A Strategy for Space Biology and Medical Science for the 1980s and 1990s

Committee on Space Biology and Medicine, Space Science Board, Commission on Physical Sciences, Mathematics, and Resources, National Research Council

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FOR THE 1980s AND 1990s

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Space Science Board
Commission on Physical Sciences, Mathematics, and Resources
National Research Council

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Foreword

This is one of a series of documents prepared by committees of the Space Science Board (SSB) that develop strategies for space science for the coming decade. Others have been published in space astronomy and astrophysics, earth sciences, solar and space physics, and planetary sciences. Preparation of a strategy for planetary biology and chemical evolution is currently underway. These strategy reports set scientific goals and priorities intended to maximize the scientific return on the nation's investment in space science.

This report develops a scientific strategy for space biology and medicine for the 1980s and 1990s. It focuses on the programs, experiments, and instruments that will be required to answer the many fundamental scientific questions that have been identified in this still emerging field of space science.

Space medicine is unique in the context of the other space sciences—primarily because, in addition to questions of fundamental scientific interest, there is a need to address those issues that are more of a clinical or human health and safety nature. The authoring committee and the Space Science Board reached an important consensus in approving this report. That is, if this country is committed to a future of humans in space, particularly for long periods of time, it is essential that the vast number of uncertainties about the effects of microgravity on humans and other living organisms be recognized and vigorously addressed. Not to do so would be imprudent at best—quite possibly, irresponsible.

This report also addresses what is known as space biology, a scientific discipline that embraces developmental biology and plant gravitropism. These two subdisciplines treat a number of topics that are of fundamental scientific interest, particularly as we move toward a future in space that could include long-term space travel and/or interplanetary missions.

Like other SSB science strategies, this document takes the position that the strategy will be stated in terms of scientific objectives to be achieved during the period of time covered by the report rather than in a series of recommended missions. It is the intent of the series of science strategy documents to provide a scientific baseline for guiding and evaluating the science content of specific missions and long-range mission planning.

The SSB adopted this report as its policy position for space biology and medicine in May 1986. It takes this opportunity to express its appreciation to the members of the committee and its panels for their diligent and untiring efforts. It particularly appreciates the contribution of the Chairman of the Committee on Space Biology and Medicine, Jay M. Goldberg, whose term ends with this major effort.

Thomas M. Donahue, Chairman
Space Science Board

Preface

The purpose of this strategy for space biology and medical science for the 1980s and 1990s is twofold: (1) to identify and describe those areas of fundamental scientific investigation in space biology and medicine that are both exciting and important to pursue and (2) to develop the foundation of knowledge and understanding that will make long-term manned space habitation and/or exploration feasible.

This scientific strategy is meant to provide NASA with a guideline for developing its long-term mission plans and a rational, coherent research program. It is also a statement of Space Science Board policy against which the scientific community and the nation can assess the adequacy and success of NASA's efforts in this area of research over the next 10 to 15 years. This effort drew upon the collective thinking of over 60 scientists from a broad range of disciplines of space biology and medicine. It was developed over the course of two and a half years in a series of meetings, both of the full Space Science Board's Committee on Space Biology and Medicine and of eight specially convened panels.

The strategy addresses 10 topical areas for research: developmental biology, gravitropism in plants, sensorimotor integration, bone and mineral metabolism, cardiovascular/pulmonary function, muscle remodeling, nutrition, human reproduction, space anemia, and human behavior. This report is unique in several aspects. For the first time, the Space Science Board, through its Committee on Space Biology and Medicine, has outlined a broad-based scientific strategy for the study of space biology and medicine, with specific scientific goals and objectives and detailed measurement requirements for each of the 10 topic areas. The inclusion of human behavior along with physiological responses and space biology is another first for a report of this kind.

Perhaps the most unusual aspect of the report is its emphasis on basic as well as clinical science. While the life sciences program can be justified by the need to guarantee the health and safety of the astronauts, we did not wish to restrict ourselves to clinical problems. There were two reasons for our decision. First, the other space sciences have had to justify their programs on the basis of their potential contributions to fundamental knowledge. In our opinion, the life sciences were under a similar obligation. Having considered the matter, we conclude that there is important basic research to be done in space biology and medicine. Furthermore, even at the start of our study, we felt that progress in this field had been impeded by a narrow focus on matters of clinical concern, important as they are. Not only has basic science been shortchanged; clinical science has also suffered since knowledge of basic mechanisms is usually essential to the understanding of symptoms and the development of countermeasures.

In adopting this perspective, we decided not to review several areas of practical concern. Two of these are the delivery of health care services in space and the development of a controlled ecological life support system (CELSS). They are important topics and must be included in the life sciences program. We did not consider them in this report because progress in these areas largely depends on technological advances.

It is the position of this committee that scientific return will be maximized if investigations into each of the topical areas addressed in this report are conducted in a systematic fashion, based upon each of the chapters' scientific goals and objectives. Two other essential requirements of this research strategy are a strong, well-planned ground-based program of research and strict experimental control of all spaceflight research.

The predecessor to this report, *Life Beyond the Earth's Environment* (NAS, 1979), was begun in 1977. While that report addressed many of the same areas as this strategy, there have been some significant events since its publication that in the judgment of the Space Science Board and its Committee on Space Biology and Medicine necessitated the development of this document.

Principal among these events was the advent of the Space Transportation System (STS), which began with the Shuttle Orbiter *Columbia*'s first flight on April 12, 1981. That mission marked the first time the U.S. had flown a manned mission since July 1975, when an U.S. Apollo spacecraft and the U.S.S.R. *Salyut* docked together in earth orbit. The recent *Challenger* disaster was a major setback for the U.S. manned space program. There seems little question, however, that the nation is committed to a resumption of the program once the engineering and managerial faults of the STS are identified and corrected.

Another significant development since the 1977 report is the January 1984 announcement of President Reagan directing NASA to proceed with the development of a manned Space Station, to be in place before the end of the next decade. *The eventual resumption of a Space Transportation System and plans for a manned Space Station in the future mandates careful and deliberate planning if we are to both maximize future scientific return and ensure the health and well-being of those human beings who go into space for months to years at a time.*

With the possible exception of materials science, life sciences in general, and space biology and medicine in particular, is, more than any other space science, in the very earliest stage of discipline development. There are any number of practical reasons for this—limited flight opportunities, finite numbers of research "subjects," and competition with other disciplines for experimental time on Shuttle missions, to name a few. Another major contributor has been the lack of a coherent, well-defined research program. Ironically, there appears to be a general perception that the absence of life-threatening medical problems in the manned space program implies that there is little need to be concerned about health-related issues on a manned Space Station or in interplanetary missions of several years duration. *Based on what we know today, this assumption of continued success cannot be rigorously defended.*

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Executive Summary

INTRODUCTION

The Committee on Space Biology and Medicine, in reviewing the various disciplines in its purview, came to several general conclusions. These are best stated at the outset since they were influential in framing the individual discipline strategies, as well as the general strategy for conducting research in the broad field.

- There is important research to be done in space biology and medicine over the next 10 to 20 years.
- Some of the research is clinical in nature and is concerned with the health and welfare of the astronauts. Much of the research is of basic interest and deals with fundamental questions concerning the role of gravity in life processes. In a properly framed strategy, basic and clinical research can complement one another.
- There is a need for the integration of ground-based and spaceflight research. Much of the research in the field is best done on the ground, where the full repertoire of modern research techniques can be applied. One goal of spaceflight research is to determine the adequacy of various ground-based models of the microgravity environment.
- Much of spaceflight research will require manned missions, first, because for many problems man is the species of choice and, second, because most research will require direct intervention by skilled, on-board scientists.
- Space biology and medicine is in its infancy. Relatively few biological experiments have been flown, most of them have not been part of a larger research strategy, and few of them have been adequately controlled or replicated. In contrast, the relevant

ground-based research has been of high quality. The main purpose of this strategy is to redress the imbalance in the quality of the two kinds of research and, so, to determine if any of life's processes can best be studied in space.

Most of the strategy was framed before the *Challenger* disaster in January 1986. Until then, the continued success of the Space Transportation System or Shuttle program and the plans to develop a Space Station led the committee to conclude that the nation had a continuing commitment to manned space travel. The committee took no position as to the merits of this policy, since it did not view that as part of its prescribed task. Nevertheless, the committee is of the firm opinion that abandoning or severely reducing the manned program will greatly impede progress in space biology and medicine. National support for a manned space program seems to remain intact. Obviously, the disaster has been a severe setback for the manned program, and years of detailed planning will be required to get the program back on track. This will mean a delay in much of the spaceflight research that the committee has proposed. In the interim, the ground-based components of the research strategy can be expanded so that we can be even better prepared to take advantage of flight opportunities once they resume.

Except for this transitory change of emphasis toward ground-based research, the committee sees no reason to change the general features of the strategy or its specific recommendations. The committee assumes that the manned space program will be resumed and will be energetically pursued. It seems reasonable to predict, as a part of such a program, that sometime in the twenty-first century there will be a call for a manned interplanetary mission, a manned lunar base, or both. Such missions will require that humans spend as much as 3 to 4 years in space. This is considerably longer than any previous mission in either the U.S. or Soviet space programs. While the committee cannot say with assurance that such long-duration manned missions are not possible, there is simply too little knowledge concerning the physiological and psychological effects of long-term space occupancy to guarantee the health and safety of the flight crew.

The success of any long-term mission demands the support of a vigorous, well-balanced program of research with both ground-based and space-based components. This research strategy is intended to provide the foundation for such a program. It addresses both the clinical research necessary to ensure the well-being of humans in space and the basic research that seeks to answer questions of general biological interest.

MAJOR SCIENTIFIC GOALS

A major concern of the life sciences is to guarantee the health and safety of the astronauts for missions lasting from a few days to over three years. Astronauts in space have experienced many symptoms, and these can be expected to become exacerbated as mission duration and mission complexity are increased. To understand these effects, we need a better description of man's adaptation to space and his readaptation upon return to earth. A program of clinical research is needed to improve selection, training, and countermeasures. The possible success of such a program will be enhanced if the mechanisms underlying the symptoms are understood. This will require a program of basic research, which can also be justified because it can answer questions of intrinsic interest. Much of the research, both basic and clinical, is best done on the ground, where the full repertoire of modern research techniques can be applied. Ground-based research is needed to elucidate the mechanisms underlying the various responses to gravity and to its absence. In addition, there are earth-based models for many of the biological effects observed in space. A comparison of spaceflight observations with ground-based research is needed to decide if any of life's processes can best be studied in space and, hence, if space represents an important frontier for biology and medicine.

From these considerations, the committee has defined four goals. The first two goals must have the highest priority, if only because they involve the well-being of the astronauts. The other two goals are entirely compatible with the first two goals and, in fact, may enhance their chances of success. For these reasons, a balanced research program is best ensured by requiring that all four goals be met. The four goals are:

1. *To describe and understand human adaptation to the space environment and the readaptation upon return to earth.*

2. *To use the knowledge so obtained to devise procedures that will improve the health, safety, comfort, and performance of the astronauts.*

3. *To understand the role that gravity plays in the biological processes of both plants and animals.*

4. *To determine if any biological phenomenon that arises in an individual organism or small group of organisms is better studied in space than on earth.*

DISCIPLINE-SPECIFIC SCIENTIFIC GOALS AND OBJECTIVES FOR SPACE BIOLOGY AND MEDICINE

Scientific goals, objectives, and required measurements and facilities for each of the major areas of space biology and medicine have been identified and described. Following is a summary of the primary goals and objectives for each of these disciplines.

Space Biology

Developmental Biology

The field of developmental biology encompasses all aspects of the lifespan of an organism, from fertilization through aging. It involves topics of research in gamete production, fertilization, embryogenesis, implantation (in mammals), the formation of organs, and the broad area of changes after birth defined as postnatal development. Developmental biologists ask questions concerned with certain phenomena that occur at certain phases of development. For example, it is known that at some point after fertilization cells become committed to developing along a certain pathway. This restriction is called determination. If, for instance, the first two cells of a sea urchin embryo are separated, each may give rise to a complete, but one-half-sized larva. But, if one of the cells from a sixteen-cell embryo is separated and raised in isolation, it does not give rise to a normal but one-sixteenth-sized larva; it develops into a specific subset of larval tissues.

With respect to developmental biology in space, there are two basic questions. (1) Can organisms undergo normal development under conditions of microgravity, or are there gravity-sensitive phases or processes that become so abnormal in microgravity that repetitive life cycles cannot occur? (2) Does the unique microgravity environment of space provide a tool to study developmental phenomena better, or exclusive of, similar studies carried out in ground-based experiments?

The committee has identified scientific goals and objectives for specific animal and plant systems that are those which are most important to understanding the influence of gravity on the processes of development. *The primary scientific goals for the study of development in space are twofold:* (1) *to evaluate the capacity of diverse organisms, both plant and animal, to undergo normal development from fertilization through the subsequent formation of gametes under conditions of the space environment* and (2) *to evaluate the use of the space environment to study specific developmental phenomena in ways that cannot be accomplished, or can only be accomplished in part, in ground-based research.*

Because of limited availability of research space and the overall cost, *the committee recommends that the highest priority for experiments actually conducted in space should be devoted to studies on "model organisms" designed to answer the question: Can development from fertilization through the formation of viable gametes in the next generation occur in the space environment?*

Gravitropism in Plants

Roots grow downward and stems grow upward. There are exceptions to this obvious generalization. Some stems, such as underground rhizomes, grow horizontally, while others, such as the branches of a tree, grow upward at an approximately fixed angle to the vertical. To make matters more complicated, some genetic mutants are completely agravitropic, while an obliquely growing tree branch will grow straight upward if its apical bud is injured or surgically removed. One can conclude that gravitropism, the curvature of a cylindrical plant organ in response to a gravitational force, is determined by genetics and development and is controlled by physiology.

The primary scientific goal of research in plant gravitropism is to understand the cellular and organismal processes involved in the plant's detection and response to the earth's gravitational field. This understanding can best be attained by answering questions about how the plant senses gravity, how this sensation is transduced into a signal that can influence cellular growth, and how the signal can cause the differential growth of the upper and lower halves of a plant organ that leads to curvature toward or away from the earth's center. *The secondary goal involves understanding why roots grow down and stems grow up and how gravity interacts with light, other external stimuli, and endogenous rhythms in determining the orientation of plant organs.*

Space Medicine

Sensorimotor Integration

The sense of gravity, provided by the vestibular end organs and by tactile and proprioceptive inputs, is a major factor in determining spatial orientation and motor performance on earth. In spaceflight, however, relative weightlessness is encountered for prolonged periods of time. This demands a reorganization in the processing of sensory information so that motor performance can be adapted to the new environment. Weightlessness offers a challenge to sensorimotor coordination that is never encountered and cannot be adequately simulated on earth.

The committee has developed and described goals and objectives for five different areas relevant to sensorimotor adaptation: (1) spatial orientation, (2) postural mechanisms, (3) the vestibulo-ocular reflex, (4) processing in the vestibular system, and (5) motion sickness. *The primary scientific goals for the study of sensorimotor integration in space are:*

1. *To describe how spatial orientation, postural mechanisms, and oculomotor performance change and adapt to weightlessness.*
2. *To determine short- and long-term effects of the absence of gravity on neural processing in the vestibular system and on parts of the central nervous system subserving orientation and movement control.*
3. *To study the role of gravity in the neonatal development of sensorimotor functions.*
4. *To establish the causes of space motion sickness and to develop recommendations for its treatment and prevention.*

Bone and Mineral Metabolism

Spaceflight has been consistently associated with a demineralization of bone (osteopenia) and with a change in the homeostatic system that regulates plasma levels of calcium. Loss of bone mineral (calcium and phosphorus) has been consistently reported as a physiologic response to spaceflight. Although the decalcification of bone has not as yet resulted in impaired functional capacity in astronauts, the extended requirements of the Space Station and missions to follow suggest that osteopenia and clinically evident fractures are likely to become significant problems. For this reason it is essential to understand the pathophysiology of the osteopenia caused by space travel, to devise appropriate countermeasures, and to understand the relation between bone demineralization and the changes in calcium homeostasis.

The primary scientific goals for the study of bone and mineral metabolism are:

1. *To understand the basic mechanisms that influence bone demineralization.*
2. *To understand the basic mechanisms of calcium homeostasis.*
3. *To determine the relationship between the above two processes.*
4. *To determine the extent to which the bone demineralization that occurs in space is similar to that occurring in various ground-based models.*
5. *To continue the development of countermeasures for bone demineralization.*

Cardiovascular and Pulmonary Function

The cardiovascular system governs the flow of metabolites, heat, and hormonal substances to and from all cells in the body and is also involved in the exchange of materials and energy between the body and the external environment. The external exchanges occur in the kidney, lungs, and skin. The system consists of pumps—the right and left hearts—and of tubes—the vascular system. There are local and more global controls that regulate blood pressure, blood volume, cardiac output, and local blood flows. These regulatory systems are triggered by a number of perturbations. One such perturbation occurs when the effect of gravity on the cardiovascular system is altered such as when a person moves from an erect to a recumbent position or is subjected to the conditions of microgravity during spaceflight. Changes in pulmonary function remain to be documented.

The primary scientific goals for the study of cardiovascular and pulmonary systems in space are:

1. *To understand the cardiovascular and pulmonary adaptation to microgravity in three different time frames—acute (0 to 2 weeks), medium-term (2 weeks to 3 months), and long-term (3 months to several years).*
2. *To determine the relation between the cardiovascular and pulmonary adaptations of spaceflight and those occurring in earth-based models such as bed rest and, so, to ascertain if the space environment offers any unique advantages for the study of human cardiovascular and pulmonary adaptations to variations in gravitational simulation.*
3. *To develop adequate measures that hasten human adaptation to microgravity and to reentry to earth.*

Muscle Remodeling

Muscle accounts for a substantial fraction of the nutritional needs of the entire body. It contributes an increasing proportion of the body's weight during growth and development, reaching a peak of 45 percent in young adults and then declining with age. Approximately 1 percent of the muscle protein in adults turns over each day, accounting for 20 to 30 percent of the body's entire synthesis and breakdown of protein. The nutrient protein requirements of muscle are high, as are its energy requirements. Even light muscular exercise, such as occurs during daily activities, can increase the metabolic rate 30 to 40 percent and heavy exercise can transiently increase caloric requirements severalfold. The metabolic status of muscle is also regulated by dietary intake, exercise, and hormones.

In space, the legs no longer experience the loads required on earth to maintain an erect posture or for locomotion, while the arms take on additional functions for locomotion and body stabilization. Given the altered force-motion environment of spaceflight, it would be expected that the activity of muscles of the lower extremities, particularly the antigravity or extensor muscles, would be decreased and that this, in turn, would lead to disuse atrophy. Data on muscle function are available from Skylab missions, and to a lesser extent, from Salyut missions. There is considerable evidence that humans experience such atrophy in leg muscles, but not in arm muscles.

The primary scientific goal for the study of muscle remodeling is to understand the basic mechanisms of activity-related muscle remodeling as they occur in space and on earth.

There are three major scientific objectives:

1. *To determine the physiological end of biochemical that control muscle function on earth.*
2. *To determine the causes of muscle atrophy in space and, so, provide a basis for the development and evaluation of countermeasures.*
3. *To ascertain if the changes in muscular function that occur in space are similar to those occurring on earth and if spaceflight offers any unique opportunity for the study of muscle remodeling.*

Space Anemia

Anemia was first noticed in Gemini missions in which astronauts were breathing pure oxygen at low ambient pressures. This presumably caused oxidation of red blood cell (RBC) membranes and a destruction of the RBCs themselves, a so-called hemolysis. In the Apollo program, normal ambient air was provided at launch but was gradually enriched so that astronauts were eventually breathing pure oxygen. When they were found anemic, it was thought to be due to the same oxidative RBC damage. A similar anemia, however, has also been seen in Shuttle missions, where the cabin air is identical in pressure and composition to that found at sea level, and so the anemia cannot be attributed to high oxygen levels.

The primary scientific goal is to determine the relative importance of the several factors that may contribute to the anemia of spaceflight.

Human Nutrition

The energy requirements of posture and motion should be less in space than on earth since the body does not have to work against the force of gravity. This would suggest that caloric requirements would be lower in space. Yet, man typically exhibits a small loss in weight during spaceflight even though the diet appears to have a nearly normal caloric content. There are several outstanding questions with respect to human nutritional requirements in spaceflight. What has been the food and fluid intake during spaceflight? To what extent are nutritional requirements modified by transient digestive disturbances, such as the anorexia, nausea, and vomiting associated with space sickness? Do the conditions of spaceflight alter gastrointestinal physiology, including the absorption of essential nutrients and the functioning of gut flora? Are there changes in energy metabolism and storage other than those due to muscle changes? Is spaceflight associated with a change in energy expenditure? What, in fact, are the energetic requirements of work in the space environment?

