the selection of the sizes of the closures would be as follows:

1. Take an initial size that is the best estimate of the minimum or slightly greater than the minimum to maintain the ecosystem, i.e., maintain the species list constant.

2. Pick a series of other sizes related in some regular way to the base size. Perhaps three other sizes, such as one half, one fourth, one eighth of the initial size (or perhaps order-of-magnitude differences) may be useful, as it is important to obtain the shape of the system response curve as a function of size.

It should be noted that for many experiments a crude estimate of the approximate state function $X(t)$ will be sufficient. This greatly simplifies the measurement procedures.

The above constitutes the primary experiment. There are other procedures that will complement it. We expect that the following will be particularly useful.

3. Develop models of the closed ecosystem, particularly of the following two kinds: (a) Past considerations of closed ecosystems, especially those to be used in space stations, have treated organisms as chemical processors whose rates were only state dependent. It would be useful to test the validity of this assumption. Models treating organisms in this way would also reveal when problems of material flux and storage might lead to failure of the enclosed system. (b) Models that attempt to take into account the best understanding of the ecosystems *prior* to closure will demonstrate gaps in this understanding.

4. Design, build, and close a system whose size and descriptor D are the same as that described in 1. Attempt by active control to maintain this system in some functioning state. This will reveal gaps in our understanding

of ecosystem dynamics and in our ability to substitute active control for natural biological control.

5. Subsequent to these initial experiments, which involve complete biological and chemical closure, experiments with other degrees of closure would be of interest.

6. In other experiments, it may be of interest to investigate deliberately depauperated systems.

Several comments are in order regarding these experiments.

An initial estimator of the minimum size of a system needed to maintain the species list, SL, constant is the size of the largest home range of any species in the natural ecosystem.

If none of the enclosures are sufficient to maintain SL, then one would conduct experiments with larger sizes. Of course, for some ecosystems the estimated size will be so large as to be impractical. Obviously one would either not do experiments with such ecosystems or would pick the largest practical size in order to follow the behavior of the descriptor D for this less than minimum size system.

It is conceivable that no size less than the earth is sufficient to maintain SL for some ecosystems. That is, some ecosystems may need to be open to the whole earth.

Temporal variation must be considered in these experiments. It seems to us that only very unusual ecosystems will not require some temporal environmental variation to maintain the species list. To the degree that closure alters the normal, temporal variation, we anticipate a greater change subsequent to closure.

One must consider the temporal pattern of the sensitivity of an ecosystem and resonance time of the ecosystem. It seems prudent to make closure during the time of minimum sensitivity, so that the effect of the act of closure is minimized and the fact of closure can be studied. For example, if one closed an ecosystem characteristic of the north temperate zone, it would seem prudent to make the closure during the winter rather than during the middle of the summer. In a desert, it would seem prudent to make closure during a dry season rather than during a rainy season.

Seldom will all the species in the system be detected and recognized. The obvious impossibility of applying an appropriate binomial name to some of the species observed is desirable, but not critical, as long as the species are distinguished one from the other.

Almost always, rapid changes can be expected in some factors. The dynamics of the decay of the system after its enclosure will usually be nonlinear, and frequently wildly so.

Variability of replicate response may be considerable, especially if important species are irregularly distributed with respect to the size scale chosen.

Homogenization prior to closure may be useful (but may have its own effects); in any event, replicate number should be chosen with care.

We expect that, following closure in order to explain some phemonena that are poorly understood, detailed examination of single species or small groups of species will be required. Thus, causal relationships and the ecological roles of those species will be determined.

Attempts have been made to develop closed, self-regulating ecosystems by synthesis, that is, essentially adding species one by one. These have proved exceedingly difficult. We conjecture that such an approach will not be fruitful in the study of ecosystem closure.

Home ranges of organisms within a closed ecosystem may be decreased subsequent to the closure without the elimination of the species. This would be particularly likely for animals whose home ranges were determined by food availability.

The above provides a general outline of a generic experiment that we believe will lead to significant increases in our understanding of ecosystems. In general, it is beyond the scope of this report to consider detailed experiments. For the sake of clarification, however, we have discussed possible specific extensions of the closed aquatic ecosystem experiments whose results we have discussed previously.

A SPECIFIC EXPERIMENT ON CLOSURE EFFECTS

An outline for a specific closure experiment similar in design to that described previously is provided in Appendix 6.D.

The outline is presented simply as an example for the help that it may provide and to suggest how our method of analysis might be implemented. Its plan and detail would clearly be inappropriate for closure experiments with many systems and might be considerably and beneficially changed even in closure experiments with sewage stabilization communities.