The primary scientific goal for the study of human nutritional requirements in space is to understand and describe the nutritional needs associated with space travel.

Human Reproduction

To date, there has been no research into the effects of space travel and the physiological adaptation to zero gravity on the reproductive system of humans. There are three conditions associated with space travel that may affect reproductive function: stress, microgravity, and radiation. There is evidence that stress alone may produce short-term effects on women. One of the more serious of these effects involves hormonal changes, particularly a decrease in estrogen production. Estrogen has significant effects on bone turnover. The osteopenia that occurs in spaceflight would be compounded by hypoestrogenism and may not be completely reversible. Microgravity could also affect the female reproductive tract by altering the menstrual flow. The effect of space radiation on male and female reproduction has not been characterized, even in animals. As radiation exposure is a certainty in spaceflight, it is important that these effects be determined to protect the reproductive capability of those individuals who plan to embark on medium- to long-term space missions.

The primary scientific goal is to study the effects of the space environment on human reproductive functions.

Human Behavior

Behavior involves the interaction of individuals with their environments. Adaptive behavior is essential to the success of any human endeavor. Humans usually behave adaptively in familiar surroundings providing that excessive or unusual demands are not made of them. In strange environments, however, normal behavior can be disrupted, particularly if intensive and or highly skilled performance is required. Spaceflight is certainly an unusual environment. While there have been no official reports of serious behavioral disruptions in either the U.S. program or that of the U.S.S.R., there is evidence that these have occurred. Furthermore, it has been suggested that behavioral and social problems will become more frequent as missions become longer and more complex and as crews become larger and more heterogeneous in their makeup.

The primary scientific goal for the study of human behavior in space is the development of a satisfactory, empirically based theory that identifies the environmental, individual, group, and oragnizational requirements for the long-term occupancy of space by humans. Although the evidence is fragmentary, it seems likely that behavioral and social problems have already occurred during long-term missions. An understanding of what these problems are and how to ameliorate them is essential if humans are to occupy space for extended periods of time. From a scientific perspective, it seems likely that significant advances in our basic knowledge of human interactions and group processes will emerge from research needed to ensure effective performance and adjustment in space.

RECOMMENDATIONS ON SCIENCE PROGRAM AND POLICY ISSUES

Many of the recommendations in this report represent a departure from the current procedures used by NASA in conducting its Space Biology and Medicine Program. These changes are necessary in order to implement the scientific strategy that the committee has devised. Proposals are made concerning the use of panels of scientists to advise NASA regarding the implementation of the research strategy; the need of researchers in space biology and medicine for continuous access to spaceflight opportunities; the advantages of organizing spaceflight into a sequence of missions, each focused on a central theme of major importance; and certain design features that will enhance spaceflight experimentation and general facilities.

Science Program Issues

Specialty Panels

Biology, like most other sciences, is dynamic. Hence, any scientific strategy will require adjustment to reflect new results and technical developments that occur. Space biology and medicine, it is our belief, will eventually emerge as a single, unified discipline. But in this, the early stages of its development, there is a need for detailed planning in each of the specialty areas that make up the discipline. At present, each specialty area has its own problems, needs, and opportunities, and requires a comprehensive research strategy. Planning is best done by panels of scientists in each specialty, working in close cooperation with NASA's Office of Life Sciences. *The committee recommends that there be standing panels of 5 to 10 qualified scientists to help NASA's Office of Life Sciences to review, update, and refine the research strategy in each specialty area.* The areas represented on the specialty panels should include: developmental biology, plant gravitropism, sensorimotor integration, bone and mineral metabolism; cardiovascular and pulmonary function; muscle biology; endocrinology, nutrition, and hematology; and human behavior.

The panels would have several responsibilities. First, they would evaluate research proposals in terms of their scientific merit and their impact on the overall strategy. Second, they would review all of the activities sponsored by the Office of Life Sciences in the particular specialty area and provide guidance as to how the various research programs—basic, clinical, ground-based, and space research—can best be integrated to meet research objectives. And, last, they would seek to identify promising but neglected areas of space biology and medicine research and seek ways to encourage interest in these areas. Establishment of such panels should provide the continuity and focus necessary to successfully oversee the implementation of an integrated scientific research strategy in each specialty area.

To oversee the implementation and coordination of the programs in the various specialties is the responsibility of the director of NASA's Office of Life Sciences. In meeting this responsibility, the director should seek the advice of more generally constituted advisory groups. These include the Life Sciences Advisory Committee, which reports to the NASA Advisory Council, and the Committee on Space Biology and Medicine, which is a subcommittee of the National Research Council's Space Science Board. A major function of these multidisciplinary panels should be to frame the overall goals of the life sciences program and to ensure a proper balance in the research funds and flight opportunities devoted to each specialty.

Dedicated Life Sciences Laboratory

One of the major reasons for the slow progress in the U.S. program of research in space biology and medicine has been the lack of flight opportunities. There were no spaceflight initiatives in human biological research between the Skylab missions and the beginning of the Space Shuttle program. The research program outlined in this strategy requires the collection of large amounts of data and the gradual improvement of research protocols and techniques. Most of the experiments require manned intervention. If significant progress is to be made by the end of this century, space biology and medicine must have continuous access to spaceflight opportunities. *Based on the dual requirements of continuous access and manned intervention, the committee recommends that there be a dedicated Life Sciences Laboratory on the Space Station. Until the Space Station becomes operational, the Space Shuttle should be used at every available opportunity to sharpen hypotheses and techniques. In the interim necessitated by the Challenger disaster, ground-based research should be expanded so that we can be better prepared to take advantage of flight opportunities, once they resume.*

Focused Missions

Most flight opportunities involving the life sciences have carried experiments from several specialties. There is a better way to meet our research goals. *The committee recommends that space biology and medicine research time on the Space Station be divided into 3- to 6-month blocks, with each block largely devoted to a single research area. Missions in each area should occur at least three times each decade. It further recommends that two or more payload*

specialists on each flight be practicing laboratory scientists in the particular specialty.

The adoption of such an approach would simplify mission planning and implementation. The same equipment and, in some instances, the same biological specimens can be used in several experiments. The scientific working group participating in the mission will have a common understanding and, presumably, a common set of goals. The mutual understanding within the working group, as well as longer mission durations, should enhance flexibility in the scheduling of individual experiments. Both flexibility and innovation are important in successful biological experimentation.

The objective in such an approach is to maximize the impact upon the particular specialty area involved by focusing on the few essential questions that need to be answered over the next 10 to 20 years. To succeed, teams of the very best scientists in the area should be recruited. There are three attractions offered by the focused-mission approach that would aid in this recruitment: (1) the promise of important results would exist, (2) there would be the opportunity to join in a team effort with other first-rate scientists, and (3) the administrative and organizational burdens of mission planning and implementation would be shared.

Flexibility in Spaceflight Experiments

Life sciences research, as conducted on earth, is usually done by a single principal investigator, working with his graduate students, postdoctoral fellows, and technicians in a laboratory designed for a specific research program. The built-in limitations of spaceflight research require a much different approach. Scientific productivity will be greatly enhanced if missions can be planned with sufficient flexibility that the design of individual experiments can be modified to reflect the latest research findings, including those obtained on the same flight. The challenge will be to mount large-scale experiments, meet engineering and scheduling requirements, and yet retain the flexibility of experimental design and execution crucial to biological research.

There are several ways in which experimental flexibility can be enhanced. First, there must be rapid feedback of results during the mission. This will require increased on-board analytical capability and the ability to communicate the results in an understandable manner both to the crew and to their ground-based colleagues. Second, it is important that the two groups be able to exchange data, information, and ideas. Third, there must be flexibility in the availability of equipment and experimental organisms, as well as in the scheduling of experiments.

General Facilities

The conduct of space biology and medicine research in space will require the availability of certain facilities. Discipline-specific facilities are discussed in each of the individual subdisciplines addressed in the strategy. Those discussed below would be of general use in life sciences research.

1. Variable Force Centrifuge (VFC). Such a device is the single most important facility in any life sciences program. A VFC has three equally important functions. (1) It provides an on-board 1-g control that can separate the influence of weightlessness from the other effects of spaceflight. (2) Microgravity has both short-term and long-term effects on biological systems. Both kinds of effects involve important biological phenomena. Their study is greatly facilitated by a VFC, which allows exposure to microgravity or to gravitational forces for varying periods of time. (3) The removal of gravitational forces is already known to have major impacts on biological systems. In such cases, it is of particular importance to determine if there is a threshold force required for a response to occur and, more generally, to ascertain the dose-response relationship. A VFC offers the crucial advantage in answering these questions, since it makes possible the introduction of fractional g forces. From these comments, it can be appreciated that a VFC should increase the scientific return from space experiments by orders of magnitude.

This committee has been apprised of the engineering problems involved in the inclusion of a large centrifuge in a freely floating Space Station. Nevertheless, *the committee still recommends that a variable force centrifuge of the largest possible dimensions be designed, built, and included in the initial operating configuration of the Life Sciences Laboratory. A VFC is an essential instrument for the future of space biology and medicine.*

2. Specimen Facilities. Humans are the subjects of choice in many areas of space research. A system for the collection and preservation of specimens, including blood, urine, and stool

samples, is essential. Animal research is essential in several areas, including sensorimotor adaptation, muscle atrophy, bone and mineral metabolism, and developmental biology. *The committee recommends that a research animal holding facility (RAHF) be included in the initial operating configuration of the Life Sciences Laboratory.* Plant research requires a chamber in which plants can be grown from seed-to-seed under conditions of controlled temperature, light, humidity, and nutrition.

3. Facilities for On-Board Handling and Analysis of Cell and Tissue Specimens. There should be facilities available for analytical biochemistry, automated radioimmunoassays, and radioactive tracer studies. Inflight histological examination requires facilities for fixation and sectioning of specimens and a light microscope with direct and phase contact optics.

4. Computational Facilities. There should be dedicated microprocessors for process control and data storage. In addition, there should be common facilities that can be used for general purpose computations, as well as data management, analysis, and display. Such capability will aid in the rapid return of data mentioned in the previous section.

Science Policy Issues

Mission Planning

The selection for spaceflight experiments generally begins with an Announcement of Opportunity (AO), which is distributed by NASA. In the past, the AOs in the life sciences have stated NASA's intention to fly experiments on a specific mission. If the focused mission approach is adopted, future AOs should be confined to a particular field and should explicitly state the major research questions that the mission is intended to address. The specialty panels should be consulted on the framing of the AOs and should be the primary peer review panel in the selection of experiments. The comprehensive research strategy in the particular specialty should form the basis of those selections.

Crew Selection and Training

Life sciences research in space, perhaps more than any other discipline, requires that the experiments be done by skilled scientists. The qualifications of such scientists should be extensive laboratory experience in the relevant discipline or disciplines and evidence of independent research abilities. It would be well to have two such scientists on each mission. Participation as a flight scientist should be structured in such a way as to enhance rather than jeopardize the individual's career in research, be it at a NASA Research Center, private industry, or a university.

Interim Strategies

Space biology and medicine, like the other space sciences, has been hurt by the hiatus in space missions necessitated by the *Challenger* disaster. During the interim, ground-based research should be expanded so that we can take better advantage of flight opportunities, once they resume. The hiatus provides an opportunity to develop research strategies in the specialty areas and a comprehensive plan for the entire life sciences. This report represents only a first step in a continual process. NASA has an obligation to fly missions to which it is committed. Many of the scheduled missions were conceived more than a decade ago. Some of them are still timely. NASA must evaluate all proposed missions in terms of a single benchmark—the impact on the overall research strategy. Finally, the future of space biology and medicine will depend on the quality of the young people attracted to the field. NASA should expand its fellowship programs to encourage predoctoral and postdoctoral training at universities, research institutes, and NASA Research Centers. Even in a period of reduced flight opportunities, there is exciting, important research to be done in ground-based laboratories. At the same time, it has to be emphasized that the full potential of the field will be realized only when there is expanded, continuous access to space.

Interagency Cooperation

While the responsibility for a coordinated program in space biology and medicine clearly rests with NASA, some aspects of the research will also be of interest to other agencies, including the National Institutes of Health and the National Science Foundation.

It would be wise for NASA to maintain a formal liasion with these agencies. One mechanism might be to appoint representatives from other agencies to serve as ex officio members of the specialty panels.

International Cooperation

There has been a long and fruitful collaboration between the United States, Canada, and the countries of Western Europe. Continued cooperation should be encouraged. The Soviet Union has made a larger investment in space biology and medicine than we have, and, in many areas, they are more accomplished than we are. The free and open exchange of scientific ideas is of interest to both nations science we share a common interest in the understanding of life's processes and in the manned exploration of space.

1
Introduction

Life as we know it has evolved in the presence of gravity. It hardly comes as a surprise that plants, animals, and humans show abnormalities in function when exposed to the microgravity environment of spaceflight. At the same time, organisms adapt to this, as they do to other novel environments. Space biology and medicine studies how individual organisms and small groups of organisms respond to microgravity and adapt to it.

There are two kinds of research, basic and clinical. With regard to space biology and medicine, basic research seeks to answer questions of general biological interest. Clinical research deals with the health and well-being of astronauts during both short- and long-duration missions. Basic and clinical research are interrelated. Effective solutions of clinically relevant problems usually involve the rigorous application of scientific methodology. Further, the study of basic biological processes has often provided essential clues to the solution of clinical questions. Finally, in many cases, the solution of a general biological question has started with a question of clinical interest from a life scientist.

CLINICAL RESEARCH

When man goes into space, many things happen. For illustrative purposes, five clinical problems are reviewed. In considering these and other clinical issues, the committee has assumed that manned missions lasting 90 days to 1 year will become common during the 1990s. Sometime after the turn of the century, the committee has further assumed, there will be a manned planetary mission, possibly to Mars, involving an outbound trip of 1 1/2 years, a planetary stay of 1 to 6 months, and a return trip of 1 1/2 years. Missions beyond 3 to 4 years duration are not dealt with here.

Sensorimotor Integration

The disappearance of gravity upsets the signaling from the vestibular labyrinth, so that astronauts can become disoriented and experience space sickness, a syndrome that shares many features with terrestrial motion sickness. Remarkably, the brain learns to adapt to the altered signaling over the course of 3 to 5 days. Space sickness can greatly diminish crew effectiveness during the first few days of a mission. Postural disturbances and vertigo can be present during the first postflight week. The problems are largely operational. The one possible implication for long-term health concerns the possible deleterious influence of prolonged microgravity exposure on the structure and function of the vestibular end organs.

Cardiovascular Adaptation

In a microgravity environment, there is a headward shift of body fluids that is interpreted by the cardiovascular system as an increase in blood volume. This is a hyperdynamic state. By a variety of neural and hormonal regulatory mechanisms, fluid is excreted from the kidneys. This may be an appropriate adjustment to microgravity, but it is still unclear whether the system remains hyperdynamic, returns to a state similar to that on earth, or becomes hypodynamic. The state achieved will determine the rate at which blood is pumped by the heart and whether cardiac muscle, in response to the demands made upon it, will hypertrophy or atrophy. Problems also arise upon return to earth. There is now an orthostatic intolerance: an inadequate amount of blood is delivered to the brain during standing. The symptoms are not unlike those that occur after prolonged bed rest, and the system may take days to weeks to readapt to terrestrial conditions. Three questions can be asked. Do the symptoms reach an asymptote for flights beyond a certain duration? Assuming that a steady state is reached, is the cardiovascular system hyperdynamic, normal, or hypodynamic? Will the symptoms that occur on return to earth be exacerbated by missions lasting months to years?

Muscle Remodeling

One of the major functions of the musculoskeletal system is the maintenance of an upright posture in the face of gravity. During spaceflight, there is no longer a need to oppose gravity, activity decreases in the so-called antigravity muscles, particularly the extensor muscles of the legs and trunk, and disuse atrophy of these muscles occurs. The atrophy has apparently not compromised crew function in flight, except possibly during the extraordinary muscle demands during some instances of extravehicular activity. Nor has the atrophy proved particularly disabling postflight. Nevertheless, recovery of muscle mass, muscle strength, and exercise tolerance can take from days to weeks.

Bone and Mineral Metabolism

In Space there is a demineralization of bones, especially the bones of the leg and probably the spine. This is most likely the result of a decrease in mechanical forces experienced by bone. The largest and most important of these forces arises from muscular contractions. Signs of altered bone and mineral metabolism have increased progressively for flight durations of up to 90 days. This may represent a major health hazard. A lengthy recovery period is required to regain lost bone. Bone loss, especially that of trabecular bone, could be irreversible. Under some conditions, kidney stones may develop. Perhaps most importantly, it is possible that clinically evident fractures will occur as a consequence of long duration.

Human Behavior

There have been relatively few official reports of maladaptive behavior leading to a deterioration in individual and crew performance in space. Evidence does exist, however, that behavioral disturbances have occurred. This is hardly surprising considering that spaceflight involves several psychologically stressful factors—social deprivation, physical confinement, demands for high performance, and the discomfort associated with crowding, lack of privacy, artificial life support, and weightlessness. Even greater psychological demands will be made on crews as mission duration and task complexity are increased and as the composition of the crew becomes more heterogeneous. A greater incidence of behavioral disturbances seems likely. These could imperil the affected individual, the crew, and the mission itself.

In each of the five areas, a program of research on selection, training, and countermeasures is needed. Such programs have a greater chance of succeeding if the basic mechanisms responsible for the symptoms are understood. What is required is a rigorous program of clinical research that rests on a secure foundation of basic research.

BASIC RESEARCH

An ambitious program of basic research, while it can be justified on narrow clinical grounds, is also warranted because it can answer questions of intrinsic biological interest. Here the committee will review, in addition to the five areas already considered, two areas that are of interest largely from the perspective of basic biology. These are developmental biology and plant gravitropism.

Sensorimotor Adaptation

The peripheral vestibular apparatus consists of two kinds of sensory receptors: (1) the otolith organs that sense linear forces, including gravity, acting on the head and (2) the semicircular canals involved in the signaling of rotatory head movements. The activity of the otolith organs is altered in microgravity; that of the semicircular canals is not affected. Spaceflight offers an opportunity to study the relative roles of two kinds of organs as well as the adaptive mechanisms the brain uses to adjust to the altered force and motion environment. Space sickness is a variant of terrestrial motion sickness. The neurological and neurohumoral mechanisms involved in the syndrome of motion sickness are poorly understood as is the biological function of the syndrome itself. The functional contributions of the various vestibular end organs, the mechanisms of sensorimotor integration, and the mechanisms of motion sickness are important areas of basic research.

Cardiovascular Adaptation

The cardiovascular adjustment to microgravity involves many of the same physiological mechanisms that are important in the control of blood pressure and blood volume on earth. This is largely accomplished by regulating the excretion of water and salt by the kidney. The mechanisms involve three sets of hormones. Atrial natriuretic factor (ANF) is released by direct mechanical stimulation of the heart. The secretion of antidiuretic hormone (ADH) from the posterior pituitary gland is inhibited by a nervous reflex triggered by mechano-receptive afferent neurons in the heart. Aldosterone release from the adrenal cortex is inhibited by a chain of mechanisms that reflects the activity of the sympathetic nervous system and the rate of blood flow through the kidney. The decrease in ADH results in a diuresis, whereas the changes in ANF and of aldosterone assure a corresponding loss of salt. Many other neurohumoral mechanisms contribute. Some of these doubtlessly remain to be discovered. The ways by which the various component mechanisms are coordinated to provide an appropriate adjustment of the entire system are by no means clear. As a result, neurohumoral regulation of pressure and volume remains an area of very active research in cardiovascular physiology.

Muscle Atrophy

The biological mechanisms that induce atrophy are largely unknown, as are the mechanisms of exercise-related hypertrophy. Even though there is a wealth of information on protein synthesis, the biochemical pathways responsible for the synthesis and degradation of contractile proteins in response to use and disuse are not understood. Muscle metabolism is regulated, in part, by various hormones, including insulin and the somatomedins, but their precise role in hypertrophy and atrophy needs to be determined. The identification of the cellular and molecular mechanisms that link active muscle contraction and changes in contractile protein synthesis remains a fundamental question of muscle biology.

Bone and Mineral Metabolism

Two systems control the metabolism of bone in adults. The first is the bone remodeling system that is responsible for the resorption of old bone and the formation of new bone. The second is a homeostatic system that controls the concentration of plasma calcium. Different cells within bone are involved in the two systems. The calcium fluxes involved in homeostasis are large and rapid when compared to those involved in remodeling. Various hormones—parathyroid hormone (PTH), calcitonin, and vitamin D metabolites—affect both systems, but in different ways. Alterations in the homeostatic system can affect remodeling, but remodeling has no direct effect on homeostasis. Three basic questions may be asked. (1) What is the precise relation between the two systems in bone health and disease? (2) How do the various hormones exert their effects? (3) What are the transduction mechanisms that couple mechanical stress to bone remodeling?