Note also that this outline differs in some respects from the general experiment discussed earlier, as all specific experiments are likely to do.

CLOSURE AS A PRACTICAL PROBLEM

An Approach to the Development of Closed Regenerative Agricultural Systems for the Support of People

We have considered the specific problems of developing a closed, regenerative, agricultural system for the support of people and, more particularly, for the support of people in space stations. We would like to note immediately that the maintenance of people in space is complicated, difficult, and expensive and as far as we can tell, can never accommodate more than a minuscule fraction of the earth's population. *Our general conclusions are that a space station must emphasize redundancy, compartmentalization, abundant energy, and human control. We reject the notion that it would be possible in the near future to devise a completely natural or completely self-regulating closed system that would provide people with food, fiber, and necessary gases. We do believe, however, that a carefully controlled and properly designed system is possible, if there is an understanding of ecological laws and the fundamental dynamics of ecosystems.*

We assume that total energy will not be limiting. In initial attempts to build such a system, normal earth atmosphere should be used and illumination should have a spectral distribution equivalent to sunlight at the earth's surface. We also assume that some artificial gravity is necessary, because many biological and ecological phenomena require it. For example, the shape and growth of plants is determined by hormones whose transport is determined by gravity. The medical and physiological problems similar to those known for man in space can be expected to occur for other animals. There are many other examples.

What are the problems that such a closed system is most likely to experience? There are at least three kinds. The first is that the storage pools for the major elements might be inappropriate, so that there would be a serious incompatibility in the rates of flux and the availability of chemical elements.

For example, if a hemisphere is placed over a corn field, the corn will stop growing within hours because the carbon dioxide required for photosynthesis will be exhausted. On earth the atmosphere, oceans, soils, and rocks provide a huge buffer for carbon dioxide and other gases. Thus a corn field open to the atmosphere does not run out of carbon dioxide. In a space station, proper compartmentalization and control of flows between compartments would have to compensate for the lack of large natural buffers. For example, two compartments containing plants could be maintained, so that each had opposite day/night cycles. These could be connected so that the respiration that goes on in the dark compartment generates part of the carbon dioxide needed in the lighted compartment. Meanwhile the plants in the illuminated compartment would produce oxygen needed for respiration in the dark compartment.

We have just used as an example the problems of balancing the flux of carbon dioxide and oxygen, and we have seen that doubling the number of compartments can provide buffering. One can expect that an attempt to balance all elements would be considerably more complex, so that a real space station would have many compartments, connected so that the flow of gases between them could be precisely controlled.

A second problem concerns biological epidemics. While it does not seem possible to eliminate all unwanted organisms, it seems prudent to minimize the number of unknown organisms. Any system containing people or for that matter any multicelled animals will have a diversity of micro-organisms at least from necessary intestinal flora. Any visitor to such a system may bring with him new micro-organisms.

The third kind of problem is the production and accumulation of trace toxins.

Given these problems, we project that the system most likely to persist and function would create complex molecules biologically and artifically degrade them. The natural degradation of compounds requires long time periods, involves soils or sediments, and requires communities of micro-organisms, which are poorly understood and contain unknown potential problems. However, the necessity for biological mechanisms to create complex molecules is reinforced when one considers that what have in the past been called chemical regenerative systems are, in fact, not regenerative. For example, some of the so-called regenerative systems require millipore filters or other manufactured devices or chemicals that could not be readily made within the space station. In contrast, the degradation of complex molecules could be done relatively efficiently by carefully controlled pyrolysis.

Thus, we believe that it would be possible to construct a system that would provide food, fiber, and gases necessary for man's survival in a closed, artificial system, only if that system has gravity, a natural earth atmosphere, compartmentalization, redundancy, a natural biological system for the production of complex molecules, and artificial chemical degradation. Redundancy is necessary to allow for control of material balance and to allow for the isolation of systems that are subject to epidemics or other kinds of failure.

If possible, natural soils should be avoided. It may be possible to grow all necessary plants hydroponically. Modern mechanized industrial agriculture is not an appropriate model for the food production in such a closed system. The proper choice of plants and animals for such a system will require an imaginative search of the world. We suspect that a model along the lines of Milpa agriculture is desirable. In this case, a particular combination of plants are grown together (corn, beans, and squash, for example), so that the combination performs some of the functions that would otherwise have to be done through human labor. The corn plant provides stalks for the growth of the vines, and in a natural soil, the vines shade the ground and help prevent competition from weeds. The beans provide nitrogen. A combination of plants of this sort, grown hydroponically under intensive management, in multiple compartments, actively controlled, could provide a sustained food source.[17]

Many plants are adapted to temporal variation, such as specific photoperiods for germination, flowering, and fruit production. A sustained yield would require compartments at different stages of development, each subject to different temporal cycles and periods. This is a further reason for compartmentalization within such a system.

Small animals might be useful. Although a completely vegetarian diet would be simpler to manage in many ways, the difficulties of maintaining human health with strictly vegetarian diets suggest that some animal protein may be useful.[18] Furthermore all plants have parts that people cannot use for food, but many of these would provide a food base for animals. Small animals, perhaps chickens, geese, or other birds, or small mammals like rabbits or guinea pigs could be utilized. It would seem unlikely that these could be free ranging or in any way live in what would resemble a natural earth habitat. Fish culture should also be considered.[19]

The experiences of human cultures accustomed to isolation should be utilized in choosing plants and animals for such a system.

The problems of trace toxin accumulation within such a system are serious. The experience of NASA and of those who work with submarines should provide some of the initial relevant technology. Any closed system must maintain monitoring instruments to detect both organic and inorganic toxins and must have mechanisms to isolate such contamination and to remove it. Problems with such compounds are increased as the size of the ecosystem decreases. Although the whole earth provides a large buffering against the detrimental effects of such compounds, even here toxin accumulation is a well-known problem.[20]

While we believe that it is possible to construct a system that would provide food, fiber, and gases necessary for human survival, we want to dispel any notions that such a system could reasonably be expected to visually mimic a natural earth landscape. The conceptual picture of the food and fiber production parts of a space station forced on us by our analysis is an array of compartments, some for vegetation, some for animals (if there are any), some for people, some for chemical processes. Each biological compartment could be subject to individual light, temperature, and atmospheric regimes. The atmosphere in each would be connected by pipes and control valves to all the others and to intermediate storage tanks. Devices would be required to carry out complete chemical and biological isolation rapidly (for example, fast-acting valves would be necessary to isolate the gas flow between compartments).

The mental image of this space station is in complete contrast to some previous ones, which, failing to take ecological realities into account, suggest that people could live along with their plants and animals in a single large enclosure, appearing like a village on earth. We reject this fanciful concept as rather implausible. The human habitation sections of a space station might have a few plants growing for aesthetic purposes, but not as part of the major production effort. The psychological and social impact of such structures must be considered carefully but are beyond the scope of this report.

RECOMMENDATIONS AND SUMMARY

Having considered the closure of ecosystems, we have arrived at the following recommendations and conclusions:

1. The closure of ecosystems is an invaluable tool to increase our understanding of ecological processes and laws. We recommend that funding be made available for the experimental study of closure of ecosystems.

2. The consideration of the concept of closure has led us to define a new methodology for analyses of ecosystems.

3. The study of closed ecosystems is an essential prerequisite for the design and development of closed regenerative agricultural systems.

4. Closed agricultural systems for extraterrestrial use must be first developed and shown to work on the earth.

5. While we believe that it is possible to develop a closed regenerative system that will provide food, fiber, and gases necessary for the survival of people, such a system must involve active control, redundancy, compartmentalization, and large external sources of energy.

6. While such a closed agriculture system seems possible, we want to dispel any notion that it would look natural or would mimic a terrestrial landscape. Instead, this system would be highly compartmentalized, redundant, intensively controlled and managed. Such a closed system should make use of biological methods for the production of complex compounds and chemical-physical technology for the degradation of compounds. Wherever possible, such closed agricultural systems should avoid the use of natural soils, to minimize the possibility of biological complications.

7. In regard to whole natural ecosystems, we conclude that a complete description of the state of each individual organism and the abundance of each species and the total flux of all elements is not possible without destruction of the system. This is a statement of an ecological indeterminancy principle somewhat analogous to the Heisenberg indeterminancy principle.

8. A sufficient description of ecosystems is provided by a measure that is a concantenation of the list of species contained in the ecosystem plus a dynamic state vector representing abundances of the few dominant or important organisms, plus the condition of a few chemical and physical characteristics.

9. This measure differs from previous attempts to describe ecosystems. It is practicable, relatively simple, rich in information, and potentially useful for the development of ecological understanding.

10. If there is any desire to pursue the development of closed agricultural systems for the support of people in space, or a desire to increase our understanding of the earth's ecosystems, then the following is a feasible time schedule for such research and development.

The first step would consist of designing experiments to study the closure of natural ecosystems and setting up a data base of species lists and related properties. This is to be used in the construction of algorithms for the analysis of ecosystems. At the end of the first step, closure experiments for several ecosystems as described in the body of this report should be under way. These would be followed for two more years at least.