Human Behavior

The study of behavior, which began in the experimental laboratory has now been extended to humans in more naturalistic settings, including real-life situations. Solutions to the psychological problems expected to arise from prolonged spaceflight will require research in several areas. The results should have applicability to confined microsocieties other than space crews and even to everyday circumstances. Research topics include the impact of environmental factors, architectural design, and task requirements on individual and group performance; the interaction between individual personality and group performance; and the effects of various factors, both social and nonsocial, on individual behavior. Much remains to be learned concerning group dynamics, including the partitioning of authority and autonomy, the evolution over time of semiautonomous task-oriented groups, and the essential attributes and functions of group leaders. A group depends on the organization to which it belongs for rewards, information, technical assistance, and material resources; the most effective modes by which these organizational supports are delivered remains to be determined. Finally, ways have to be found to integrate the various environmental, individual, group, and organizational factors into an effective whole. Most of these issues are not peculiar to spaceflight, but are of importance in many highly organized social endeavors.

Developmental Biology

Two questions are raised. (1) Can organisms undergo normal development under microgravity conditions, or is development so abnormal that multiple generations cannot survive? (2) Does the microgravity environment provide opportunities to study developmental processes better than they could be studied on earth? Virtually no information exists that bears on these questions. Few organisms have been kept in space through one life cycle—from fertilization through subsequent production of progeny. Only a relatively small number of organisms have been flown at all, the results have been inconsistent, and almost all of the experiments have lacked necessary controls. The situation is unfortunate because satisfactory answers could be obtained by flying a few model organisms, both animals and plants. Simple morphological examination should suffice as a preliminary screen. Ground-based research, involving the use of gravity equalization on a clinostat, can be used to identify developmental processes that are potentially gravity-sensitive, and so, are possible candidates for study in microgravity. There is also a need for ground-based research on the biological and biochemical processes involved in the developing systems that are chosen for space experiments.

Plant Gravitropism

Plant growth has a definite orientation with respect to gravity. Roots grow in a downward direction, while stems grow upward. Several processes are involved: the perception of gravity, its transduction into a physiological signal within the sensing cell, the transmission of the signal from the sensing cell to other regions of the cylindrical plant organ, and the differential growth of the two sides of the organ that determines whether it will curve upward or downward. The sensing of gravity is done by amyloplasts, starch-containing organelles contained in specialized cells, the statocytes. Since the density of amyloplasts is greater than that of the surrounding cytoplasm, they will settle to the bottom of the statocyte. The transduction mechanism that intervenes between amyloplast settling and signaling is unknown. Signaling is most likely done by growth hormones. The concentrations of growth hormones, including indoleacetic acid (IAA) and the gibberellins (GA), are higher on the rapidly growing side than on the slowly growing side of plant shoots that are stimulated by gravity. In addition, abscisic acid (ABA), a growth inhibitor, may be involved in the tropistic curvature of roots. The mechanisms of transduction, the roles of the various hormones, and the physiological mechanisms by which they stimulate growth remain to be elucidated. Both ground-based and spaceflight research is needed to resolve these issues.

GROUND-BASED AND SPACE RESEARCH

There is important research to be done on each of the 10 problems. Much of this research is best done on the ground, where the full repertoire of modern research techniques can be applied. Ground-based research is needed to elucidate the mechanisms underlying the various responses to gravity and to its absence. In addition, there are earth-based models for many of the biological effects observed in space. Some examples can be cited. Many of the cardiovascular responses to microgravity can be simulated by bed rest, by water immersion, or by other procedures that eliminate the differences in hydrostatic pressures along the body's long axis. Some aspects of muscle atrophy and of bone demineralization can be reproduced by bed rest or by limb immobilization. A clinostat, by continually reorienting the specimen relative to the earth-vertical axis, can eliminate the orientation cues provided by the gravity vector. Clinostats have been used to study the role of gravity in axial determination during early development, to examine the influence of hypogravity on tropistic and other responses of plants, and to estimate the discharge that otolith afferents would have in the absence of gravity.

In some biological systems, the effects of microgravity cannot be simulated on earth. The vestibular system is one such system where the long-term effects of weightlessness can only be studied in space. Microgravity conditions can be produced on earth during free fall or during parabolic maneuvers, for example, on airplanes or rollercoasters. Technical considerations, however, limit the duration of weightlessness on earth to several minutes at most. Clinostats can be used to simulate hypogravity, but their use has its interpretive difficulties. This is so because the required rotations about an earth-horizontal axis result in a mixing of intracellular contents, and for larger specimens, centrifugal forces, tangential forces, and a gravity-induced flopping of parts also occur. Clinostats will remain an important tool in gravitational biology, but any results obtained with these instruments must be verified in spaceflight. A similar conclusion holds for those fields where there are other earth-based models of weightlessness. The models seem plausible, and they reproduce many of the reported symptoms of spaceflight. Yet, there is simply too little empirical evidence to decide if they are adequate. One example will suffice. The cardiovascular response to microgravity should, according to both conceptual and experimental models, involve a transient increase in central venous pressure followed by a diuresis. The expected diuresis during spaceflight has not been documented. Measurements made during the *Spacelab-1* mission failed to confirm the predicted increase in venous pressure. There is a need to determine the adequacy of various models, and this will require a detailed comparison between earth-based and spaceflight observations.

Does the space environment provide a unique opportunity to study any of life's processes better than it can be studied on earth? Here, again, there is not enough experience to decide. More needs to be known about the kinds of biological adaptations that take place in space and whether they can be duplicated by models on earth. It is absolutely essential in this regard to be able to distinguish effects due to microgravity from those that are the result of radiation or other stresses of spaceflight.

We concentrate on the effects of microgravity. There are two families of models to be considered. The first attempts to eliminate the mechanical forces that affect a system because of the presence of gravity. The use of bed rest or water immersion in cardiovascular studies is an example. Should such models reproduce the essential features of the space environment, then those fields of space biology will largely become earth-based sciences, with space missions being used to verify results obtained in ground-based laboratories.

The second family of models is used in those situations where the effects of gravity cannot be eliminated on earth. These depend on a logical, rather than a mechanistic, analogy. An example is found in the vestibular system. Suppose one wishes to study the neural processes of adaptation to an altered force-motion environment. On earth there is no way to eliminate the influence of gravity on the otolith organs, except for brief periods. So one would need to study a logically analogous situation. Fortunately, there are a number of earth-based experimental paradigms that would allow one to do this. One of these involves having subjects wear reversing prisms or other optical devices. Another would have individuals live in a so-called slow-rotating room. By comparing a variety of such models with space observations, we can learn whether there is anything happening in space that cannot be reproduced on earth.

There is no way to decide these issues a priori. Both ground-based and spaceflight experiments are essential components of the research strategy and must be tightly coordinated. The earth-based part of the strategy is no more challenging than many large-scale programs in the life sciences. The spaceflight part of the plan is considerably more ambitious than any previously planned flight program in the life sciences. It should have the following characteristics. (1) There has to be an overall research plan that identifies important questions and provides a reasonable framework in which they can be answered. (2) Ground-based and space research have to be coordinated. (3) The mass of data that needs to be collected requires that researchers in space biology and medicine have continuous access to space. (4) The scope of the spaceflight experiments is such as to require focussed missions and a team-research effort in each relevant field. (5) The experiments have to be controlled. A variable force centrifuge (VFC) is essential. Ways of implementing the strategy will be considered in the Chapter 12.

It must be emphasized that the field of space biology and medicine is in its infancy. Relatively few biological experiments have been flown; most have not been part of a larger research strategy; and few of them have been adequately controlled or replicated. The experiments have demonstrated the qualitative effects that the space environment has on biological organisms, especially man. But, for the most part, they have contributed little to our understanding of basic mechanisms, to the clinical questions raised by manned spaceflight, or to basic biological questions. In contrast, the ground-based research in the various areas of relevance, whether supported by NASA or by other sources, has been of high quality. The main purpose of this strategy is to redress this imbalance and to determine if space is an important frontier for the study of biology and medicine. The solution is not to diminish support of ground-based research, but rather to enhance spaceflight research. Space biology and medicine experiments will continue to be flown, if only to guarantee the health and safety of astronauts. If properly planned, the experiments can make important contributions to both clinical and basic science.

2
Developmental Biology

INTRODUCTION

Traditionally, developmental biologists have considered their domain to encompass all aspects of the lifespan of an organism, from fertilization through aging. Topics of research have included gamete production, fertilization, embryogenesis, implantation (in mammals), the formation of organs (organogenesis), and a broad area including changes after birth defined as postnatal development. Moreover, developmental biologists are accustomed to asking experimental questions concerned with certain phenomena that occur at certain phases of development. For example, it is known that at some point after fertilization, different in diverse organisms, cells become committed to developing along a certain pathway. This restriction in fate is called determination. For instance, if the first two cells of a cleaving sea urchin embryo are separated, each may give rise to a complete, normal, but one-half-sized larva. But if one of the cells from the sixteen-cell stage is separated and raised in isolation, it does not give rise to a normal but one-sixteenth-sized larva; it develops into a specific subset of larval tissues. During early cell divisions in most animal embryos, there are gradual restrictions in developmental potentiality; this is not the case in plants. Sooner or later in all animals the cells in the embryo can usually give rise only to a certain tissue or organ. They have lost their plural potentialities. The second process of development is differentiation, an all-encompassing term that designates the processes whereby the differences that were "determined" become manifest. In other words, differentiation is the selective expression of genetic information to produce the characteristic form and functions of the complex, fully developed embryo. The mechanisms of determination and differentiation (i.e., selective gene expression) are two of the fundamental issues of early embryonic development that are at the cutting edge of current biological sciences. A third aspect of early development, the mechanisms whereby the determinations and differentiations occur at the right time to produce the normal organisms to which we are accustomed is called the formation of pattern. It is a complex and abstract way of saying that not only do they realize these fates, but they do so in the correct place at the correct time. These three issues, determination, differentiation, and pattern formation, are the cornerstones of normal embryonic development of all animals as well as plants.

It is difficult to visualize the entire developmental process at one time or in one organism, because the formation of the various tissues and organs (organogenesis) not only spans several developmental stages, but also continues after birth (or hatching) and into the natal period. Further, the transition from the neonatal period to adulthood is marked by fundamental developmental events, such as cytodifferentiation (cell specialization), developmental transitions (isoforms) at the molecular and possibly the cellular level, cell-cell interactions and inductions, the development and integration of many physiological and biochemical functions, and growth. Regenerative processes are fundamental developmental responses to postnatal tissue loss and injury. In many situations, developmental processes along with adaptive functions are responses to pronounced changes in the overall environment to which an individual is exposed.

In this chapter two basic questions are considered. (1) Can organisms undergo normal development under conditions of microgravity, or are there gravity-sensitive phases or processes, e.g., fertilization, that are abnormal in microgravity such that repetitive life cycles do not occur? (2) Does the unique microgravity environment of space provide a tool to study developmental phenomena better than, or exclusive of, similar studies carried out in ground-based experiments? In approaching such questions, the committee was impressed at the outset with the paucity of controlled experiments that have been carried out in space. A few additional ground-based experiments using a gravity-compensated approach such as the clinostat have also been performed. Only one plant and no animal has ever been carried through one complete life cycle—fertilization through subsequent production of progeny—in the microgravity of space. In fact, relatively few organisms have been flown at all, and the results of such experiments have been inconsistent. Both normal development and developmental abnormalities have been observed, depending on the organism. Evaluation of the data, however, reveals that a lack of in-flight controls maintained a 1 g in almost all cases, and minimal knowledge of the effects of stress on developmental phenomena therefore exists. Stress and/or adaptational effects on plants may lead to failure of normal developmental and reproductive pathways independent of microgravity effects. Similarly, stress and adaptational effects could lead to problems in the physiology encountered in the environment of space as they might relate to specific kinds of developmental events. Finally, while the genetic effects of radiation in space have been analyzed, and there is general agreement that no synergism exists between radiation and microgravity, the effects of radiation, especially that by high-energy particles (HZE radiation), on morphogenesis of specific structures such as the brain remain unknown.

In what follows, strategies for evaluating the influence of gravity, or more specifically, microgravity, on the processes of development in plant and animal systems are discussed. Different types of organisms have undoubtedly evolved different strategies to deal with gravity, or its absence, and it is customary among developmental biologists to discuss and evaluate certain questions based on the kind of organism studied. For example, some invertebrate organisms display highly ordered patterns of cleavage, which allow precise studies on cell lineage but are less well suited for studies on tissue interactions. Few nonmammalian organisms provide a model for understanding mammalian development, which, for the most part, must occur inside of the female. Thus, for simplicity of presentation, this chapter is divided into subdivisions according to organism type. That representing animal development includes further subdivisions such that invertebrate organisms, lower vertebrates, and mammals are discussed separately. Since one of the most promising areas of research is concerned with the postnatal development of animals, the latter topic is discussed in a separate section. Plant development is discussed in another section. Finally, there is a separate discussion of developmental genetics and radiobiology, followed by a summary of the committee's recommendations.

MAJOR SCIENTIFIC GOALS

The overall goals for the study of development in space are twofold:

1. *To evaluate the capacity of diverse organisms, both plant and animal, to undergo normal development from fertilization through the subsequent formation of gametes under conditions of the space environment.* It is hoped that a data base regarding the ability of organisms to develop through multiple generations will thus be established.
2. *To evaluate the use of the space environment as a tool to study specific developmental phenomena in ways that cannot be accomplished, or can be accomplished only in part, in ground-based research.*

DEVELOPMENT OF ANIMALS

Invertebrates

Invertebrate animals, those without backbones, have been used to investigate the basic processes of development since the beginnings of modern biology. While the organs that form in these creatures can be quite different from those of vertebrates, they serve the same purposes of nutrition, respiration, reproduction, and the like, and are formed during early development by the same fundamental processes.

The supposition of most scientists is that changes in gravity, or exposure to microgravity, will have little effect on these processes. This is especially true for aquatic invertebrates, which often are not oriented with respect to gravitational fields as they are buffeted by the physical forces in oceans, lakes, and rivers. Terrestrial invertebrates are exposed to 1 g, and certain of their developmental processes might be more susceptible to microgravity. However, judgments remain largely intuitive because of lack of information.

The classical literature contains many experiments in which the mechanisms underlying early development have been studied through application of centrifugal force to developing marine invertebrate eggs. Centrifugation at several hundred times the force of gravity has little or no effect (occasionally there is twinning) on development, in contrast to the situation for frogs and birds. Localizations of various substances thought to affect determination of early cell types are generally influenced by these centrifugal forces, which are far in excess of those encountered in space vehicles. While some of these older experiments may need reevaluation, the use of microgravity would not obviously benefit investigations of this type; ground-based research is more appropriate at present.

Because of documented changes in bone calcium in mammals exposed to microgravity, studies on the formation of skeletal hard-parts in invertebrates during later development may be worth pursuing. The formation of exoskeletons (shells and the like) and endoskeletons (internal spicules of echinoderm larvae are an example) in invertebrates usually involves calcium carbonate; the bones of vertebrates are formed from calcium phosphate. In both instances, however, the insoluble calcium salts are deposited on a proteinaceous matrix, or scaffolding. It is thought that the matrix serves as an armature that determines the overall outlines of the skeletal element, and is also crucially involved in the actual deposition of the insoluble calcium salts. The matrix of vertebrates is a mixture of very high molecular weight macromolecules composed of both protein and carbohydrate that are called proteoglycans and glycoproteins. The precise chemical details of just how the calcium forms crystals at the right time and at the right place are still a mystery. What we do know is that the skeletal elements of both vertebrates and invertebrates are not simply crystals, but intimate associations of both the organic glycoprotein matrices and the inorganic salts. Some research has been carried out on the matrix proteins and the process of biomineralization in invertebrates, including the outer exoskeleton carapace of crustacea, shells of glycoproteins that are high in acidic amino acids. Since biomineralization is not well understood in either higher or lower animals, it may be argued that invertebrates could very well serve as a useful "model system" in which to investigate the basic processes of the formation of calcified tissues.

Many invertebrates also possess sensory organs that are used to sense the orientation of the organism in the earth's gravitational field, and these are analogous to vestibular functions of vertebrates. One might inquire whether gravity-sensing organs, like statoliths, develop normally in microgravity. This is a little like asking whether an eye can develop in the dark. In every case in which the development of a sensory organ has been followed in the absence of the particular stimulus that is later sensed by this organ, development has been normal. In a similar way, the development of statoliths and other invertebrate gravity-sensing organs may not be affected by microgravity. We simply do not know.

Scientific Goals

The primary scientific goals for the study of invertebrate developmental biology in space are:

1. *To determine whether microgravity has any effects on the basic processes of early development from fertilization through larval formation.*
2. *To determine whether microgravity alters the normal development of a larval invertebrate.*

Scientific Objectives

1. *To obtain visual observations on space-based living specimens as well as microscopic evaluation of fixed material to determine if development is "normal" compared to ground-based and 1-g centrifuge controls maintained in space.*
2. *To conduct both ground-based and space-based (using a 1-g centrifuge control) experiments designed to measure the effects of microgravity on the development of various organ systems including bone.*

Measurement requirements

These objectives could best be met by making morphological observations on the development of appropriate organisms and comparing them to ground-based and space-flown, 1-g centrifuge controls. Organisms need to be chosen on the basis that a great deal is known of their biology and that simple observations of morphology can be revealing. Thus the objective is to choose appropriate organisms and allow them to develop in microgravity.

Among the terrestrial invertebrates, the nematode, *C. elegans*, would appear suitable. The other leading contender, the diptera (fly), is much more difficult to study and to evaluate with respect to its early development. Hence, the goals of investigating the effects of microgravity on normal developmental processes can be best served by using the soil nematode. These simple organisms are self-fertilizing hermaphrodites that undergo development very quickly under simple conditions. There is a great deal known about their genetics and about their normal development. The precise destiny of every single cell is known throughout the brief period of embryonic development, and the number of cells in the organism is absolutely constant and arranged with unvarying geometric precision. Abnormalities that occur may be diagnosed for the precise time and place of the developmental accident because of this stereotyped developmental pattern. Experimental manipulations would consist only in fixing embryos at various stages of development so that their morphology could be compared to appropriate controls by using microscopic and histological techniques.

Since invertebrates do form skeletal hard parts of great variety, the effects of microgravity on establishment and formation of the skeleton might offer a convenient way to carry out controlled observations on the effect of microgravity on biomineralization. Many suitable marine invertebrates develop rapidly in a closed aqueous environment, require no sources of nutrition, and are so small they can be handled much like microbes, which simplifies the taking of samples for fixation and subsequent microscopic analysis. The goal of these studies is to increase our general knowledge of biomineralization since this is an important area of basic research. Spaceflight experiments can be used to study the influence of microgravity of skeletal development. There is also a need for ground-based research on the basic mechanisms of biomineralization.

Echinoderms are thought to represent the invertebrate phylum most closely related to the vertebrates (including humans). Embryos of the sea urchin or sand dollar can be studied on the ground. They can also be fertilized on the ground, transported to space, and raised in automated culture chambers. Samples can be removed from the culture and fixed automatically for later examination on the ground. Complete development of these forms, including the formation of the skeleton, takes about 2 days. The best studied species is the sea urchin, *Stroonglyocentrotus purpuratus*, which has a hearty embryo that may well be optimum for the studies envisaged.

Lower Vertebrates

Several animal eggs including those of birds, turtles, and amphibia, display an unequivocal response to gravity in establishment of the embryonic axis. For example, while frog eggs within the ovary are randomly oriented with respect to gravity, fertilized eggs, fertilized rapidly, orient so that the darkly pigmented animal hemisphere is opposite the gravity vector. This rotation allows for reorganization of the egg cytoplasm, which leads to establishment of dorsal-ventral polarity. Frog eggs normally display a bilateral symmetry specified by the site of sperm entry; the dorsal lip (site of gastrular invagination) forms opposite sperm entry. Inverted eggs, for example, display dramatic rearrangements of cytoplasmic components, and, in some instances, these rearrangements correlate with specific pattern reversal. These results have led to several models to account for the mechanism(s) by which the presumed gravity-derived rearrangements change a radially symmetrical egg into a bilaterally symmetrical one.

A test of the role of gravity in cytoplasmic rearrangements using amphibian eggs could be conducted ideally in spaceflight. Fertilized frog eggs were flown on *Biosatellite II*; normal morphogenesis occurred. However, eggs were exposed to microgravity only after the first cleavage, by which time cytoplasmic rearrangements no longer occur even under conditions of inversion. As an alternative approach, several laboratories have conducted clinostat experiments on fertilized frog eggs. In all cases, there was little or no effect on subsequent development, even when eggs were fertilized on the clinostat. Large percentages of the clinostatted eggs displayed normal axial structure morphogenesis. Thus, one might predict that normal development in the microgravity environment of space would occur, and that gravity-driven cytoplasmic rearrangements are not essential. Interestingly, the location of the dorsal lip in clinostatted eggs was random relative to the sperm entry point suggesting that simulated microgravity uncouples the natural sperm entry site-dorsal lip polarization.