Concurrently, to develop closed agricultural systems for the support of people, it will be important to select the most appropriate plants and animals. This selection may involve the cooperative effort of anthropologists, ecologists, nutritionists, and agricultural scientists, for example. It should involve a consideration of combinations of plants and animals from the entire world and not just those of conventional agriculture. The data base could be used in this study. The development of physical designs of such a system should be initiated during this period as well.

At the end of this stage, one would review what had been learned from the experimentally closed ecosystems. One would then complete the design of the first experimental enclosure on the earth that would include people. Concurrently, new basic ecological experiments should begin.

OTHER COMMENTS CONCERNING SPACE BIOLOGY

One of the functions of space ecology is to be operative in terrestrial problems of interest. It seems that we have identified or will in the future identify problems of biological importance that are simply too dangerous to be carried out in terrestrial laboratories. Such experiments can be carried out remotely (for example, on the palette of the Shuttle) and then sent into escape orbit. We recommend that NASA maintain an ongoing monitoring of this class of experiments and readiness to collaborate in their implementation.

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APPENDIX 6.A: A SIMPLE CLOSURE EXPERIMENT

In this experiment a modified factorial design was used in which three different kinds of communities were studies. The first was a waste stabilization pond community. The second was an aquarium community, which was the result of many additions through a number of years to a laboratory aquarium. The third was a community raised from the mud of an ephemeral pond near Gothic, Colorado. In all, the largest organisms were small crustaceans. In the first two, the largest organism was a small ostracod, and in the third, it was a small cladoceran.

Three different levels of food addition were studied. There were two levels of physical complexity as the result of addition of Pyrex tubes to half of the replicates. The physical complexity of the systems was further complicated by the utilization of different volumes of water, with the result that in the large communities there was a deeper bottom layer of flocculent green material composed of algae, fungi, and other organic detritus. The volumes of the communities used were 12.5, 125, 250, and 1250 ml, so that the total size range was varied through two orders of magnitude. All communities were sealed in volumetric flasks, which were chosen because it was easy to seal their tops without heating the communities appreciably. In all instances, the flask was about half full, so that the ratio between the volume of the community containing water and the air above was constant.

Subsamples of each of the three kinds of ecosystems were stirred vigorously and subsamples of these were distributed at random between treatments.

In the sewage stabilization pond community, the dominant organisms were *Schizothrix*, *Chlorella*, *Scenedesmus*, *Paramecium bursaria*, the two rotifers, *Lepadella* and *Philodina*, the ostracod *Cypradopsis*, about four fungi, ten bacteria, and a few smaller protozoa, as a minimum estimate. In addition to this species list, the data that were gathered from these communities were of two kinds. One, the ostracods (or cladocera in the case of the ephemeral pond communities) were counted, and two, the color of the flocculent layer on the bottom of each flask was recorded. Figure 6.A.1 illustrates the number of flasks in each replicate of the stabilization pond system that contained active ostracods through time.

The data from the sewage pond community are presented as a percentage of the number of flasks set up at each volume. The smallest of the closed communities, those that contained 12.5 ml, showed an exponential decline such that no ostracods remained alive at the end of 280 days. None of the

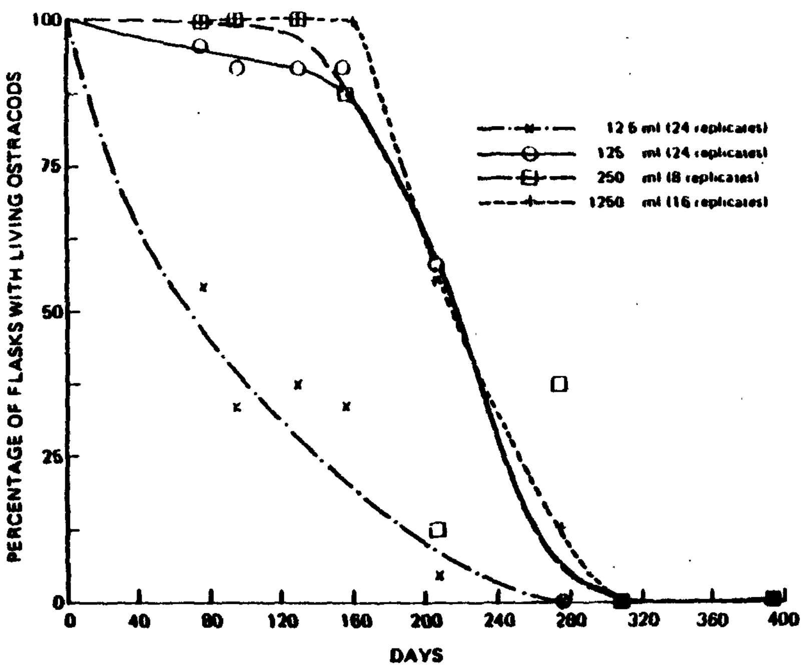

FIGURE 6.A.1 Number of stabilization pond communities containing living ostracods.