In chick embryos, the positioning of the body axis also is known to be affected by gravity. During the passage of the fertilized egg down the oviduct, the egg axis is always formed with a definite orientation with respect to gravity, and some of the cells of the embryonic blastodisc delaminate and then "float" into the fluid between the yolk and the very early embryo. This process, termed hypoblast formation, may be affected by gravity. Further, removing the egg from the oviduct and placing it in a new orientation with respect to the earth's gravitational field causes changes in the orientation of the primary body axis. Clearly, it is of interest to ask if a plane of bilateral symmetry can be established in eggs passing down the oviduct in microgravity, and whether the hypoblast layer (essential to normal development) can form under such circumstances. Birds form all the organ systems formed in mammals, but do not require the presence of the mother for development, nor is there any postnatal nurturing of any consequence. Hence, one might argue that birds are a vastly superior animal for investigations of the effects of microgravity on homeotherms. The influence of microgravity on organogenesis, including the formation of the major organs, could easily be investigated in fertile chicken eggs. In particular, since bone metabolism is of very great importance in space travel and chick embryos do form cartilage and bone in the same way as mammals, the formation of bones during embryogenesis of chick eggs is of interest.

Finally, the developing bird embryo is surrounded within the shell by a complex of vascularized membranes, collectively called the chorioallantoic membrane, and this membrane is important in calcium metabolism and also serves as the medium for gas exchange in the developing embryo. The effects of microgravity on the formation of the shell (composed of calcium salts) as well as on the development and function of these membranes and on the skeletal system has not been investigated.

Scientific Goals

1. *To determine if axis formation is normal in amphibian eggs fertilized in microgravity.*
2. *To determine if avian development, including axis formation, chorioallantoic membrane formation, and organogenesis, is normal in microgravity.*

Scientific Objectives

1. *To make visual observations on living material as well as microscopic evaluation of material fixed and sectioned at various stages to determine if development is normal.*
2. *To measure the effects of microgravity on development of various organ systems, including bone.*

Measurement requirements

The primary requirements of initial studies include visual observations on living and/or fixed frog and avian material to determine if development is normal. Most, if not all, of the potential questions and/or models concerned with postfertilization events in amphibians, as well as events associated with ovulation and oocyte maturation, could be answered by a spaceflight experiment of a few days duration. Such an experiment ideally would involve the induction of ovulation, fertilization, and subsequent development through organogenesis in space. This kind of experiment is scheduled to be flown in space shuttle experiments by both the European and U.S. space agencies. Unless the outcome of these experiments is radically different from that anticipated from ground-based work, it is likely that fertilization and subsequent development will occur normally under microgravity conditions. Additional experiments on the putative role of gravity in establishing the sperm entry site-dorsal lip polarity could perhaps be done at least as well in continuing ground-based experiments, which should be encouraged.

The conduct of experiments on avian eggs similar to those described above would involve a determination of whether or not any axis forms in eggs exposed to microgravity during the first 16 hours after fertilization, while eggs pass through the oviduct. However, this simple measurement is in fact very complex. Chickens are notorious for shutting down egg laying whenever they are disturbed, and there are a large number of behavioral and environmental factors, including potential effects on the endocrine system due to stress, that could interfere with the conduct of the experiment. In view of technical difficulties, plans to evaluate the effect of microgravity on axis formation in amphibia would command higher priority.

In contrast to the problems suggested above, it is a relatively simple matter to send fertile avian eggs into space, requiring only an incubator and a system for fixing the eggs so that they can be examined later on the ground. Since the skeletal system is so close to that of mammals, and the requirements are much simpler, the development of bones during avian embryogenesis is the preferred model system for learning about the effects of microgravity on the development of various organ systems including bone. In addition, there is a tremendous amount of background on the developmental anatomy and physiology in the developing chicken. Of course, experiments should include a ground-based control and the 1-g centrifuge in space.

Experiments in which fertile hens' eggs are sent into space and are periodically fixed for microscopic examination on the ground are highly recommended for initial exploratory types of studies. Observations of all organ systems by dissection and preparation of histological specimens is recommended, with particular emphasis on the bones and chorioallantoic membranes.

Mammals

Early Mammalian Development

The development of mammalian embryos occurs within the body of the mother. Consequently, to understand the effects of the space environment on mammalian development, it is necessary to be concerned also with physiological responses of the female to a microgravity environment. For example, it is clear from previous spaceflights that crew members have experienced redistributions and volume changes in body fluids, and changes in the concentrations of plasma electrolytes, notably calcium and potassium. These kinds of changes could affect the composition of oviductal fluid and uterine or vaginal secretions, which could have effects at the level of fertilization as well as early embryogenesis. Similarly, marked changes in the concentrations of electrolytes to which the embryo and developing fetus are exposed could be teratogenic and even lethal.

Cosmos 1129 carried five female and two male rats for 19 days in space. The rats were intended to mate in space, resulting in pregnancies of 1 to 16 days duration before reentry. Birth was to occur on the ground. Neither the flight animals nor synchronous controls exposed to the simulated stress of reentry successfully gave birth. Simulated flight research at Ames Research Center, performed to obtain information on possible reasons for the reproductive failure of both flighted rats and synchronous controls during the *Cosmos 1129* experiments, showed that reproductive failure was not due solely to the stresses of launch and reentry.

Reproductive failure could result from aberrant preimplantation events, suggesting the need to evaluate more closely the effects of microgravity on these events. When the preimplantation embryo reaches the uterus, it must have attained two goals: (1) it must consist of a minimum number of cells and be at the developmental stage that will be compatible with survival in the uterus, and (2) the first goal must be reached when the uterus is capable of supporting implantation of the embryo.

During cleavage, the human embryo's cell number increases to produce the "morula," which consists of 16 to 32 cells (60 to 70 hours after fertilization). The embryo then "cavitates," which is a process with two major outcomes: (1) the production of the blastocoele and (2) the creation of two cell types, trophectoderm and inner cell mass (ICM). The embryo is now a "blastocyst." The trophoblast is the only cell type that can "implant" the embryo into the uterine lining, while the ICM is the only cell type that can form the embryo proper. For normal embryonic development to occur, the ICM must consist of a least 4 to 8 cells. This will not happen if cleavage is delayed so that less than 16 cells have been produced by the time the embryo cavitates. Consequently, the proliferation rate—the rate at which cleavage produces new cells—can affect the size of the ICM, which in turn affects the ability of the ICM to form an embryo.

Previous space missions have failed to reveal any effects of the space environment on cleavage rates and early stages of development in nonmammalian embryos. Thus, it does not seem likely that microgravity would have direct effects on cleavage in mammalian embryos. On the other hand, the drop in plasma potassium observed in crew members deployed in space for 3 to 4 weeks or longer is worrisome from the standpoint of reproductive failure because this ion can regulate the rate at which preimplantation mouse embryos develop into blastocysts. If the rate of embryonic development becomes too much out of step with the uterine cycle, implantation can be adversely affected. In addition, the concentrations of electrolytes (notably potassium, calcium, and sodium) can affect sperm motility and other features of sperm function and, so, interfere with its fertilization potential.

Mammalian Development—Organogenesis

The interval between the time of implantation and birth can be roughly subdivided into two main periods—the period of organogenesis and the period of fetal development. In human development, the period of organogenesis occurs between the third and eighth week of embryonic life. The period between the ninth week and birth is called the fetal period. The dominant developmental activity during the period of organogenesis is the structural establishment of the major organ systems of the body. This occurs as a well-ordered sequence of events. By the end of the eighth week, the structural basis for most of the major organs in the body has been established, and the embryo as a whole has an unmistakably human appearance. However, these newly formed organs are functionally and biochemically immature. During the fetal and neonatal period, these structures undergo both functional maturation and continued structural development to accommodate the increasing functional requirements of the organ.

Each organ or structure has specific times in development when it is extremely sensitive to the effects of exogenous influences or defective gene expression. Sensitive periods during which environmental disturbances can lead to morphological anomalies are known in considerable detail. Less is known about the times when functional development is highly sensitive to exogenous influences, but, in general, the sensitive periods during which disturbances can lead to functional disturbances occur later in development than those leading to gross structural anomalies.

During the period of uterine development, mammalian embryos display no gravity orientation and organogenesis and fetal development might be expected to be relatively insensitive to a microgravity environment. The caveat is that because of documented changes in bone calcium loss, muscle atrophy, fluid shifts, and decreases in plasma volume in humans exposed to microgravity, indirect effects of such changes on the development of certain organ systems could become a problem.

Scientific Goals

1. *To determine whether a male and female mammalian species can copulate in space.*
2. *To determine whether or not completion of the many developmental processes that occur during preimplantation development, organogenesis, and fetal development can occur normally in a microgravity environment.*

Scientific Objectives

1. *To make visual observations on living material to determine whether animals can successfully mate in space.*

2. *To make visual observations on living material as well as morphological and microscopic observations on fixed material at various developmental stages to determine if development is normal.*

3. *To establish an experimental system in which cell lines can be induced at the will of the investigator in order to distinguish between the effects of spaceflight on cell proliferation and differentiation.*

Measurement requirements

1. The house mouse, *Mus musculus*, is well suited for most of the proposed work although the possible use of small marsupials should be considered. Use of the latter would necessitate that supporting ground-based studies be undertaken and/or extended. One advantage of using marsupials is that they exhibit short gestation periods and complete embryonic and fetal development in an extrauterine environment.

Successful mating is easily confirmed in mice by checking mated females for vaginal plugs.

2. If copulation is successful, additional developmental studies could be accomplished using the same females. If copulation is not successful, then one would need to fly female mice that had recently copulated on the ground. This would prohibit studies on the process of fertilization, but would allow all other observations. Pregnant animals would need to be sacrificed at various times, and developing embryos and fetuses would need to be fixed for subsequent microscopic and histological analysis. If anatomically normal offspring can be obtained from pregnant animals, many important questions would have been answered. If, on the other hand, abnormal embryos and fetuses were obtained, intensive investigations would be required to sort out the variables that led to defective development. From the standpoint of developmental design, this can become a very complex question, dependent in part on the proportion of abnormally developing animals, and could require a full teratological screening protocol of the sort used to evaluate the safety of experimental drugs.

3. As a third experimental system, cell lines that can be induced to differentiate at the will of the investigator have the potential of enabling one to distinguish between the effects of spaceflight on cell proliferation and cell differentiation. The mouse embryonal carcinoma stem cell lines are well suited to this type of investigation. The cells can be maintained indefinitely by serial passage on feeder layers of mitotically inactivated fibroblasts. When the cells are passaged without feeder layers, they mound up and differentiate into mature cells from all three germ layers (nerves, muscle, teeth, epidermis, intestinal epithelium). If reproductive failure were to be observed during on-board mating experiments, then the use of this cell line could enable a distinction to be made between an effect on cell proliferation per se and an effect on the ability of a cell to undergo phenotypic change like that typical of cell differentiation.

Postnatal Development

There is no information as to whether or not microgravity would alter postnatal developmental events. As a prelude to further discussion, it is instructive to summarize some of the major postnatal developmental phenomena. These can be subdivided into three broad categories: (1) processes that represent continuations or terminal phases of prenatal developmental events, (2) developmental processes that are characteristic of the normal growing and stable postnatal body, and (3) developmental processes that are elicited by trauma or major changes in the functional environment. There is a continuum between some of the developmental events in category 3 and responses that are usually considered to be adaptive in nature.

The muscular system is a good example of postnatal development as a terminal phase of an embryonic process. In most newborn mammals, the muscles are almost all present in their final morphological configuration, but a typical muscle is still incompletely developed in many respects. Gross contractile properties reveal that neonatal "fast" muscles actually contract very slowly. With time, the muscle contractions speed up and stabilize at normal adult levels. Paradoxically, the soleus muscle of the guinea pig, a classical slow muscle, is fast at birth. In this case maturation consists of a slowing of the contraction time. These changes in gross contractile physiology are correlated with predictable changes in histochemical properties (especially myosin ATPase). At birth, the fibers of most muscles stain homogenously, and as they become functionally stable, distinct populations of muscle fiber types with fast and slow myosin and high or low oxidative activity (as reflected in numbers of mitochondria and mitochondrial enzymes) differentiate. Many of these changes are indicative of shifts in myosin isoforms (developmentally regulated subtypes of enzymes) and, as such, reflect changes in gene expression.

These changes, in turn, depend largely upon neural input and are a good example of cell-cell interactions in development. Many aspects of the motor nervous system are immature at birth, and the postnatal maturation of the neuromuscular junction involves functions and activities such as recognition and stabilization of synaptic units (neuromuscular junctions) at levels ranging from competition among terminals from different nerve fibers for the same site, the differentiation and stabilization of acetycholinesterase molecules and acetylcholine receptors, and the maturation of the nerve and muscle, as well as of the transmission of a nerve impulse, in lamina. In many species, muscle spindles and the afferent feedback system are just becoming established at birth.

The muscle fibers themselves are still immature. Small numbers of new muscle fibers are still formed from myoblasts in the early neonatal period. The proportion of satellite cells, which are precursor cells for muscle fiber growth, drops from about 33 percent at birth to 4 percent at maturity. The muscle fibers grow in length by the terminal addition of sarcomeres (protein contractile units) and, in cross section, by the formation of new bundles of contractile filaments. The capillary vascular bed (small blood vessels) around a muscle fiber becomes more or less dense according to the differentiation of the muscle fiber. Metabolic properties of the muscle also change as the muscle fiber differentiates and undergoes functional specialization. At a higher level, the development of the internal connective tissue framework and the location of tendinous attachment to the bone are coordinated with the growth and functional environment of the tissues surrounding the muscle.

Changes of similar complexity accompany the postnatal development of most other organs, but in the interest of brevity, only those developmental steps that might be especially sensitive to the effects of microgravity will be outlined here. On the basis of what is known about postnatal muscle development, several aspects would be very sensitive to the effects of microgravity. Because of the normally continuous impulses between the muscle and the central nervous system, the development of postural muscles, such as the soleus, would be expected to be most noticeably affected. NASA research involving the tail suspension model in rats has shown that the soleus muscles are subjected to severe atrophic changes when gravity loading is removed.

The skeletal system, like muscle, is exceptionally sensitive to microgravity in the adult, and certain aspects of postnatal development could be equally sensitive. The general pattern of the skeleton is genetically determined and is laid down early in embryonic development, but many of the finer anatomical features of the bones and joints reflect the mechanical environment in which they develop. Many of these effects may be mediated through the electromechanical properties of bone and are manifested by the deposition and resorption of bone. Attention should be paid to the formation of the trabecular patterns in normally weight-bearing bones, as well as to the functional morphology of ball and socket joints. Of particular importance is the potential for mechanical problems when skeletons that have developed in space are subjected to a steady gravitational environment.

The role of connective tissues and fascia of the body in coping with gravitational stresses and the role of gravitational forces in shaping the connective tissues are poorly understood at best. Although the adult connective tissues are virtually ignored by contemporary developmental biologists, they are among the first tissues to react to mechanical stresses and are important as mediators of mechanically generated morphogenetic phenomena. One of the more obvious examples is the role of tendons and ligaments in the shaping of normal bony processes.

The cardiovascular system and the fluid compartments of the body, in general, are normally adapted to life at 1 g. Certain components of the blood, vascular, and the lymphatic systems are constructed to facilitate the movement of blood or lymph in a direction that is opposed by gravity. Structural adaptations, such as the valves of venous or lymphatic channels, are specifically designed to prevent fluid reflux under normal gravitational conditions. The pronounced fluid shifts to the head that are commonly experienced by people in space provide ample evidence of the role of gravity in the fluid dynamics of the body.

The developmental physiology of control of blood pressure is a potentially rewarding field. The functional development of the carotid sinus is of interest. A developmental question that could be easily answered is the role of gravity in the formation of venous and lymphatic valves. One would merely have to observe the structure of veins and lymphatics of rodents raised from embryos in space for an answer to that question. Loss of cardiac mass and possible fibrosis have been suggested as potential negative adaptations to life in space. Similar adaptations might occur during development. How, or if, these would relate to the growing heart, would, for example, a cardiovascular system that matures in microgravity have a reduced capacity? Could the system adapt to terrestial conditions?

One effect of spaceflight is a significant reduction of red blood cell mass. In adults, the adaptation involves, among other mechanisms, a reduction in erythropoiesis or red blood cell formation. This is one of the more active postnatal developmental systems. The regulation of erythropoiesis in animals raised in microgravity poses several intriguing questions.

Many aspects of neural development continue after birth. The general developmental problem is whether there is a well-defined time during which certain structural and functional aspects of sensory systems must be set into place. A major function of postural systems is to allow animals to stand in the face of gravitational forces. Postnatal maturation of the motor nervous system was discussed along with muscular development, and the vestibular system is being treated in depth in Chapter 4. Suffice it to say that the ability to compare the development of postural control in the presence or absence of gravity opens up new and exciting possibilities.

Scientific Goals

1. *To determine whether postnatal development is normal in microgravity, with particular emphasis on development of the musculoskeletal, cardiovascular, nervous, and reproductive systems.*

2. *To determine if the organ systems referred to above that have developed in space are able to function normally after return to a 1-g environment.*

Scientific Objectives

1. *To assess the specific effects of microgravity upon specified mammalian structures and functional systems.*

2. *To monitor the effects of return to 1 g on animals that have undergone development in space.*

3. *To establish whether mammals can successfully suckle in space during the preweaning period.*

Measurement requirements

1. These various scientific objectives could be addressed by making simple observations of carefully controlled "normal" animals maintained in microgravity. Systems that are found to develop abnormally should be the subject of further experimental analysis. The structure and functional systems that should be examined carefully are: (1) the postural muscles, (2) muscle spindles, (3) weight-bearing bones and joints, (4) intervertebral discs, (5) the architecture of the connective tissues to the body, (6) the structure of blood and lymphatic vessels and the heart, (7) the development of control of blood pressure, (8) red blood cell production, (9) late-developing components of the central nervous system, especially those components related to coordination and balance, (10) the development of circadian (daily) rhythms, and (11) the development of the reproductive cycles. Specific features of these systems that are likely to be sensitive to microgravity effects have been described in the previous section.

2. There are two primary reasons why animals that have undergone early development in space and returned to 1 g should be closely monitored. (1) Developmental deficiencies might be more clearly manifested in a 1-g environment, and (2) adaptation to 1 g of such animals could result in injury, such as stress fractures or muscle degeneration, that would have to be repaired by healing or regenerative processes.

As in previous sections, the methodology required to carry out the studies for objectives 1 and 2 would involve visual observation of living animals and the fixation of specific tissues and organs at appropriate times for subsequent visual, microscopic, and histological examination. As an adjunct to these morphological studies, on-board measurements of some parameters (e.g., blood pressure) in living animals as well as photographic techniques to study behavior and allow visual monitoring of organ function (e.g., limbs) would be useful.

While investigating many of the problems and processes mentioned above, one must be cognizant of the potential impact of other secondary factors that could influence the results or the interpretation of these results. Of prime importance is nutrition and altered dietary requirements of animals subjected to the stresses of spaceflight, including the microgravity environment. Altered patterns of hormonal secretions and biological rhythms may also be variables that must be considered when animals in space are compared with their terrestrial counterparts.

3. Nutrition poses a special problem for very young postnatal animals, which have critical and often rapidly changing nutritional requirements. In mammals, it must be established that they are able to suckle properly during the preweaning period. If this proves to be a problem with standard laboratory rodents, it might be worthwhile considering marsupials, in which there is a firm bond established between the newborn individual and the maternal teat. Even if the mechanical act of suckling proves to be successful, it is important to ascertain that the quantity and the quality of the maternal milk are appropriate and comparable with that of earth controls.

Newborn birds would not be subjected to the potential problems of obtaining nutrition from maternal milk, but they, too, could be subject to nutritional disturbances resulting from altered requirements. Even on earth, poultry raisers change the formula of the diet of young birds at different times for optimal growth and development. In space, nutritional requirements would have to be carefully studied.

A good example of a potential nutritional problem is calcium intake. Should the calcium content of food be higher in both birds and mammals in light of the greatly altered calcium dynamics in microgravity? Mammals could pose a special problem—would maternal milk in microgravity contain a higher or lower concentration of Ca^{2+} than normal?

In mammals, the effect of spaceflight upon other components of maternal milk, e.g., growth factors and antibodies, could be a critical variable. It might be necessary to study the composition of milk formed by spacebound lactating females. Another option would be artificial feeding with milk of known composition.

From the practical standpoint it would be useful to separate problems of the sort outlined above that are due to microgravity from those that are due to the general environment of spaceflight—including stress from takeoff, vibration, and so on. The extent to which these need to be investigated in the context of this section depends upon the degree of precision required in the analysis of the effects of spaceflight upon postnatal developmental events, in general. This is likely to vary considerably depending upon the nature of the problem.