larger sizes showed an exponential decline. The pattern of disappearance among the three larger sizes was very similar. In these larger sizes, the rate of loss was very low until about day 150–160, following which there was a precipitous decline such that by the 310th day, all the ostracods in all of these larger communities were dead. These patterns suggest that there was some kind of toxic material produced by the dynamics of the system, a material that was not utilized or destroyed rapidly enough by that system, and that by day 160, it was still increasing and approaching lethal levels.

It appears that this toxic material may have been carbon dioxide. This is in part supported by Robert J. Byers's observation that similar enclosed communities in stronger light survive longer, possibly because of greater photosynthesis.

Also, when the longevity and the average number of individuals (ostracods or cladocera) are compared between those replicates with and without glass tubes, the differences are small and not significant. For the Colorado communities, however, it appears that those with tubes had greater longevities. Perhaps the glass tubes served as refuges. Most striking, however, is the increase in estimated number of ostracods and cladocera as a function of the presence of refuges.

When the means for each set of replicates of the various experimental conditions were compared in refuge–nonrefuge pairs, 19 of those pairs had more crustaceans (ostracods or cladocera) in the refuge-containing flasks, three had more in the flasks without refuges, and in the other two, refuges appeared to make little difference. This is a highly significant difference and suggests that the refuges were important in protecting nutrient cycling or photosynthetic species from predation, or that the presence of the additional physical heterogeneity permitted the development of greater chemical heterogeneity and a resultant increase in rates of some kinds of biological processes.

There was very little difference in the longevities of the various cultures that had different levels of food, although there were greater numbers of individuals per flask in the more heavily fed treatments.

The differences between the three different communities were striking. In neither the ephemeral pond community nor the aquarium community was there the plateau and then falloff of numbers that was so striking in the sewage stabilization pond communities. In the smallest of the community sizes (12.5 ml), there was exponential dropoff regardless of source. It was more rapid in the aquarium communities and less rapid in the ephemeral pond communities than in the stabilization pond communities. The larger size (125 ml) aquarium communities showed an initial decrease in number of flasks containing ostracods that was almost as rapid as in the 12.5-ml communities, but by day 100 or so, the nearly 30 percent of the cultures that still contained ostracods apparently became nearly stabilized. On the other hand, loss of cladocera through the 400-day period was very low in the 125-ml ephemeral pond communities, suggesting that they were not being poisoned and very possibly were carrying on nutrient cycling quite successfully.

APPENDIX 6.B: A NEW DESCRIPTOR FOR ECOLOGICAL SYSTEMS

Since there are approximately 10^6 known species of organisms, a species list is but an array of 10^6 yes–no evaluations. Mathematically, one can think of this array as a vector composed only of 0's and 1's from a 10^6 dimensional space. Thus, a species list *corresponds* to a particular vertex on the unit hypercube in this high-dimensional space. From this point of view, the set of all theoretical species lists, a set with $2^{1,000,000}$ objects, would correspond to the set of all verticies on this hypercube. The number of naturally occurring species lists is far smaller.

For instance, it is hard to conceive of a species list for an ecosystem that does not contain primary producers. The heterogeneous distribution of the verticies that correspond to extant species lists is a reflection of the fact that the lists embody a vast historical background of evolutionary and physiological information, which form the basis of the ecological inferences.

The assumption we then make from these empirical generalizations is that an ecosystem is characterized (except for its state or condition) by a species list (SL). If two spacially separated habitats have the same SL, they are in some sense equivalent ecosystems.

The notion of a species list has some uncertainties since there are dormant species, secondary species, rare species, and cryptic species. Cryptic species may either combine rarity and hiding or may be present as propagules (seeds, spores, cysts, etc.) only. It is not clear at the moment whether propagules must be treated differently from other cryptic species. Certainly, cryptic species may produce experimental noise in formulating the initial species list, and this must be dealt with; however, our basic assumptions are that a species list will contain far less uncertainty than other characterizing parameters and that it can be obtained with minimum damage to the system under study.

As a system ages, either under natural conditions or under perturbations, the species list may change by local extinction or by immigration or, over a long enough time scale, by evolution. From our perspective, a change in the species list is a change in the ecosystem. Such a change will be called an ecological transition. As a special case, we will also recognize a transition in which the species list goes to the array composed only of zeros, that is, the biota are completely eliminated.