DEVELOPMENT OF PLANTS

Results from both Soviet and American experiments show that cytological abnormalities have been encountered frequently in various organs examined from plants grown in spacecraft. In many instances, the anomalies seem to have arisen from adverse growing conditions, especially water stress; but in some experiments the effects have probably been attributable to the space environment. Clearly for the short term, it is of the greatest importance to investigate this further, since the competence for executing normal mitosis, meiosis, karyokinesis, and cytokinesis is a prerequisite for long-term growth of plants in space. Moreover, the influence of microgravity on the fundamental processes of orderly replication of genetic material and increase in cell number must be established before other experiments on growth, organogenesis, and development can be interpreted fully.

Current research in the developmental biology of higher plants in space can be focused on the following questions: (1) How do the meristems function to produce the differentiated tissues and organs of the plant. (2) How does a cell within the plant grow in an oriented way along a preferred axis and then differentiate as one of the approximately 12 cell types that constitute a higher plant?

To determine the way in which terminal meristems of the plant function, investigators traditionally have examined the following questions: (1) Does the meristem contain permanent or persistent initial cells that are the progenitors of all cells in the organ? (2) If initial cells exist, what is the lineage relationship between them and the derivative structures? These questions have been addressed in ground-based studies by application of the techniques of histology, cytochemistry, cell cycle time determination, mutagenesis, and clonal analysis. From these studies, it is clear that from one to many initial cells occur in the meristem of different species, that they may be permanent and persistent, that they need not be continuously mitotically active, and that the lineage relationships are sufficiently precise to be specified in a predictable manner.

The principal analytic approach used to determine how the cell wall specifies cell growth and shape has been to examine growing cell walls by a variety of light or electron microscopic procedures. These have revealed that the position and axis of the mitotic spindle are determined by the orientation of a preprophase band of microtubules (mt), which also determines the position of the new cell plate. Microtubules orientation also determines the orientation and spacing of the cellulose microfibrils (mf) that are the principal strengthening components in the cell wall. Orientation of the mf specifies the axis of growth of the cell as it enlarges.

A variety of possible test systems, making different demands for in-flight facilities and requiring different durations for the completion of a cycle of observation, is available. For example, suitable material for the study of somatic cytology would be seedling roots of barley, a monocot, and those of corn and oat, while other plants would be required for studies on reproductive cytology. Studies on cleavage planes, cell growth, and wall morphogenesis may be performed best on yet other plant species. Two plants, *Arabidopsis thaliana* and *Azolla* (*A. filiculoides* and *A. pinnata*), are especially attractive. They have been used to obtain much of the current results on plant development, and there is good baseline data for these species. They are both small plants with rapid growth cycles. The result is that much can be learned on short-duration flights, and the effects of microgravity on single life cycles and on multiple generations can be explored on longer flights. These species can be viewed as "model systems" to obtain initial data on possible effects of microgravity on the several questions concerned with plant development.

Arabidopsis grows 10 to 30 cm tall, has a life cycle of about 35 days, is self-fertile, and produces up to 40,000 seeds per plant. Its genome is the smallest of any flowering plant and only 20 times that of *E. Coli*. Many morphological and biochemical mutants have been isolated and mapped to the five linkage groups. *Arabidopsis* can be regenerated from protoplasts and transformed by DNA introduced into cells by the Ti plasmid of *Agrobacterium tumefaciens* associated with crown gall tumors.

Azolla is a floating water fern that produces roots from the lower surface of its horizontal stem. Each root grows to a length of about 5 cm. All cells in the root are derived from a single tetrahedral apical cell. There is a precise lineage relationship between the apical cell and the derivatives, and a narrow range of total cell number in the root (about 15,000). It should be pointed out that the attractiveness of *Azolla* as outlined above is minimal if a floating water fern cannot be cultured properly in microgravity. In such cases, the ground fern *onoclea* might be considered, but additional earth-based experiments would be required to provide baseline data.

Scientific Goals

1. *To determine how meristems function to produce the cells, tissues, and organs of the plant.*
2. *To determine how cell shape, which in the absence of cell movement is the basis of organ shape, is determined.*

Scientific Objectives

1. *To examine the effects of microgravity on plants raised in space for at least one and preferably several life cycles.*
2. *To establish whether a specific level of gravity and/or other orienting forces is needed at any stage in the normal development and morphogenesis of plants.*
3. *To study the sensitivity and responsiveness to gravitational forces at various levels of plant organization (isolated cells, tissues, organs) and at various developmental stages.*

Measurement requirements

Progress in this field requires the identification of appropriate species and experimental methods. Some of the criteria for choice of species are small size, predictable pattern of development, and availability of mutants. Promising techniques include x-ray mutagenesis for clonal analysis, antibodies, recombinant DNA technology, and Ti-plasmid mediated gene transfer.

Prolonged growth in space, through at least one and preferably several life cycles, should be examined as soon as possible. Effects may be cumulative over several generations. The U.S.S.R. seed to seed experiment with *Arabidopsis* began with a seed that had developed in a 1-g environment. Ground-based studies on root development have already provided an adequate base of data, so that microgravity effects on cell lineages could be determined at this time. Additional baseline data on organ development in *Arabidopsis* at 1 g would be needed if the initial experiment in a microgravity environment indicated effects on cell division, cell wall formation, or growth. The required ground-based observations would include clonal analysis of the *Arabidopsis* shoot using variegated color mutants, lineage analysis of root development, and comparison with *Azolla*. To analyze the potential role of microtubules in the developmental processes referred to above, it should be possible to alter the amount and availability of tubulin by introducing additional tubulin genes into *Arabidopsis*. Such transformed plants could also be examined under microgravity conditions.

The above experiments should be capable of demonstrating the extent to which higher plant development is affected by the absence of gravity cues. A question of particular interest is whether plant cells require a specific level of gravity and/or other orienting forces at any stage in morphogenesis or development. Thus, while plant cells can respond to gravity cues, must they respond? What constitutes the minimal gravimorphogenetic responsive unit? Can single isolated cells behave in a gravimorphogenetically responsive way? It may be that the degree of sensitivity or responsiveness varies at different levels of organization or stages of morphogenetic complexity.

This could be studied by the use of a variable gravity centrifuge in space. The minimum gravity force required for normal development can be determined, as can the threshold force needed to produce any detectable response.

All stages of the life cycle of *Arabidopsis* are amenable to experiments of this type. Because it can be grown as a tissue culture and made to regenerate entire plants, and because its reproductive development can be described in precise terms, this plant may be a model system. The results of these experiments should indicate the extent to which mitosis, meiosis, and cytokinesis are dependent on gravitational cues, whether the precise pattern of early divisions of the embryo are subject to alteration, and whether cell wall structure and composition are altered when the gravitational environment is changed.

DEVELOPMENTAL GENETICS AND RADIOBIOLOGY

The field of developmental genetics has as a goal, an understanding of the role of genes in the ontogenic process. Put another way, we would like to understand how the linear information encoded in DNA is translated into the three-dimensional structure of the adult organism. Two overlapping types of investigation are in progress. The first is an analysis of those genes that apparently regulate development directly. The second is the manner by which genetic information is expressed (regulated) in the proper temporal and spatial pattern in ontogeny.

The process of development is studied through those genes that control ontogeny as it happens as well as those genes that function to maintain the final adult form or the determined state. There are at least three forces present in the space environment (or that act during lift-off or reentry) that might affect normal development and the genes that regulate the process. These are gravity (both hypergravity and hypogravity), vibration in lift-off, and radiation.

There is, at present, no obvious need for space experiments focused on developmental genetics. Perhaps, once we better understand the role(s) of genes in ontogeny, we can ask the more complicated questions about altered environments and how they affect gene regulation. However, if long-term survival and colonization are a goal of the space program, then an eventual understanding of the effects of the space environment's impact on developing systems at the level of the gene and gene function is essential.

Aside from microgravity, the other aspect of the space environment most likely to affect gene structure and function is radiation. The radiation environment in space includes gamma rays and x rays, galactic cosmic rays, solar flare particles (SPEs), and trapped charged particles of the radiation belts. This radiation includes low and high linear energy transfer (LET), high charge and energy (HZE) ionized particles, protons, and neutrons. In addition, there will be secondary radiation such as proton recoils, neutrons, bremsstrahlung (x rays secondary to electrons interacting with nuclei), and other products of the interaction of primary radiation with spacecraft materials. Finally, there will be trapped electrons from high-altitude nuclear tests as well as gammas and neutrons from on-board power sources.

The radiation environments are sufficiently different at the various altitudes that it is very difficult to discuss them as one entity. For example, in low earth orbits (LEO), such as are proposed for the Space Station, orbiters at altitudes of about 450 km will be exposed to geomagnetically trapped protons. Trapped electrons and the secondary bremsstrahlung will dominate the exposure in missions in geosynchronous orbit (GEO). Beyond the magnetospheres the radiation environment consists of galactic cosmic rays of high energy. Galactic cosmic rays are primarily protons with a contribution from helium and heavier ions. The exposure to heavy ions and the radiation in solar particle events (SPE) is influenced markedly by the degree of shielding by the magnetosphere. In the Space Station orbit the geomagnetic field provides shielding and SPEs will not add significantly to the radiation. In contrast, SPEs are of concern for missions in polar orbit and GEO. The importance of SPEs increases in the free space radiation environment and becomes a determining factor in the design of craft and in the planning for extended flights to other planets.

Previous studies have mainly focused on the effects of radiation in space on DNA stability. A number of studies using a variety of organisms have shown that spaceflight can cause an increase in mutation rates due in large part to effects of increased radiation exposure. The genetic risk, particularly the excess incidence of dominant mutations expressed in the F_1 generation induced by the low linear energy transfer (LET) radiation in low earth orbits, is considered to be low. Because of the relative biological effectiveness (RBE) of high-LET radiation, these radiations have a greater effect than low-LET radiation, but the contribution of high-LET radiations to the total dose in low earth orbits is small.

The putative effects of high-LET radiation on the fertility of parents (e.g., gametogenesis) could be significant. For example, the RBE for neutrons lies between 10 and 40, meaning that even small neutron doses become magnified in their contribution. Thus, Chinese investigators reported that low-level chronic x-irradiation (RBE = 1) at a dose rate of 0.15 to 0.8 rad/day rendered Rhesus monkeys aspermatogenic after 36 months of treatment. For comparison, the results from the Skylab missions indicate an average daily exposure of about 50 to 90 mrads/day with a small high-LET radiation component. The approximately 2 rads of high-LET radiation of 20 to 40 RBE would lead to almost an order of magnitude more mutations per gamete than the equivalent low-LET radiation.

There are two kinds of concerns about heavy ions. First, HZE particles can penetrate tissues and kill cells that are in the particle track core path by acting essentially as microneedles; the particle track core has a diameter as large as 50 A. These microlesions pose a special risk to nondividing cells such as neuroblasts that must migrate to the cerebral cortex during a specific point in embryonic development, or to stem cell populations, e.g., the hemopoietic system and to proliferating gametes. Very little information on the effects of high-LET heavy ions on embryonic development is available.

Second, it has become increasingly clear that high-LET radiation, especially that from heavy ions, is carcinogenic although the relative contribution to risk is not clear since the RBE for cancer induction is undetermined. Most data for dose-response relationships for the induction of cancer by high-LET radiation have been obtained by exposing rats or mice to fission neutrons. However, recent experiments have studied the influence of LET on tumor induction using the heavy ion facilities at Lawrence Berkeley Laboratory. Preliminary data suggest that the RBE to LET relationship for cancer induction plateaus at 100 to 200 keV/μm as has been seen for other endpoints. Further, irradiation with heavy ions of iron, the predominant HZE particle in space, is highly carcinogenic. These studies have obvious relevance from a developmental viewpoint, since they relate to the questions that concern the stability of the determined state.

Scientific Goals

1. *To determine the effects of the radiation environment in space on the stability of DNA.*
2. *To determine the effects of radiation in space on both gametogenesis and development, with particular emphasis in the latter instance on effects on tissue and organs in which differentiation depends on the integrity of stem cells or the integrity of migrating but nondividing precursor cells.*
3. *To determine the effects of radiation, especially the high-LET radiation from the heavy ions, on the frequency of malignant transformation in cell populations.*

Scientific Objectives

1. *To measure the specific effects of radiation versus gravity on genomic stability and appearance of aberrant cell lineages over several generations of representative organisms.*

2. (a) *To investigate whether high-HZE radiation enhances the probability of malignant transformation.*

(b) *To establish an extended program of research into the effects of heavy ions on developmental events.*

Measurement requirements

1. If the effects of radiation are to be determined, any effects of microgravity must be controlled. On the other hand, if gravity is the variable, the experiments must be radiation-shielded. This would seem to be a fairly elementary requirement; however, much of the past experimentation in this area has lacked the proper controls, and the interpretation of the results obtained is therefore clouded by uncertainty. Due in some part to flight duration, multigenerational data have not been obtained in the past. It is necessary to determine the effects of genomic alterations over several generations since the results of these changes will not be revealed until they have had a chance to segregate in the germ cells. Additionally there are gene products that function to regulate important early embryonic events such as cleavage patterns. However, the time of action (transcription) of the gene occurs during organogenesis. The impact of the space environment on these maternally expressed genes has not been assessed. The necessity to have several generations grown in space can be met by choosing the proper organisms and cell culture systems. Two particularly suitable organisms are the fruit fly *Drosophila melanogaster* and the freeliving soil nematode *Caenorhabditis elegans.* Both of these organisms have the advantage of an excellent repertoire of genetics, including a number of mutations affecting a variety of ontogenic processes. The nematode, as pointed out earlier, has the added advantage of being a normally self-fertilizing hermaphrodite, a fact that obviates many of the problems associated with mating in a zero-gravity environment. The life cycle is short (2 days), and the entire cell lineage from zygote to fertile adult is known. The organisms show a highly ordered mosaic pattern of development, and any perturbations can be quickly assessed by alterations in adult morphology and/or behavior, and the proximate cause can

be traced back through cell lineage of the defective organ(s). This approach can be further augmented by the observation of developing worms to find if the observed defects can be associated with a particular abnormal event in ontogeny. This type of experimentation in the vehicle itself will require that an individual capable of making the observations be included in the crew. Therefore, either a scientist familiar with the organism(s) or an individual trained in a laboratory working with the experimental material will be necessary, as well as the requisite culture conditions and microscopes.

2. The observation that high-LET radiation, especially that from HZE particles, enhances the probability of malignant transformation should be the subject of additional experimentation. Several questions need to be addressed, including (1) the RBE to LET relationship for transformation, including additional studies to document observations indicating that RBE is higher at lower doses, (2) the ability of cells to repair lesions induced by heavy ions, and (3) the mechanism(s) of heavy ion-induced cell transformation. At the outset, additional ground-based experiments such as those currently being conducted at the Bevalac facility should be continued and extended using both animal and cultured cell systems. Such studies should be extended to include research on effects of heavy ions on developmental events, such as gametogenesis, and effects on crucial nondividing cell populations, such as in the central nervous system. Dose-response relationships could be established for production of developmental lesions at the same time that experiments on tumor induction are performed if pregnant animals are utilized. Currently, such baseline information does not exist.

SUMMARY AND RECOMMENDATIONS

We return to the two questions, raised in the introduction, that have influenced the committee's overall discussion. (1) Can organisms undergo normal development under conditions of the space environment, or are there phases of development that are so abnormal as to preclude the progression through multiple generations? (2) Does the unique environment of space provide a tool to study specific developmental phenomena better than, or exclusive of, similar studies that could be carried out in ground-based experiments? The committee's conclusion is that insufficient evidence exists concerning the developmental capacity of any organism in the environment of space to be able to provide a definitive answer to either question. Thus, in what follows, a series of experiments is presented that will determine whether or not the field of developmental biology has a place in the long-term strategy for space research. The committee's bias at the outset is that most of the events associated with fertilization and early embryogenesis, with the possible exception of those for mammals, will be unaffected by the microgravity environment of space. It appears also likely that the major events of organogenesis will be immune to disturbances by the microgravity environment. Conversely, postnatal development represents an area in which the potential for major effects can be visualized. In all cases, however, these kinds of presumptions can be tested directly only by flying the initial rudimentary, largely observational experiments.

The committee cannot overemphasize the necessity of performing state of the art ground-based experiments before undertaking experiments on either the Space Shuttle or the Space Station. In some cases, such experiments might preclude the need to do space research. For example, clinostat studies, while only providing equalization of the gravity vector, nevertheless can be useful as predictors of possible effects of weightlessness on developmental phenomena. More generally, however, there is the need for additional ground-based experimentation on basic biological or biochemical events that have obvious direct relevance to ultimate studies conducted in space. For example, differentiation of the vestibular apparatus during development is an area of investigation that has obvious relevance to the space program. Similarly, basic studies on calcium mobilization and the processes of biomineralization using model systems would be extremely useful. Continued ground-based research on cell wall growth and meristem differentiation in plants is useful and necessary. Studies on the potential effects of HZE radiation on the development and differentiation of specific structures using accelerator-generated particles should be encouraged.

Because of limited availability of research space and the overall cost, the highest priority for experiments actually conducted in space should be devoted to studies on "model organisms" designed to answer the question: Can development from fertilization through the formation of viable gametes in the next generation occur in the space environment?

The committee recommends that two representative invertebrate species be flown under conditions in which fertilization occurs in the microgravity environment of space. One organism should be a marine invertebrate, and the sea urchin appears best suited for this purpose. The development of sea urchin eggs exhibits both regulative and mosaic development, the cell lineage of each major differentiated tissue and organ is known, and tissue-specific genes have been identified. In addition, the formation of a calcium-based internal skeleton provides the opportunity to study microgravity effects on biomineralization. The other organism is a land-based soil worm (nematode), *Caenorhabditis elegans*, whose development is highly mosaic. This organism has the advantage of small size, short life cycle (3 days), and a small genome. It is hermaphroditic, the genetics are well analyzed, and the adult animal has a constant and relatively small number of cells; the cell lineage of every organ system is worked out. Thus, any developmental abnormalities arising over several generations can be pinpointed as to in which cell(s) and when during embryogenesis a defect arose.

The committee recommends that two representative nonmammalian vertebrates be subjected to the microgravity conditions of space. Amphibians would represent a logical choice as one representative. The South African Frog, *Xenopus laevis*, has been a favorite organism for study by developmental biologists for years. Studies on the embryology of *Xenopus* eggs and embryos are well known, and the eggs respond to gravity by establishing dorsoventral polarity. An avian species would be a good choice as the second representative, largely because organogenesis in these homiothermic animals is very similar to mammalian organogenesis. Further, postnatal development may be studied most efficiently using avian eggs. Avian eggs also are known to respond to gravity in the establishment of initial axial polarity. From a practical viewpoint, some additional ground-based experiments may be required to establish ideal fixation conditions inside the shell.

The committee recommends that a representative mammal be placed into the environment of space for a time sufficient to determine if early embryogenesis and organogenesis as well as postnatal development can occur normally. Ideally, such an experiment would require 3 to 4 weeks, assuming that pregnant mice were flown at the outset. The use of mice has the additional advantage that a variety of strains exist that are both sensitive and resistant to alterations of specific developmental events. Cleft palate formation is just one such example. Correlated with the type of study implied above would be a "reproduction" study to determine whether or not animals can copulate in space as well as whether ovulation, fertilization, and implantation are normal.

The committee recommends that at least one plant experiment be flown in which seeds are required to germinate in space and the experiment is of sufficient duration to allow production of seeds. The potential for experimentation provided by both *Arabidopsis* and *Azolla* is impressive. Both plants are small with rapid growth cycles. *Arabidopsis* has a small genome size and many morphological and biochemical mutants have been identified; it is transformable, providing the possibility of inserting foreign genes. *Azolla* is a floating water fern that produces roots from the lower surface of its horizontal stem, and, as pointed out earlier, the pattern of cell division is unique, allowing precise lineage studies. Thus, developmental abnormalities can more readily be pinpointed to specific cells and developmental time.

The committee concurs with the earlier report *Life Beyond the Earth's Environment* (NAS, 1979) that studies in genetics and in cell and molecular biology need not be performed in space, at least not for the near future. Many of the questions posed in the preceding pages concerned with developmental phenomena include, of course, questions of obvious relevance to the field of cell biology. Aberrant patterns of chromosomal segregation would have obvious developmental effects at some point. Similarly, cytoskeletal defects and unusual patterns of cytokinesis would have obvious impact, especially in the mosaic eggs and embryos mentioned above. Thus, such abnormalities, if they occur, would be a natural result of studies on model organisms.