Given a particular ecosystem, added characterization is provided by description of its dynamic processes. Formally, let $X(t) = \{x_1(t), \ldots, x_n(t)\}$, denote a vector of real-valued functions, where the independent variable may be thought of as time. The vector $\{x_1(t), \ldots, x_k(t)\}$, where k is less than n, will denote the best estimate of the census at time t for the k most abundant species (in terms of biomass or possibly some other parameter) in the system. If k is properly chosen, then this can be obtained without excessive perturbation of the system. The remaining components of $X(t)$, namely $x_{k+1}(t)$, . . . , $x_n(t)$ include the measurement of abundances of potentially important species as well as physical and chemical measurements on the system such as nutrient flux, temperature, concentrations, etc. The choice of these components depends on the evaluation by an individual who has studied the given ecosystem. It may be different for each system. We are, however, asserting that the ecologist's understanding of the habitats that they have studied is sufficient to select these parameters.

Given a particular ecosystem, E, the vector valued function $X(t)$ is said to be an nth approximate state function for the system E. The set of n indices that are used for a particular nth approximate state function $X(t)$ is called the protocol of $X(t)$.

Thus, an ecosystem is defined up to state by its species list, SL, and an approximation to its state at time t is a point in an n-dimensional vector space (the reduced state space), that is, the value of X at time t. The trajectory of that point in time then describes the approximate dynamical behavior of the system. A mathematical simulation of an ecosystem should be required to generate the vector $X(t)$, thereby providing the opportunity for a major test of the model—the agreement or disagreement of the theoretical and actual trajectories.

For a given ecosystem E with species list SL and an nth approximate state function $X(t)$, we shall call the ordered pair [SL, $X(t)$] a descriptor D of the ecosystem E. SL and $X(t)$ are themselves interrelated. The simple existence of each species influences the abundances of all other species and affects to some degree each physical parameter. Conversely, the state of the system exerts controls on the composition of the species list. However, to avoid this interdependence would require either the omission of SL or $X(t)$ with the loss of valuable information, or the obtainment of the complete state vector for the system. But the possibility of determining the complete state vector has been rejected as being mathematically intractable and, moreover, in violation of the ecological uncertainty principle. We assert that D is the best one can do experimentally and, therefore, limits the observables against which theory can be tested. We further assert that the structure of ecosystems (which reflect so much evolutionary, physiological, biochemical, constraints, ethological patterns, and a variety of other biological and physical-chemical laws) is such that D is sufficient for substantial understanding of that structure.

In summary, our definition of a descriptor of an ecosystem contains two nonindependent parts: a species list and an approximation of the state of the ecosystem. The short-term behavior of the system is best reflected by the trajectory of the reduced state vector. Transitions in the ecosystem, that is, changes in the species list, may require the introduction of a new reduced-state vector. Moreover, the changes in the reduced-state vector that occur during a small number of changes in the species list may give insight into the problem of defining a "distance" between species lists. Putting it another way, it is clear that a large number of changes in the species list is significant (the lists are, in a sense, far apart); however, it is not clear what the effects are of small changes in the lists. The measure of the effects (or distances between lists) is certainly more complicated and less uniform than the simple number alterations.

Two other areas of research interest are the actual distribution on the hypercubes of those vertices that correspond to naturally occurring species lists and the interesting asymmetrical property of D reflected in the fact that if you give an ecologist a species list, then he can tell you a great deal about the reduced state functions, but if you give the ecologist a reduced state function, then he can tell you much less about the species list. This is simply a reflection of the fact that the functional relationship from SL to $X(t)$ is not one-to-one (i.e., many species lists would have the same reduced state function, assuming a fixed protocol) and is thus not invertible. If it is invertible (or nearly so) for a particular $X(t)$, then this is possibly a reflection of an ecosystem that is under severe stress or existing at the extreme edge of its natural regime. It is interesting to conjecture which systems might more easily endure closure.

Finally, since species lists carry with them so much biological information about an ecosystem, the dimension for the approximate state space may be quite small, and the components of $X(t)$ may need be only crudely measured. For example, in the closed aquatic experiment discussed earlier, the reduced-state function was composed of only the readily observed abundance of crustacea, whose numbers usually were estimated visually.