Finally, *the committee recognizes the need to perform additional ground-based experiments on the effects of high-LET radiation both on the development of specific tissues and on cell transformation.* Sources that provide neutron radiation would provide baseline information relative to both areas of investigation. However, it is especially important to obtain baseline data on the relative effects of HZE particle irradiation.

There will be those who contend that the examples suggested above may not be inclusive enough to answer the major questions posed earlier. In this case, the committee can only reaffirm the position taken by other study groups—that it is not necessary, nor even possible, to conduct all combinations of biological experiments in space. The committee believes that, given the present state of knowledge, it would be best to concentrate on the planning and execution of a small number of well-chosen experiments.

3
Gravitropism in Plants

INTRODUCTION

The observation that "roots grow down and stems grow up" cloaks a problem that is simple in concept, but complex in detail. Like most generalizations, this description of the reactions of plant organs to the force of gravity is not strictly true, for some stems, such as underground rhizomes, grow horizontally, while others, such as the branches of a tree, grow at a fixed angle to the vertical. Similarly, prop roots of corn grow downward at a 45 degree angle from the vertical, branch roots usually differ in their orientation from main roots, and some mutants are completely agravitropic. To make matters more complicated, these behaviors need not be fixed. A tree branch growing obliquely will grow straight upward if the apical bud is cut or removed. Even from these few examples, one can conclude that gravitropism, the curvature of a cylindrical plant organ in response to a gravitational force, is determined by genetics and development and is controlled by physiology.

It is customary to dissect gravitropism into partial reactions, including perception of the force of gravity by specialized cells, transduction into a physical or chemical event within the cells, transmission of a signal from the region of perception to the region of response, and finally the differential growth response on the two sides of the cylindrical plant organ that leads to curvature. The response involves extension of already existing cells, rather than the creation of new cells by cell division.

The generally accepted scenario for plant gravitropism is as follows: Certain cells, the statocytes, contain dense starch-containing plastids or amyloplasts that sediment within several minutes when the orientation of the plant organ is changed with respect to the vertical. Since amyloplast displacement appears to be the first step in the perception of the earth's gravitational field, the plastids have been called statoliths. Amyloplast displacement causes contact with other organelles within the statocyte, such as endoplasmic reticulum, cytoskeletal components, or the plasmalemma. A process triggered by the contact is probably the first step in the transduction of the gravitational stimulus into a signal that is transmitted to the growing part of the organ.

According to the classic Went-Cholodny theory, the signal is the asymmetric distribution of the growth hormone, auxin. The theory states that in vertically oriented shoots and roots auxin moves longitudinally from the tip of the organ to the growing zone in a symmetrical manner. Following placement of the organ in a horizontal position, a lateral migration of auxin is superimposed on the longitudinal transport so that the growth hormone will accumulate on the lower side of the organ and be depleted on its upper side. The accumulation of auxin is envisioned as increasing the relative extension of the lower side of the stem and, hence, resulting in its upward curvature. A rather ingenious argument was presented as to why an accumulation of auxin on the lower side of the root would result in its downward curvature. Little evidence has been obtained for the argument, and it has been more or less discredited. The main idea of the theory, that the differential growth on the two sides of a gravitropically stimulated organ is due to the asymmetric distribution of plant hormones, has survived and has guided much of the research in the field. This remains the case despite the fact that the hormonal theory of plant tropisms has recently been challenged.

MAJOR SCIENTIFIC GOAL

The major goal of current research in plant gravitropism is the attainment of understanding of the cellular and organismal processes involved in the plant's detection and response to the earth's gravitational field. The goal can best be attained by answering questions about how the plant senses gravity, how this sensation is transduced into a signal that can influence cellular growth, and how the signal can cause the differential growth of the upper and lower halves of a plant organ that leads to curvature toward or away from the earth's center. Subsidiary goals involve an understanding of why roots grow up and stems grow down and how gravity interacts with light, other external stimuli, and endogenous rhythms in determining the orientation of plant organs.

GRAVITY SENSING AND TRANSDUCTION

The Amyloplast as Gravisensor

The sensing of the earth's gravitational field by higher plants most likely involves the sedimentation of a dense organelle, the starch-containing amyloplast, within a specialized cell, the statocyte. In roots, the statocytes are found in the root cap; in stems they are usually distributed in the bundle sheath, a layer of parenchymatous cells surrounding the vascular bundles. Several lines of evidence point to amyloplasts as the gravity sensors or statoliths of higher plants: when gravitropically sensitive organs are changed in their orientation within a 1-g field, the large amyloplasts located within the statocytes are the only organelles that sediment rapidly. Mutant strains of maize with smaller or less dense amyloplasts show a decreased gravitropic sensitivity. In maize roots, surgical removal of the statocyte-containing root cap abolishes gravisensitivity without inhibiting growth rate. Regeneration or replacement of the root cap restores gravisensitivity. The excised tip can be gravistimulated; when it is replaced on the unstimulated root, it induces curvature. Artificial displacement of amyloplasts or sudden jarring causes curvature in a direction determined by displacement of the amyloplasts, not the rest of the cell. Depletion of starch from gravisensitive organs results in a decreased sensitivity or, at least, a retardation of the gravitropic response. Recovery of starch content in amyloplasts restores the sensitivity.

It should be noted that in rhizoids of *Chara*, an alga-like plant, similar statolith function is assumed by dense crystals of $BaSO_4$. This suggests the possibility that alternative statoliths could serve the same function in higher plants if amyloplasts fail to develop or are made to disappear.

Characteristics of Amyloplasts and Statocytes

There are two kinds of amyloplasts, distinguished in terms of size and number of starch grains. The larger, multigranular organelles usually contain eight or more grains; the smaller, unigranular plastids have one or two grains. Multigranular amyloplasts are thought to be important in gravisensing since they, unlike the unigranular variety, are readily moved by gravity and are found in gravity-sensitive tissue. Amyloplasts are not merely static, heavy particles that fall under the influence of gravity; they contain DNA, RNA, thyalkoid membranes, and ribosomes, as well as starch grains. Their sedimentation is blocked by 5 mM Ca^{2+}. They have a zeta potential of about -20 mV, and they contain Ca^{2+}. The results indicate that the amyloplast is a dynamic organelle with the machinery necessary for transcription and translation.

Statocytes from roots and stems contain 10 to 20 amyloplasts per cell. Each amyloplast is 4 to 10 μm in diameter. In stems and coleoptiles, the cells are elongate, contain one or several large vacuoles, and exhibit vigorous protoplasmic streaming. Root cap statocytes are isodiametric with many small vacuoles and show particle saltations instead of streaming.

Dynamics of Gravity Sensing

Gravity sensing and statolith fall both occur within the presentation time and are amenable to the reciprocity law, $gt = k$, where g is the gravoinertial stimulus, t is the presentation time, and k is a constant. Early estimates of the presentation time were in the range of 5 to 20 min, but more recent estimates range from 10 to 90 s. The threshold signal is 100 to 300 gravoinertial seconds for oat coleoptiles and short periods of gravistimulation can be additive. The effect of gravistimulation persists in gravity-sensitive tissues for several minutes, even at low temperatures not conducive to growth.

Transduction Mechanisms

The asymmetric growth patterns that result in gravitropic curvature are presumably caused by the altered distribution of amyloplasts within statocytes. There are at least three ways in which amyloplast displacement could be transduced into growth-regulating signals:

1. Amyloplast motion. Since the organelle is negatively charged, its movement through an electric field could generate an electric current. However, it is unclear how movement per se could result in a memory for tropistic stimuli that can last for several minutes.

2. Contact of amyloplasts with cell components. Contact of the amyloplast membrane with the endoplasmic reticulum, with cytoskeletal components (microtubules or microfilaments), or with the plasma membrane could lead to the exchange or release of ions or to altered movement of hormones or other physiologically active substances.

3. Deformation. Sedimentation of amyloplasts might apply pressure to a region of the plasmalemma or internal membranes, influencing phospholipid/protein packing, creating new protein domains, and influencing enzymatic activity. But theoretical calculations of amyloplast pressure yield values that seem too small to account for a significant response.

The Clinostat As a Model of Microgravity

Before the advent of spaceflight, clinostats were used in an attempt to simulate microgravity and prevent sedimentation of statoliths. On a clinostat, the specimen is rotated about a horizontal axis so that it has no fixed orientation with respect to gravity. The result may be termed gravity equalization or gravity compensation. Gravity is by no means abolished, and there are mechanical effects that arise as the specimen is rotated. The mechanical effects can induce the release of ethylene, a gaseous plant hormone that induces growth retardation, stem thickening, and upward or downward movements of leaf stalks, so-called nastic responses. True microgravity can be realized on earth only during brief periods of free fall or during parabolic flight maneuvers. Whether the clinostat is an adequate model of microgravity will obviously depend on the phenomenon under study. The only way to determine this is by empirical test; the results obtained on a clinostat have to be compared with those obtained in orbital flight. In those instances where both kinds of experiments have been done, the results from clinostat experiments have yielded results that are qualitatively similar to those observed in space.

Scientific Objectives

1. *To study the cytochemical and cytophysical characteristics of amyloplasts, their developmental pathway, and their morphological relation with other cellular components.*

2. *To understand transduction mechanisms by describing the interactions of the amyloplasts with other components of the statocyte and specifying the physical and chemical changes that result from such interactions and lead to a gravitropic response.*

3. *To determine the adequacy of the clinostat in simulating the microgravity environment.*

Measurement Requirements

1. Amyloplasts can be isolated by differential centrifugation. Studies of the chemical and physical characteristics of isolated amyloplasts, as well as their metabolic activities, should help us understand their role in the regulation of statocyte function and in the regulation of plant growth.

2. Because the mechanisms of transduction are so poorly understood, study of the interactions of amyloplasts with the other organelles of the statocyte is important. The distribution of endoplasmic reticulum, cytoskeletal elements, and their relation to the plasmalemma should be studied in statocytes from a variety of tissues. The morphological relation of the amyloplast to these other cytological elements should be compared in statocytes that are or are not gravistimulated. These studies will require fluorescence, as well as electron microscopy.

3. The effect of microgravity on statocyte differentiation and organelle position requires investigation. Although a previous experiment examined the ultrastructure of roots flown on the Shuttle, the plants were fixed for microscopy after they had returned to earth. Thus it was difficult to assess the effects of landing and return to 1 g on structure and organelle position. The experiment should be redone with rapidly germinating seeds whose young roots can be fixed in space. This would answer the question as to whether amyloplasts and statocytes can differentiate under microgravity to produce a final complement of organelles comparable in quality and size to those of ground-based controls.

It would be important to compare organelle position in statocytes from plants that have been centrifuged in space at 1 g with those that have experienced only microgravity forces. Ground controls should include plants germinated and fixed with and without clinostatting to help define differences induced by clinostatting and by microgravity conditions.

4. Experiments on the range of gravity forces over which reciprocity holds and the changes in presentation times under conditions of microgravity would be of great theoretical interest. For these experiments, coordinated studies in space and on the ground would be needed and a regulated centrifuge would be required in both locations. Here, again, a comparison between microgravity in space and clinostatting on earth would be revealing. The simplest organ to use is probably the oat (*Avena*) coleoptile, which can be generated in 3 days and gives rapid and quantitative graviresponses.

HORMONE MEDIATORS OF GRAVITATIONAL RESPONSES

The Role of Hormone Distribution

Gravity induces changes in the relative growth rates of the upper and lower sides of horizontally placed shoots and roots. The changes may be as drastic as a complete cessation of growth on the upper side of a shoot, together with growth stimulation on the lower side. Since growth rate in plants can be hormonally controlled, it is relevant to inquire whether changes in hormone levels on the upper and lower sides are responsible for the growth curvatures induced by gravity. First to be considered are coleoptiles, the first leaf in the germination of grasses, where the hormonal mechanisms of gravitropism have been most extensively studied and are best understood.

Gravitropism in coleoptiles is achieved by the growth rate of the lower side increasing and that of the upper side decreasing by the same amount as compared to the growth rate of vertical controls. As early as 1935, bioassays were used to estimate the relative amounts of auxin that diffused out of the base of detached, gravistimulated oat (*Avena*) coleoptiles. During the subsequent 50 years, this work was confirmed and extended. The effective auxin was identified as indole-3-acetic acid (IAA). IAA is twice as abundant on the lower side of a gravistimulated coleoptile as it is on the upper side. The source of IAA is the apex, from which it is transported in a basipetal (apex to base) direction. When a coleoptile is laid on its side, a directed lateral transport, from upper side to lower side, is superimposed on the basipetal transport. This lateral transport is required for gravitropism, since insertion of barriers preventing lateral movement also prevents tropistic curvature. Other growth hormones may be involved. The gibberellins (GAs) are a group of closely related substances that are growth-promoting hormones. GA-like activity was found to diffuse asymmetrically from gravistimulated corn (*Zea mays*) coleoptiles. No evidence of a lateral transport of GAs has been detected. The involvement of inhibitors on cell extension has received too little attention to exclude their participation in the gravitropic response.

The growth-regulating mechanisms underlying the gravitropic response of roots is less well understood than in coleoptiles. Gravitropism requires the movement of growth regulators in a basipetal direction from the root cap to the growing zone. IAA is found in roots, it can become asymmetrically distributed if the root is gravistimulated, and it can cause curvature. Nevertheless, the role of IAA in gravitropism is unclear since its transport is in an acropetal direction, from the base of the root toward the tip. A growth inhibitor arising in the root cap and transported laterally from the upper to the lower sides has been implicated. The involvement of an inhibitor would explain the positive gravitropic response of roots. A possible candidate is abscisic acid (ABA), which is a generally inhibitory plant hormone. Quite recent evidence suggests that another, as yet uncharacterized hormone may play an essential role.

The growth-regulating mechanisms underlying gravitropism in dicotyledonous shoots is not understood and does not conform to the Went-Cholodny hypothesis. Gravitropism in sunflower (*Helianthus annuus*) involves a marked increase in growth of the lower side and a cessation of growth on the upper side. In etiolated stems of *Cucumis sativus*, curvature appears to be due to a cessation of growth of the upper side with little change in that of the lower side. The large changes observed in *Helianthus* seem inconsistent with the small asymmetries of IAA found in this species. The growth pattern in *Cucumis* does not conform to the Went-Cholodny hypothesis, which envisions that the increased growth on the lower side be matched by the decreased growth on the upper side. A possible role for the gibberellins has been suggested. But recent work in which sensitive radioimmunoassays were used failed to detect asymmetries in the distributions of IAA, GA, or ABA in *Helianthus* stems after 2 h of gravistimulation, by which time a substantial curvature had developed.

Gravitropism in grass nodes does not involve the redistribution of growth hormones from the upper to the lower sides. This is convincingly demonstrated by the fact that growth can be induced in half-segments that have been bisected longitudinally. Growth occurs if the half-node is placed horizontally with the epidermis directed downward. It does not occur if the epidermis is directed upward or if the half-node is placed vertically. In addition, transport studies indicate little polar transport. Nevertheless, in intact nodes, there are asymmetries in the concentrations of IAA and the GAs. To explain these results, it has been suggested that gravistimulation causes an increase in hormone concentrations on the lower side, either by a transformation of hormones from inactive to active forms or by an increase in their synthesis.

A stimulation of ethylene production has been observed in plants exposed to clinostatting or if their static orientation with respect to gravity is changed. This enchanced ethylene production, which can inhibit elongation, may occur as a result of mechanical stimulation imposed by gravistimulation. Elevated auxin levels stimulate ethylene production, so the change in ethylene may be secondary to auxin changes. There appears to be a close agreement between the concentrations of auxin causing root curvature and those eliciting ethylene production. Stimulated ethylene production occurs in some systems before and in others after bending is initiated.

If the gravitropism is causally related to altered hormone distribution, then the first signs of hormonal effects should precede the first signs of curvature. For most systems, critical data are lacking.

Cellular and Molecular Mechanisms of Hormone Action

No plant hormone receptor has yet been identified or purified. This is the largest single deficiency in plant hormone biochemistry. It has been suggested that auxins act in at least two ways. (1) Auxin may activate a plasmalemmal ATPase that functions as a proton pump, thereby promoting proton efflux from the cell, which would result in acidification of the extracellular media. This last effect may activate enzymes capable of hydrolyzing wall polysaccharides to soften the wall and allow cell extension. (2) Auxin can rapidly alter gene expression in a variety of organs and organ sections, and it does so by acting at the transcriptional level. The effects on protein synthesis may very well be similar in cells whose ultimate response to the hormone may be quite different. The initial events in hormone action that occur after receptor binding, including the role of potential second messengers, are poorly understood. It seems doubtful that the actions of auxin are limited to those mentioned. A similar situation exists with respect to the actions of other hormones. In animal systems, an understanding of the cellular and molecular mechanisms of hormonal action has shed light on the physiological effects of hormones. The same may be anticipated in the case of plants.

Scientific Objectives

1. *To understand the cellular and molecular mechanisms involved in the action of plant hormones.*
2. *To understand the role of the various plant hormones in gravitropism.*

Measurement Requirements

1. A vigorous ground-based research program is needed to elucidate the cellular and molecular mechanisms of hormone action.
2. Ground-based research is needed to study (1) how and when hormone asymmetry is established during gravitropic curvature, (2) which, if any, hormones are primary and which are secondary in initiating gravitropistic curvature, and (3) how the hormones act to promote growth and curvature.
3. Spaceflight experiments are needed to determine the effects of microgravity on the concentration of various hormones, including auxin, the gibberellins, abscisic acid, cytokinins, and ethylene. The Went-Cholodny theory postulates that there is no net change in the total amount of auxin moving from the tip of a tropistically stimulated stem or coleoptile, only a change in distribution such that more hormone is transported to the more rapidly growing, lower side. The theory would predict no change in the

concentration of indole-3-acetic acid (IAA) in a stem growing in microgravity as compared to one growing in 1 g. The same prediction requires testing in roots, where a growth inhibitor, rather than auxin, may be the primary hormonal mediator. The influence of microgravity on hormonal concentrations would also be of interest in dicotyledonous shoots and grass nodes, where a lateral redistribution of hormones apparently cannot account for the salient features of gravitropism. Here gravity may alter the synthesis of the relevant hormones or their conversion from an inactive to an active form, so one might anticipate a change in concentrations as a result of exposure to microgravity. A broad-ranged study of the effects of microgravity should help to distinguish the mechanisms of hormonal control in different kinds of plants and plant organs.

4. Spaceflight experiments are also needed to investigate the influence of microgravity on the polar and nonpolar transport. Polar transport is unidirectional, while nonpolar transport is bidirectional. There is evidence that the rate of longitudinal transport is influenced by gravity. The case is clearest for auxin, where the transport is polar. Gravistimulation affects this transport, at least in stems. Transport rates are greater on the lower, faster growing side than on the upper, slower growing side. Hence, there is reason to believe that microgravity may influence transport rate, if not direction. The transport of other hormones, the gibberellins to cite one example, is nonpolar. Appropriate space experiments could determine whether microgravity affects polar transport, nonpolar transport, or both.

5. Can one orient plants in space by asymmetric hormone application? By light? Will such control have practical implications for space horticulture?

NONHORMONE MEDIATORS OF GRAVITATIONAL RESPONSES

Three nonhormonal events—asymmetric H^+ efflux, asymmetric Ca^{2+} movements, and altered electric currents—have been proposed to be involved in the transduction mechanisms leading from the perception of gravity to the differential growth response.

Asymmetric H^+ Efflux

Recent evidence suggests that gravistimulation results in asymmetric acid secretion. In both roots and shoots, the efflux is greater from the more rapidly growing side, that is from the upper surface of roots and the lower surface of shoots. The magnitude and kinetics of this phenomenon have not been determined with the same precision as comparable measures of gravitropic curvature. Nevertheless, observations made with pH-sensitive dyes indicate that acid efflux is initiated in 30 min or so and that the secreting surface has a pH below 5.3.

Proton (H^+) secretion is closely related to auxin action. Acidic solutions promote elongation to an extent comparable to that attained in response to auxin. Acid pH stimulates the growth of roots. Auxin induces H^+ efflux from stem and coleoptile tissues and the enhancement of H^+ efflux precedes hormone-induced elongation. Under appropriate conditions, concentrations of auxin that promote growth also promote acid efflux, while concentrations of auxin inhibitory to growth inhibit acid efflux. Furthermore, auxin transport inhibitors can prevent asymmetric acid effluxes in gravistimulated shoots and roots. These results can be explained if auxin asymmetry produces gravitropic curvature by controlling asymmetric H^+ concentrations. The possibility has already been mentioned that auxin might stimulate a plasmalemma-bound proton pump and that the resulting acidification of the extracellular media could facilitate the softening and elongation of the cell wall.

Asymmetric Ca^{2+} Movements

Gravistimulation results in an asymmetric distribution of Ca^{2+}. In stems and coleoptiles, the ion accumulates on the more slowly growing side, where it may inhibit growth. The Ca^{2+} asymmetry is detectable within 10 min after the start of gravistimulation of oat coleoptiles and is, thus, rapid enough to play a causative role in gravitropism. That this is the case is suggested by the observation that application of calcium chelators to root caps makes roots insensitive to gravity and that the sensitivity is restored when the chelator is replaced with Ca^{2+}. Other evidence that Ca^{2+} gradients may be important in gravitropic responses can be cited. (1) A Ca^{2+} gradient across the tip of intact or decapped, vertically oriented roots leads to a gravitropic-like curvature toward the high side of the calcium gradient. (2) Ca^{2+} movement is linked to auxin movement in shoots and roots. (3) Calmodulin is a Ca^{2+}-binding regulatory protein important in the mediation of many of the intracellular responses to calcium. The calmodulin inhibitor, chlorpromazine, blocks both gravitropism and the lateral redistribution of calcium in oat coleoptiles.

The site of accumulation of Ca^{2+} has been studied by the use of an antimonate precipitation histochemical procedure. Ca^{2+} was found to accumulate in the apoplastic region, the cell wall, and intercellular spaces, in the upper, more slowly growing side of oat coleoptiles. More recent studies in corn roots indicate an accumulation in vacuoles of the upper, more rapidly growing side. The last results are contrary to those observed in both shoots and roots. There have been two suggestions as to how Ca^{2+} might exert its growth-regulatory effects. (1) It might control the efflux of acid by modulating the activity of a proton pump or by participating in a coupled H^+-Ca^{2+} exchange or transport system. (2) It might inhibit an enzyme involved in the H^+-initiated wall loosening. Ca^{2+} redistribution is linked to auxin movement. There is evidence that auxin movements affect Ca^{2+} distribution and that the reverse may also be true.

Electric Currents

The earliest signals induced by gravistimulation are electrical changes of undefined origin. They have been observed in both shoots and roots within less than a minute after the start of gravistimulation. This is at least several minutes before the earliest noted changes in Ca^{2+} or IAA distribution. The electrical changes may reflect gravireception or the earliest steps of transduction.

In stems, a transverse voltage asymmetry can be measured 1 to 2 min after gravity stimulation, especially in the region that will ultimately bend most rapidly. This timing coincides with that for the falling of amyloplasts in oat coleoptiles. In roots, depolarization of statocytes occurs within seconds after rotation of 45 degrees from the neutral position. Also, changes in the pattern of electric currents around the primary root tip of *Lepidium sativum* occur within 30 s after tilting the root to a horizontal position. Coleoptile cells from corn (*Zea mays*) exhibit an electrical polarity with respect to gravity whether they are oriented with their apical ends up or down. The electric potentials across the plasma membrane of the lower part of the cells are about 2 mV more negative than across the upper part, irrespective of cell orientation.

Summary

Three nonhormonal events induced by gravistimulation have been reviewed and their possible roles as transducers of differential growth and their relation to growth hormones evaluated. The asymmetric H^+ effluxes, which may be particularly important in regulating cell elongation, are likely to be the result of asymmetries in the activity of auxin and possibly of other growth hormones. The asymmetric Ca^{2+} movements appear both to affect and to be affected by hormone activity, but the biochemical mechanisms that link the two of them are unclear. The electric currents, which occur early during gravitropism, may be associated with reception and the earliest events in transduction. These same mechanisms are also important in the regulation of straight or nongravitropic growth. Further study of these processes and their interrelations is required to clarify the transduction mechanisms, which at present are poorly understood.

Scientific Objectives

1. *To understand the role of nonhormonal mechanisms in regulating both gravitropic and straight growth.*
2. *To understand the relation between hormonal and nonhormonal mediators of growth.*

Measurement Requirements

1. The transport of H^+ and Ca^{2+} ions is important in the regulation of both straight and gravitropic growth. Earth-based experiments are needed to understand how the transport of these ions is regulated and to identify the specific roles they play in the regulation of growth. Observations need to be made at all levels, including the intact tissue, the isolated cell, and subcellular processes. Specific questions are: (1) What are the early kinetics of Ca^{2+} and H^+ asymmetric transports following a gravitropic stimulus? (2) To what subcellular compartments and through what pathways do these ions move between the onset of stimulation

and the initiation of differential growth? (3) How is transport affected by auxin and other growth hormones?

2. To relate ion movements in intact tissues to the asymmetrical growth responses of gravitropism, we need a detailed description of (1) the regions where differential growth occurs, (2) the kinetics of the differential growth, and (3) the magnitude of curvature as a function of time.

3. On the subcellular level, we need to learn more about basic transport mechanisms that control ion movements across membranes. Methods for studying these mechanisms by the use of isolated vesicles are now well described. Different H^+ and Ca^{2+} transport systems have been identified on various subcellular membranes. Further characterization is required. Specific questions are: (1) H^+-pumping ATPases have been identified on the plasma membrane and the tonoplast, the membrane surrounding the cell vacuole. How are the ATPases regulated by Ca^{2+} and other factors? (2) Ca^{2+} pumps have been localized in the plasmalemma, in mitochondrial membrane and in the tonoplast. Does calmodulin regulate these pumps? (3) The transport of auxin is mediated by an anion carrier that is currently being isolated and characterized. Do pH and Ca^{2+} concentrations regulate the carrier and auxin transport? (4) How is the transport of K^+ across the plasma and vacuolar membranes regulated? The transport of K^+ and of other ions known to be important for growth is only poorly understood.

4. Electrophysiological studies are needed to study the electric currents possibly involved in the early stages of transduction. At present, observations are available for whole roots. Experiments need to be done on individual organs and single cells.

5. There is a large body of information obtained from terrestrial experiments that describes H^+ fluxes and movements of Ca^{2+} and K^+ that occur subsequent to gravitational stimulation. Whether similar responses can be obtained in spaceflight, where there is no background gravitational force and where gravitational stimulation can be introduced by brief exposure on a centrifuge, is of interest.

6. Spaceflight offers a unique opportunity to study the possible role of early electrical responses in the initiation of gravitropism. It is known that externally applied electric fields (EAEF) can regulate the direction of root and shoot growth. Can the electrotropic

stimulus completely substitute for gravitropic stimulation in inducing curved growth or does gravity provide a background influence other than its specifying the desired direction of growth? The answer to this question requires the microgravity environment of spaceflight. The question is of particular interest because gravity induces an electric polarization in statocytes that is independent of cell orientation. Presumably the polarization will disappear in microgravity. Specific questions are: (1) Are the threshold field strengths needed to induce curvature similar in microgravity and 1 g? (2) What is the relative effect of EAEF on statolith position at 1 g and in microgravity? Are the induced effects independent of statolith position? Do they persist after removal of the root or coleoptile tip?

EFFECTS OF GRAVITATIONAL FORCES ON PLANT RESPONSES

In previous sections of this chapter, we considered the phenomenon of gravitropism, a directed response of shoots and roots to changes in their orientation with respect to the gravitational vector. This section considers other responses that may be influenced by gravity and that can be profitably studied in the microgravity environment of spaceflight. These include a variety of tropistic responses, epinastic responses of lateral branches and leaves, circumnutation, and circadian rhythmicities. In many instances, the responses have been studied in orbital flight. In others, a clinostat has been used in an attempt to simulate the microgravity environment. Some responses have been investigated in both true and simulated microgravity. The clinostat is a potentially powerful tool for the study of microgravity effects. This is so because there is easier access to clinostats than to spaceflight opportunities. In addition, the clinostat can provide preliminary observations to indicate which of several species are most likely to yield important results in space. Some of the limitations of clinostats have been discussed previously.

General Plant Function

Beginning with the second Shuttle mission, several tests of plant function in microgravity have been accomplished. It was found that sunflower (*Helianthus annuus*) seeds would germinate and develop for more than one week in microgravity with the same dependence on soil moisture content as on earth. In several plant genera, predicted root disorientation was confirmed. Tissue lignification was found to be retarded. Abnormal mitotic processes, reminiscent of previous Soviet and Biosatellite II observations, were noted in root tips.

Prolonged clinostatting leads to a number of physiological and structural changes. *Avena* (oat) roots respond with increased growth and respiration. Coleoptiles react after clinostatting with an increased sensitivity to gravitropic and phototropic stimulation; growth rate is uninfluenced. Tomato plants produce twice as much ethylene during the first 2 h on a clinostat, possibly due to unavoidable mechanical stimulation. Remarkable structural alterations in statocyte cells have been found in *Lepidium* roots that were cultivated under normal conditions and were then rotated on a clinostat for 2 h at 2 rpm. Specifically, the polar arrangement of cell structures, a characteristic feature of statocytes, is lost. The endoplasmic reticulum, normally located at the distal pole of the cell, becomes randomly dispersed throughout the cell. The starch content of the amyloplast decreases, and the size of lipid droplets increases. If, on the other hand, the plants are rotated on a clinostat from the beginning of seed soaking, no alterations in polarity are seen; whether this represents a developmental adjustment or an effect of exposure time is unclear. There are clear species differences. The starch content of *Lepidium* amyloplasts is decreased by clinostatting, while that of amyloplasts of oat coleoptiles actually increases. This last result may explain the increased gravitropism of clinostatted coleoptiles, but it can hardly explain their increased phototropic sensitivity.

If we assume that the clinostat adequately simulates microgravity, then there are some lessons to be learned from the above results about the conduct of space experiments. The differences obtained between species would indicate that representative examples of different genera will have to be flown before generalizable conclusions can be made. This is especially true for processes as complicated as gravitropism, where ground-based experiments have already indicated that there are marked differences between species, not to mention differences between different organs of the same species. In addition, attention must be paid to the time of exposure to microgravity. One of the most important uses of spaceflight is to measure responses to hypogravic stimuli. Here one has to control for adaptation to microgravity. If the results are to be applicable to earth, it will be necessary to hold at least some specimens on a 1-g centrifuge and remove them only for the minimal time necessary for testing.

Gravitropism and Other Tropistic Behaviors

The orientation of shoots and roots can be influenced by a number of external stimuli, including gravity, light, and electric and magnetic fields. The response to electric and magnetic fields may reflect a direct action on amyloplasts. These organelles have a zeta potential and are thus capable of being polarized by external fields. Similarly the organelles are diamagnetic, and this may be responsible for the organism's magnetic sensitivity. These possibilities can be studied by comparing the response to electric and magnetic fields in roots and coleoptiles where the gravisensing tissues have and have not been removed.

It would be of interest to study all of these responses in the absence of a background gravitational force. There are two quite different reasons for wanting to do this. The first is to determine the immediate influence of removal of background gravitational forces on tropistic responses. The second is to study the adaptation to microgravity. As noted above, the first class of experiments calls for minimal exposure to microgravity. The second requires continuous exposure.

Epinasty

Certain plant organs, including lateral branches and leaves, exhibit a preferred direction of growth, usually not coincident with the plumb line. The oblique orientation that these organs assume can be viewed as the interaction between two opposing responses. One is a hyponastic response that returns the organ to the plumb line or the main axis of the plant; the other is an epinastic response that moves the organ in the opposite direction. Experiments done on a clinostat indicate that gravity stimulation results in the reduction of epinasty. A similar result was obtained in Biosatellite II, in which pepper (*Capsicum annuum*) plants were placed in orbit for 45 h. The plants showed an epinastic response similar to that of ground-based, clinostat-compensated controls.

More recent ground-based experiments, in which a combined clinostat and centrifuge were used, show that the epinastic response is reduced in a systematic way as a centrifugal force along the main plant axis is increased in the range from 0 to 1 g.

Circumnutation

Circumnutation refers to a rotary movement of plant organs in space. The helical growth movements shown by the tips of some seedlings provides an example, as do certain leaf and tendril movements. There have been two theories concerning the origin of the motion. One envisions that the circular motion is the result of autonomous oscillatory processes residing in the organ, the other that it involves an underdamped or overcompensated gravitropic feedback response. Since the theories are not mutually exclusive, the response of any particular plant or organ could conceivably involve some combination of the two mechanisms. Such would appear to be the case for the hypocotyl of the sunflower seedling (*Helianthus annuus* L.). When the plant is gravity-compensated on a clinostat, the amplitude of rotation is reduced, but not eliminated; the responses become erratic, sometimes stopping for several hours and then starting up again. An experiment flown on *Spacelab 1* gave similar, but not identical, results. Clearly, circumnutation can occur in the absence of gravity. The investigation should be extended to other plants and other organs. Given the qualitative similarity of simulated and true microgravity, species should be chosen for spaceflight on the basis of their responses on a clinostat. It would be of particular interest to choose species for spaceflight based on whether clinostatting did or did not have marked influence on their circumnutational responses.

Circadian Rhythms

Plants can measure astronomical time, as demonstrated by persistent rhythms having daily (circadian), lunar, or yearly (circannual) periods. Such rhythms may underlie circumnutation, a possibly key process in tropistic response. Accordingly, any discussion of gravitropism must consider rhythmic behavior. Photoperiodism, wherein flowering occurs at a specific time each year, probably involves a correlation of daily daylength (or nightlength) measurements with circadian rhythm.

Circadian rhythms have been documented at every level of eukaryotic organization and may be viewed as the expression ("hands") of an underlying oscillator ("clock"). Typically, the two of them can be synchronized or entrained by imposed diurnal light or temperature cycles to nearly 24-h periods. Entrained rhythms can be rephased by reversing or otherwise shifting the imposed light or other entraining regimes. Circadian rhythms can also free-run for long time spans (3 to 4 days and often much longer) with a natural period of close to 24 h, even when most environmental cues are held constant. The period is rarely precisely equal to 24 h and this is particularly important in distinguishing between passive systems driven by environmental cues and truly endogenous, self-excitatory oscillators.

There appears to be a selective pressure for temporal adaptation, especially to solar periodicities. These adaptive features have been attained by organisms through some sort of timing mechanism(s): an autonomously oscillating biological clock having an innate but mutable genetic basis that responds appropriately to those environmental periodicities encountered by organisms throughout their evolution.

Simulated weightlessness (clinostatting) can affect such rhythmic functions as the mitotic index of broad bean (*Vicia faba*) and leaf movements of pinto beans (*Phaseolus vulgaris*). In addition, clinostat experiments indicate that the photoperiodic requirements for flowering in the short-day plant *Xanthium pensylvanicum* are altered by changes in the gravitational field. As noted previously, this phenomenon depends on the interaction between light and biological clocks. There have been some reports that hypergravity produced on a centrifuge can also alter circadian periodicities. Circadian timing may be involved in gravitropism as the response to gravitational stimulation varies with time of day. Thus there may be a bidirectional interaction between circadian clocks and gravity sensing: altered gravity fields may influence circadian timekeeping, and circadian timing may modulate gravitational responses.

Spaceflight experiments have been conducted with two different types of fungal growth rhythms. Cultures of the ring-forming fungus *Actinomyces levoris* were flown on *Soyuz 16* and *Apollo-Soyuz*. The ring-formation rhythm persisted in space with a 24- to 48-h period. Unfortunately, there is little evidence that this rhythm is truly circadian since it does not exhibit the required light dependency and temperature independency.

On the STS-9 *Spacelab-1* flight, the well-studied circadian rhythm involving the formation of bands of conidia-forming cells in the fungus *Neurospora crassa* was monitored. In constant darkness, the circadian period was approximately 22 h both in space and on the ground, but the contrast between the "band" and "interband" interval was markedly reduced in space and some arhythmicity was apparent after 6 days of spaceflight. There was evidence that a 4- to 6-h phase advance of the conidiation rhythm occurred on the first orbit in space.

Gravity (or any other factor) could influence circadian rhythms in any one of four ways. (1) There could be a direct effect on the clock machinery. (2) Some other physiological process could be affected, and this, in turn, could affect timekeeping. (3) Clock mechanisms may be unaffected, but the overt response used to measure timing may be altered or abolished. (4) Neither the timekeeping nor response mechanisms need be affected. Rather the flow of information between the two may be influenced. At present, too little is known about the influence of gravity on circadian rhythms to justify experiments to distinguish among these possibilities. For now and especially in higher plants, descriptive studies should be confined to determining whether altered gravitational force influences circadian rhythms and, if it does, how general and reproducible are the results.

Scientific Objectives

1. *To study the influence of gravity on a variety of plant functions.*

2. *To determine the immediate effects of removal of gravity on plant responses.*

3. *To determine the adaptation of plants by study of the long-term effects of microgravity on plant responses.*

Measurement Requirements

Ground-based research

1. Clinostat experiments are needed to explore whether there is a measureable (nonzero) gravitational intensity threshold for a detectable gravitropic response. Stated more precisely, is there a

level of gravity stimulation below which the reciprocity rule fails, even though the stimulus presentation time is made arbitrarily long? This would set limitations on the physical mechanisms of gravity sensing and also on the memory of the gravity sensing system and later stages of transduction.

2. The plant can store the effects of successive episodes of gravity stimulation. This is a form of memory, but one that lasts only for several minutes. In what form is the information stored? What role does statolith position play in information storage? Are there any chemical changes, including redistributions of growth hormones and ions, that have a relaxation time even roughly approximating the observed storage time?

3. Epinasty is responsible for the fact that plant organs exhibit a preferred direction that is usually not coincident with the plumb line or the main axis of the plant. There is evidence that the nastic responses are the result of an interplay of at least two growth hormones, auxin (IAA) and ethylene. More detailed studies are needed of the hormonal and nonhormonal mechanisms involved. Gravity is involved since increasing gravitational force results in a decrease in the epinastic angle. What are the mechanisms of gravity sensing in those organs? How (and where) is gravity sensed—diffusely or locally? Are there specialized sensing cells involved?

4. What are the biochemical mechanisms underlying the endogenous oscillatory processes responsible for those circumnutational responses that are not dependent on gravity?

5. What are the mechanisms responsible for the tropistic responses to electric and magnetic fields? To what extent do these involve a direct action on amyloplasts and statocytes? To answer these questions, it would be of interest to determine whether the responses persist in roots and coleoptiles whose gravity-sensitive tips have been removed and to correlate tropistic responses with statolith position.

6. In some but not all root and shoot systems, the presentation of light potentiates or modulates the gravitropic response. An obvious example is provided by the roots of seedling corn, which fail to respond to a gravitropic stimulus unless they are exposed to white light. The mechanisms by which light modulates gravitropism are not understood and require study.

Spaceflight experiments

1. What are the kinetics of gravitropic responses that occur in the absence of a significant background gravitational stimulus? Clinostat experiments show that a background force has a qualitatively large effect, but detailed studies are lacking.

2. There is a need to study the influence of a background gravitational response on the threshold and reciprocity relation for gravitropism.

3. Does microgravity influence the function relating gravitational force to the reduction in epinastic angle? The relation has been studied in several species on a clinostat. Would the same relation hold in the microgravity environment of spaceflight?

4. How general is the *Spacelab-1* finding that circumnutations persist in the absence of gravitational forces? To date, only one organ (hypocotyl) in a single species (*H. annuus*) has been studied. It would be well to choose species in which circumnutation was not particularly sensitive to clinostatting. The *Spacelab-1* experiments were conducted in a noisy environment, and the circumnutation, which was sporadic, may have been triggered by brief episodes of shock or vibration. In future experiments, vibration levels should be recorded to see if the incidence of circumnutation is correlated with such episodes.

5. What are the characteristics of phototropic responses in the absence of background gravitation stimulation? Ground-based tests in simulated hypogravity demonstrate that clinostatting has large effects on phototropic responses. The effects of microgravity on phototropism should be studied in spaceflight.

6. How do plants respond in the near absence of a magnetic force field? How do they respond to magnetic and electric fields in the absence of background gravitational forces? Are the responses similar in roots and coleoptiles whose gravity-sensitive tips have been removed?

7. The possibility that circadian rhythms can be altered by microgravity should be investigated in both microorganisms and higher plants. Numerous rhythms, including photosynthesis, cell divison, bioluminescence, phototaxis, and several enzyme systems, have been documented in single-celled algae. These organisms are particularly useful for experiments designed to probe clock mechanisms. Two types of systems should be studied in higher plants: (1) rhythmic leaf and petal movements in a nyctinastic

(night closure) plant and (2) floral induction in a photoperiod-sensitive plant.

8. In all of the above experiments, with the possible exception of those involving circadian rhythms, it is important to distinguish the immediate effects of removing the background gravitational response from the long-term effects of microgravity. The first requires brief exposures to microgravity that are confined to test periods, the latter requires continuous exposure to microgravity. All experiments should be compared to 1-g inflight controls and ground-based controls with and without clinostatting.

Instrumentation for space-based research

1. The present plant growth unit (PGU) is primitive and unsatisfactory. First priority must be given to the development of a plant growth chamber in which plants could be grown in space from seed to seed under conditions of controlled temperature, light, humidity, and nutrition.

2. An in-flight centrifuge would accomplish two different research objectives: (1) provide experimental access to the hypogravity range of acceleration levels between 0 and 1 g, and (2) provide a 1-g "control" test condition in space.