APPENDIX 6.C: CLOSED ECOSYSTEMS

We shall consider a class of experiments for which a uniform ecosystem is divided into subsets of closed systems by various barriers. An example of such an experiment is the partitioning of a lake with clear plastic bottles. Following the closure, the species list and reduced state vector for each system are observed in time. Up to ecosystem transition, the appropriate measure is a reduced state function $X(t)$. Let $X_c(t)$ denote a reduced-state function for the closed system, closure occurring at time t_0, and let $X(t)$ denote the corresponding approximate state function for the unclosed system. The measure of interest then becomes

$$C(t) = X_c(t) - X(t),$$

where $t > t_0$. Consider a number of idealized cases:

(a) $C(t)$ remains at 0 vector for all $t > t_0$;
(b) $C(t)$ moves to a new point in n space and stays fixed;
(c) $C(t)$ describes a limit cycle;
(d) $C(t)$ describes a noncyclic trajectory.

Still assuming that we have had no ecosystem transition, each of these cases describes a different and interesting phenomena. Case (a) essentially says that closure has had no effect. Case (b) reflects that the closed system has moved to a new position that is in steady state with respect to the state of the unclosed system. Case (c) would be an indication that the closed system has moved to a new stable dynamic mode but that this mode is not constant with respect to the unclosed state. Ecosystem transition may have occurred. Case (d) indicates a dynamic and unstable state that is quite different from the unperturbed (i.e., unclosed) state and that in all likelihood, ecosystem transition has occurred.

In analyzing each of these idealized outcomes, our capacity for interpretation would be enhanced were the unclosed ecosystem in a steady state of some sort. Finally, the total change of dynamical state over a time interval (t_0, τ) can be measured by:

$$|C(\tau)| = \frac{1}{\tau}\int_{t_0}^{\tau}|C(t)|dt.$$

As indicated earlier, aside from the total number of ecosystem transitions, a metric for measuring species list change or the importance of a specific transition has yet to be devised. Consequently, at this point the emphasis is on the changes in the approximate state vectors. Notice that if a system had been biologically closed and if its species list were complete, then transition can only occur if a species were eliminated.

APPENDIX 6.D: A SPECIFIC EXPERIMENT ON CLOSURE EFFECTS

The experiment described here is a direct extension of the one described in Appendix 6.A. The general procedures will be the same, with various volumes of community-containing water being sealed in flasks of various sizes, etc.

Observations will include all parts of the descriptor, D:

1. The species list, SL (in these communities the number of species will be approximately 50).
2. Abundance of the most important species in terms of number, biomass $[x_1(t), x_2(t), \ldots, x_k(t)]$.

3. Nonabundant but potentially important species and selected levels of physicochemical characteristics [O_2 and CO_2 of the atmosphere, total carbon, reactive and nonreactive phosphorous (to the molybate test), pH, total nitrogen, NH_3, and ATP], $[x_{k+1}(t) \ldots x_n(t)]$.

Observations of mass balance and fluxes will be made before the beginning of the experiment, results will be used to produce a model that may suggest some change in the following experimental plan. Standard conditions are 500 ml, light of a clear greenhouse, presence of refuges, atmosphere-to-water ratio 3:1, and temperature fluctuation normal. Treatments will be

(a) 4 sizes (H_2O volumes): 20, 100, 500, and 2500 ml;
(b) 3 light levels: full greenhouse sun, 50 percent and 75 percent shade;
(c) 3 levels of added physical heterogeneity: none, refuges, refuges and sand;
(d) 3 levels of atmosphere : water volume relationship: 1:1, 1:3, 1:9;
(e) 3 levels of temperature fluctuation: full, moderately damped, and greatly damped.

There will be communities from a waste stabilization pond and from the Colorado pond; ten replicates of each treatment. In addition there will be several special series:

1. A wet–dry series where two connected flasks will have the water first on one side and then on the other. These will contain the Colorado pond community along with some of the mud from which it was produced. Also ten replicates of standard flasks but containing mud in addition will be set up to serve as controls.
2. Three series of 20 standard flasks (10 with stabilization pond communities and 10 with Colorado pond communities) will be set up and provided with mechanisms by which particular nutrient pools may be selectively augmented. Either phosphorous, nitrogen, or chelated trace minerals (including iron) will be added at six-month intervals (while the systems remain sealed).

Predictions concerning the outcome of the experiment are that D will change *least* rapidly in flasks of the largest size, at the highest light level, with the greatest heterogeneity, with the highest atmosphere-to-water ratio, and with greatest temperature fluctuations under standard conditions (defined above).

Each factor is varied through three or four levels. Results should, therefore, permit some estimation of the shape of $X_c(t)$ and will provide increased understanding of mechanisms important in the maintenance of normal stabilization pond and Colorado pond ecosystem structure and function.

APPENDIX 6.E: THE NATURE OF BIOLOGICAL TAXONOMY

Some explanatory comment is required about the process of taxonomy or the giving of names to biological entities. Organisms are arranged by a box-in-box classificatory hierarchy in such a way that the contents of each box are designated by sharing some common properties. The actual name of a species, therefore, is a shorthand expression for the information used to distinguish that species from the next most closely similar species and, at the same time, contains reference to all of the biological information used to define the broader categories of which that species is a member. As pointed out in most of the more archaic elementary biology tests, the designation of *Felis domestica* for the house cat serves to distinguish it from other members of the genus *Felis*, which includes both large and some of the small wildcats. It is understood that all the properties that are associated in the definition of that genus are possessed by the house cat also, as are the properties of the broader classificatory categories to which the genus belongs: the order, the family, the phylum, and so on. Therefore, by knowing the designation of the cat, we are saying it is a vertebrate, it is a carnivore, it has shearing teeth, and so on. The name in that sense can be thought of as the name of an extensive data file about cats. The array of information that is available about organisms from a name simultaneously defines an array of requirements of the organisms habitat. Therefore, when we construct a species list we are incorporating a great amount of information about the ecological system itself.

It is quite often the case that the taxonomic situation is not so well worked out as it would be for the domestic cat. The soil worms, fungi, and other groups do not have so clear a classificatory history. Even in these cases, assigning an organism to some category that may be considerably broader than that of a species still is a reference to a great amount of information about that organism. Even if our species list were to be modified to include slightly broader taxonomic categories than the species where we do not have specific information, it is acting as an information-rich measure.

7
Advisory Panels and Peer Review

The following chapter on advisory panels and peer review was proposed and drafted by Samuel Silverstein, a member of the Panel on Genetics and Developmental Biology. It was considered by the entire study group and, after some revision, was adopted unanimously for inclusion in this report.

The relative expense and difficulties involved in studies in space demand that they be of the highest quality and that they focus on broad issues of widespread interest to life scientists. At present, the number of life scientists who are prepared to take advantage of space as a tool for research is comparatively small. NASA had made strenuous efforts to acquaint life scientists with opportunities for space research, but as of this date there is only a small number of life scientists who understand the problems and requirements for present and future studies in the life sciences in space.

In the past, advisory panels in the life sciences have been convened periodically by NASA. In most instances, these panels met for short periods (a few days or weeks), produced a report, and were disbanded. In nearly all instances, the membership of an advisory group empaneled on one occasion has not been enlisted when a similar advisory group was organized at a later date. These panels, thus, had no long-term responsibility for, or involvement in, the outcome of their advice. In addition, three AIBS panels composed of experts in (a) medical sciences, (b) space biology and plant biology, and (c) planetary biology and quarantine review intramural and extramural research proposals on a continuing basis. These panels are, of necessity, multidisciplinary in composition. This multidisciplinary approach has the disadvantage of affording little opportunity for vigorous discussion and dissent among members of a single discipline about issues about which all are knowledgeable. These AIBS panels perform the traditional scientific review function, but they have no responsibility for suggesting modifications of experimental protocols, or collaborative research, or for suggesting further earth-based or space program developments. Moreover, NASA has insufficient opportunity to inform these review groups of the special problems or requirements of space-related research.

With the advent of the Space Shuttle there will be increased opportunity for space-related research in the life sciences. To use the opportunity effectively will require that NASA develop new methods for reviewing, processing, and implementing research programs in the life sciences. For this reason, we have examined the advisory and review process currently employed and we suggest modifying these processes along with lines outlined below.

Our goals in making these recommendations are as follows:

1. To provide NASA with a wider and more flexible base for scientific advice in the life sciences;
2. To establish discipline-based, as well as multidisciplinary, advisory groups;
3. To maintain continuity in membership of the various advisory groups;
4. To enlarge the responsibilities of these advisory groups beyond the traditional process of grant review; and
5. To provide NASA with opportunities for informing these groups about the special problems of space research.

We envisage that these advisory groups would have multiple functions, extending beyond the peer review system characteristic of an NIH study section. They would not only review and evaluate individuals proposals but could help to assemble large collaborative groups needed to carry out multifaceted studies. This might involve requesting that groups of individual proposals be coalesced into a large project or that specific new proposals be developed. In addition, specific laboratories or individuals might be asked to provide needed methodology, critical evaluation, or technical quality control for specific studies. This may require more active participation in experimental design or in ongoing experiments (especially ones conducted in space) than is the case for NIH study sections. In the case of experiments to be conducted in space, it is especially important that proposals be reviewed rapidly and that the results of the review be communicated immediately to the investigators so that, where necessary, modifications in the proposal can be made. In making this recommendation we do not imply that a review panel's amendments be a precondition to acceptance of a proposal by NASA.