3. Automated experiment termination and sample preservation devices are urgently needed. These could function in unmanned long-duration satellites or in a Shuttle without obligating crew time.

4. Vibration and shock isolation systems are essential. Any spacecraft produces vibrations and shocks that are not easily predictable in advance. The most sensitive plant systems show up to 100 percent change in some processes due to moderate seismic stimulation. Therefore, mechanical shock isolation systems must be developed to permit other measurements to be made with confidence.

5. Small, portable recorders must be developed with appropriate interfacing to common computers for data read-out. The recorders can be designed to include capabilities for recording data from various kinds of sensors (e.g., thermometers, photocells, accelerometers, and pH electrodes).

6. Photographic recording devices are important for recording many kinds of data: control of on-off signals, intervals, and cycling are important.

4
Sensorimotor Integration

INTRODUCTION

The sense of gravity, provided by the vestibular end organs and by tactile and proprioceptive inputs, is a major factor in determining spatial orientation and motor performance on earth. In spaceflight, relative weightlessness is encountered for prolonged periods. This demands a reorganization in the processing of sensory information so that motor performance can be adapted to the new environment. It offers a challenge to sensorimotor coordination that is never encountered and cannot be adequately simulated on earth.

Central to the study of spatial orientation in weightlessness is an understanding of how the otolith organs, the linear accelerometers in the vestibular or nonauditory portion of the inner ear, are affected by microgravity. The otolith organs respond to gravity and provide the central nervous system with signals that encode head position and provide a continuous estimate of the upright. As with other physical linear accelerometers, however, the otoliths respond equally to all inertial force of the same magnitude and direction. Thus, the end organs not only sense head position with respect to gravity, but also linear accelerations that accompany head movements. It is important to understand that the otolith organs do not become inoperative in microgravity. According to present knowledge, the afferent nerve fibers will emit a background discharge in space and will continue to respond during any head movement that includes a component of linear acceleration. Perhaps the most important difference is that static reorientation of the head with respect to external references, such as the floor of the spacecraft or the vector pointing toward the earth's center, will no longer give rise to a change in otolith activity. As a result, portions of the central nervous systems responsible for spatial orientation and movement must accustom themselves to the absence of this signal and function without it.

Initially, the lack of gravitational force during spaceflight can have severe disruptive effects, causing spatial disorientation and space motion sickness. Within several days the symptoms disappear as continued exposure to microgravity leads to adaptive changes in sensory processing and motor control. Adaptive changes promote more efficient performance in microgravity, but they can cause difficulty if the space traveler reaches another gravitational environment or returns to earth. The neural mechanisms responsible for adaptation to microgravity are as yet poorly understood, but are of considerable importance. A program of basic research can develop information that will facilitate adaptation to space and readaptation to earth and can also lead to new therapies for space motion sickness. In a broader context, however, the orbiting Space Station will provide a unique resource for studying spatial orientation and motor performance in the absence of gravity. It offers the opportunity to ask fundamental questions about neural processing and adaptation in sensorimotor systems involved in perceiving and responding to gravitoinertial force. This chapter identifies some of these questions and describes a research program that is intended to lead to a better understanding of the mechanisms responsible for man's ability to adapt successfully to the sensorimotor challenge of weightlessness.

MAJOR SCIENTIFIC GOALS

1. *To understand the basic mechanism underlying spatial orientation in humans and the changes that occur in the absence of gravity.*

2. *To determine short- and long-term effects of the absence of gravity on neural processing in the vestibular system and on other parts of the nervous system that are also involved in spatial orientation and movement control.*

3. *To establish the causes of space motion sickness and to make recommendations for its treatment and prevention.*

SPATIAL ORIENTATION

Introduction

Spatial orientation is the relation established between a body-oriented coordinate system and external reference frames. It results from the integration of sensory signals from the visual, vestibular, tactile, and proprioceptive systems and from a comparison between them and the motor-command or efference-copy signals arising in the brain (Figure 4.1). A sense of spatial orientation helps to guide behavior at conscious or perceptual levels as well as at unconscious or automatic levels. Static visual cues to the direction of the vertical or horizontal, which normally interact with graviceptor cues on earth, become increasingly dominant in establishing spatial orientation in weightlessness. Tactile cues such as pressure on the soles of the feet may also promote a sense of vertical and of the upright.

The semicircular canals, the vestibular end organs that detect angular head rotation, appear to be little affected by weightlessness and probably provide much the same information in space as on earth. The discharge of otolith organs, on the other hand, must be fundamentally different in microgravity. As linear accelerometers, they should continue to signal linear head movements, but can no longer serve their usual graviceptive role of indicating static head position with regard to gravity. This may lead to various illusions of spatial orientation on entering weightlessness, including sudden reversal of orientation, the so-called "inversion illusion." In addition, moving visual fields that produce sensations of self-motion and postural adjustment are unhindered by constraints from the otolith organs, which do not confirm or deny body tilt. Thus, the visually-induced illusion becomes stronger in space.

Cues used for spatial orientation in initial phases of adaptation to weightlessness vary. Some individuals become strongly dependent on vision, orienting with respect to familiar vertical references such as equipment racks, the floor of the spacecraft, and other crew members. Dependence on vision as a substitute for otolith and proprioceptive information begins on entry into weightlessness and can last for many days. Other crew members are more "body oriented" and align their exocentric vertical to lie along their long body axis. These people do not become as disoriented when working in unusual attitudes relative to external

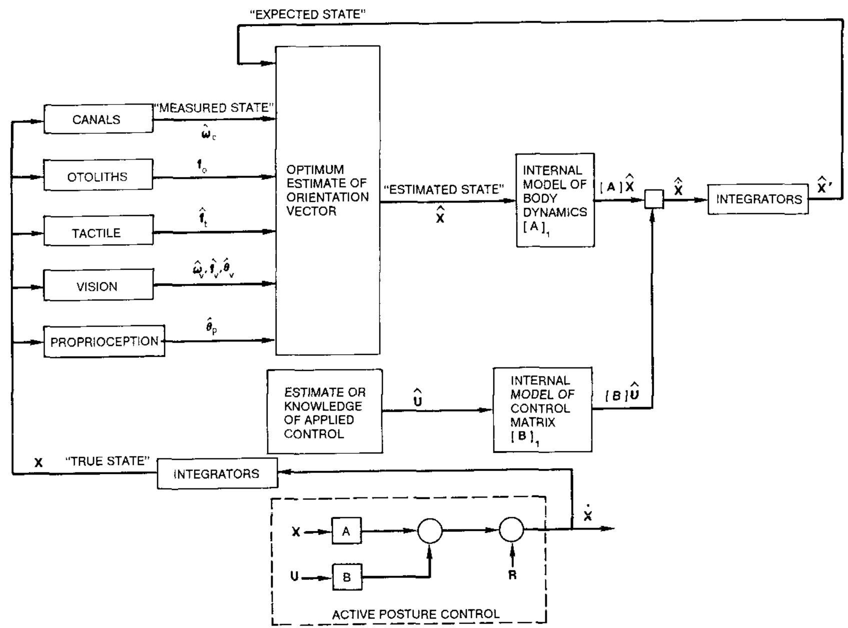

FIGURE 4.1 Schematic representation of spatial orientation process. "True state" vector **X**, consisting of linear and angular positions and velocities, is produced by changes resulting from three sources: unforced behavior of body $\hat{\mathbf{X}}$ processed by A, commanded body changes, commands **U** processed by B, and unmeasured disturbances **R**. Various sensors are each responsive, especially to one or more components of measured state. The caret indicates an estimate of the vector: $\boldsymbol{\omega}$, angular velocity; **f**, specific force, gravity minus linear acceleration; $\boldsymbol{\theta}$, angle. Measured state signals are combined with "expected state" $\hat{\mathbf{X}}'$, derived from a presumed internal model of the body, in optimum estimator to produce estimate of orientation $\hat{\mathbf{X}}$.

references or when traversing places where visual cues for vertical orientation are absent. Thus far, it has not been possible to predict individual differences in visual-field dependence from ground-based tests of visual-vestibular interactions.

There are also post-flight alterations of spatial orientation and motor performance. Several illusions are commonly reported, including a feeling of heaviness, a sense of disorientation when making sudden pitching or rolling head movements, an inability to move about in the dark, and an illusion of floor motion during vertical body movements. The threshold of detection of linear acceleration may change, and visual influences on orientation appear stronger than before the flight. At the time of reentry and shortly thereafter, tilting movements of the head may cause a sense of sudden linear translation in the opposite direction.

It is hypothesized that in space the nervous system comes to reinterpret afferent signals from the otolith organs. One possibility is that the brain now interprets the signals as arising solely from translational head movements, rather than from a combination of such head movements with changes in attitude with respect to the vertical. This "otolith reinterpretation" hypothesis must be verified, but if correct, could be useful as a basis for devising strategies for preadaptation to flight.

Scientific Goal

To understand the mechanisms that underlie spatial orientation on earth, in space, and after return to earth.

Scientific Objective

To use psychophysical methods to determine the relative contributions of vestibular, visual, proprioceptive, and tactile inputs to perception of spatial orientation and self-motion before, during, and after spaceflight.

Measurement Requirements

1. Psychophysical experiments on perception of linear and angular motion should include measurement of sensitivity, time constants, thresholds, dynamic response, and trajectory and should

measure responses to visual and vestibular stimuli and their interactions. These studies require a human rotator, a sled, and a human centrifuge.

2. Tests of spatial orientation should include measurements of perceived static body attitude and the perceived vertical during rotation, linear motion, and tilt.

3. Measurements of visual-vestibular interactions using horizontal, vertical, and torsional eye movements will require a flexible wide field of view visual stimulator, a sled, and an angular rotational device.

4. A study of proprioceptive changes in weightlessness should be done through measurements of joint angle and pointing accuracy.

POSTURAL MECHANISMS

Introduction

An important function of posture control is to coordinate muscular activity so as to maintain the orientation of the body with regard to gravity. This requires the integration of orientation and motion information from the visual, vestibular, and somatosensory systems. Convergence of this information is required because no one modality measures the state of body orientation directly. Animal models of upright posture and equilibrium are of limited usefulness. Hence, most of the required studies of postural control must be done in humans.

Posture and equilibrium appear to be mediated by automatic mechanisms that are largely independent of awareness and voluntary control. Consequently, conscious reports of subjects are not sufficient to reveal how postural mechanisms operate. Strategies for organizing incoming sensory information and the resulting muscle activity patterns are interdependent and appear to be planned in advance. The way a subject intends to move influences how the senses are interpreted. Further, sensorimotor coordination can be influenced by experience.

Current research suggests that automatic postural actions may be organized into a set of relatively fixed "strategies." In this view, incoming sensory information is interpreted according to prescribed formulas, and muscle activities are organized into fixed patterns of interaction. These strategies are used to return the center of gravity to a stable position when the body is perturbed. Postural strategies can be altered. A basic question is how they must change to meet the mechanical demands of space. On earth, the repertoire of fixed strategies appears to be limited. Subjects are able to adapt postural control to changing environmental conditions by using different combinations of the same repertoire of strategies. The pattern of muscle contraction necessary to execute a given movement depends to a large measure on the configuration of support surfaces provided to the subject. The elimination of the need for antigravity postures in microgravity renders much of the postural repertoire irrelevant. This creates a unique context for the interpretation of sensory inputs and the coordination of muscular actions.

Observations on adaptation of automatic postural systems to microgravity are limited, yet they suggest that changes in the interpretation of sensory inputs and in the coordination of muscular actions are significant. Voluntary pointing accuracy and perception of static limb position are impaired in microgravity, and naive subjects, when asked to orient themselves vertically in relation to visual surroundings and support surfaces, assume skewed postures. The H (Hoffman) reflex, which reflects supraspinal and otolithic control of spinal motorneurons, appears to be depressed in flight and may be enhanced for several days postflight. Returning crew members routinely experience difficulties in walking and standing with eyes closed, and in making quick turns. These symptoms occur even after missions of relatively short duration, where changes in muscular strength are minimal. The symptoms thus cannot be ascribed to changes of skeletal muscle. Clearly, there is a change in central motor programs.

Scientific Goal

The primary scientific goal for the study of human postural mechanisms in space is to understand how automatic postural control systems adapt to microgravity. Such an understanding should contribute to our knowledge of the adaptive mechanisms that operate both on earth and in space. Microgravity requires the reorganization of postural control mechanisms in a situation where elements of the vestibular input are altered on a long term basis. This set of conditions would be difficult, and probably impossible, to simulate on earth.

Scientific Objectives

1. *To determine how sensory inputs and coordination of muscular actions are organized before, during, and after flight.*

2. *To use the tools of neurophysiology and kinesiology to measure postural movements and the associated muscle activation patterns elicited by external perturbations imposed under a variety of surface conditions.* These studies will help determine the extent to which subjects adapt their posture to microgravity by recombining terrestrial strategies or by learning new strategies.

3. *To develop training programs that will allow flight crews to learn postural strategies that will be useful in microgravity.* Such a program will have practical consequences and will provide a test of the concepts developed in other more basic studies. It is conceivable that similar methods could be used to retrain neurologically impaired individuals.

Measurement Requirements

1. Changes in the patterns of muscle activation and muscle strength should be quantified. Initially these tests should be done before and after flight so as to provide clues about changes that occur in microgravity and to help design in-flight postural experiments associated with visual-vestibular and somatosensory inputs. Post-flight testing should begin immediately after debarkation and at regular intervals following return to earth.

2. The analysis of movements of the body and associated muscle activation patterns requires multichannel surface electromyography (EMG) recording and a means to measure joint angles. A standard video recording of the body with pressure targets placed at desired points should provide sufficient temporal and spatial resolution for analysis of movement. Such recording can be stored on tape for off-line analysis.

3. Subjects should be tested for their ability to stabilize posture during eye-hand, eye-head, and head and trunk movements while they are being displace by an external device or as a result of the inertial reaction to limb movement. Drop tests should be compared on earth and in space, as should postural responses produced by visual, vestibular, and somatosensory stimuli.

THE VESTIBULO-OCULAR REFLEX

Introduction

The vestibulo-ocular reflex (VOR) provides ocular compensation so that stable gaze and clear vison are maintained during head movements. Adaptation of the VOR to weightlessness is of fundamental importance if one is to function appropriately in space, since errors in stabilization of gaze during head movements can create disorientation and motion sickness. The VOR in the yaw or horizontal plane has been studied extensively, both in animals and humans. Quantitative models exist that predict how eye movements are related to activity in the central vestibular system. Consequently, study of the horizontal VOR is useful, not only for determining how eye movements are adapted to compensate for head movement in an altered force environment, but also for understanding the nature of central vestibular system processing that produces this compensation. It is likely that the VOR in the sagittal and roll planes is quite different on earth than in space and this should be studied. How information about head movement in three dimensions is integrated within the central nervous system is not well understood and is currently being investigated. Quantitative three-dimensional models of the VOR that are now being developed may provide a theoretical basis for understanding alterations in the VOR in weightlessness.

It is likely that every portion of the labyrinth contributes activity to the ocular compensation related to head movement and head position. Semicircular canal activity during rotational head movements is primarily responsible for producing compensatory eye movements. The otolith organs can alter the VOR gain. Whether this gain change will be altered by exposure to microgravity is unknown. Other contributions of the otolith organs to the VOR include ocular counter-rolling during head tilt, and vertical, horizontal, and torsional eye position changes during translational acceleration. Tests using linear acceleration on earth have indicated that ocular counter-rolling is reduced after about a week in space, but the horizontal component of the eye movement response appears to be maintained. If this is confirmed, it would suggest that adaptation of induced eye movements is direction-specific and appropriate to the change in gravitational force. Rotation about axes tilted from the vertical (off-vertical axis rotation) activates the otolith organs with a rotating gravity vector on earth, producing horizontal, vertical, and torsional eye position changes and nystagmus—an involuntary back-and-forth movement of the eyeball. As yet, there is little information about how the response to off-vertical axis rotation is affected by adaptation to space.

Although the VOR is a reflex response, its characteristics depend on a variety of factors including general state and level of alertness, intent to view near or far targets, whether one watches targets moving with the head, and whether head movements are active or passive. Each of these factors must be considered when studying effects of weightlessness. Stuctures that mediate adaptation of the VOR during abnormal input are only now becoming understood. Most studies of adaptation of the VOR have been done on head and eye movements in the horizontal plane, and comparatively little is known about the vertical VOR or about visual-vestibular interactions during pitching or rolling head movements. Study of the vertical and torsional VOR may provide insight into factors that could lead to disorientation and symptoms upon insertion into space.

Scientific Goal

The primary scientific goal for the study of the vestibulo-ocular reflex (VOR) is to determine how it is altered by an absence of gravitational input. Of particular interest are those portions of the VOR that involve vertical and torsional eye movements. Measurements should be taken to determine whether coordination of gaze is altered in space during head movements and to establish quantitative three dimensional models of the VOR that will explain and predict the changes in weightlessness.

Scientific Objectives

1. *To describe how head movements in the horizontal (yaw), vertical (pitch), and torsional (roll) directions in space affect stabilization of gaze.*
2. *To establish a three-dimensional model of the human VOR and of central vestibular processing that will account for alterations in eye movements in microgravity.*
3. *To understand how the VOR adapts in microgravity and if it can be preadapted prior to spaceflight.*

4. *To investigate the effects of conflicting visual and vestibular stimuli on gaze-stabilization during active and passive movement. These data should be used to predict and improve gaze stabilization under the various conditions that the flight crew encounters.*

Measurement Requirements

1. It is essential that there be accurate techniques for continuously recording horizontal, vertical, and torsional eye and head movements. The value of electro-oculography and cinephoto techniques, which have heretofore been utilized for measuring eye movement, is limited. They are either not accurate enough or require extensive processing that precludes continuous on-line recording. New techniques utilizing magnetic scleral search coils in soft contact lenses may overcome these difficulties but require extensive technical development.

2. Comparative studies should be done in mammals other than humans, particularly in monkeys, to determine the relationship between eye and head movements, and activity in the central nervous system.

3. An Orbital Vestibular Research Facility (OVRF) capable of providing controlled linear and angular acceleration, and variable levels of centripetal acceleration is essential for these studies. The facility should be designed for both human and animal subjects.

PROCESSING IN THE VESTIBULAR SYSTEM

Vestibular Signals in Microgravity

The utricular and saccular maculae are the portions of the labyrinth that sense gravity. It is essential to know how their function is affected by microgravity if we are to understand the adaptive response to this environment. The only direct information comes from a NASA-sponsored study in frogs during a 7-day orbital flight conducted by T. Gualtierotti and his colleagues. A floating microelectrode continuously monitored changes in the resting activity of single otolith afferents and their response to centrifugal forces. Interpretation of the data was made difficult because of the small number of nerve fibers sampled, the possibility of injury discharges, and the inadvertent presence of suprathreshold vibrations. As a result, the characteristics of the input from the utricle and saccule in space, which form the physiological basis for alterations in function in weightlessness, remain unknown.

If it is assumed that the vestibular end organs function normally in space, then predictions of the response of the vestibular apparatus to microgravity can be made from ground-based studies. Current knowledge suggests that in the absence of gravity and other inertial forces, otolith afferents should revert to a zero-force or resting discharge. This profile of resting activity would be consistent with only one terrestrial condition, free fall. This would be contradicted by visual and proprioceptive information that indicates that the subject is in a stable environment. This conflict, by itself, might be expected to cause disorientation and malaise.

The discharge of the otolith organs should also be different on earth and in space when the head is pitched and rolled. These movements elicit three force components from an erect posture on earth: a gravity-related component, a tangential component parallel to the direction of motion, and a centrifugal force perpendicular to the head trajectory. In orbital flight, the gravitational component is eliminated while the other components remain unchanged. Visual and semicircular canal components are presumably also unaffected. The result should be a disparity between the way that sensory inputs associated with pitch or roll head movements are experienced on earth and in space. On the other hand, yaw or horizontal head movements, i.e., movements about the long axis of the body, should elicit the same visual and vestibular inputs in space as on earth.

It has been suggested that microgravity might be deleterious to the otolith organs in any of several ways. Removal of gravity might alter the activity of receptor cells in the saccular and utricular maculae and their innervating afferents, leading to a change in structure and function of the end organs. In addition, the dynamic equilibrium between the calcium carbonate in the otoconia and ionized calcium in extracellular fluids might be altered over the long term. The activity of otolith hair cells might be altered by an absence of compressional forces related to gravity. There may be changes in inner-ear fluids. These could accompany the rostralward shifts in body fluid that occur in space or the changes in plasma concentrations of calcium and other divalent ions. While these mechanisms would not explain the rapid onset of symptoms of motion sickness upon insertion into orbit, they are of interest in determining the role of gravity in the normal development and functioning of the vestibular apparatus. They may also be of importance during and after long-term flights, and may bear investigation.

Processing in the Vestibular Nuclei

The vestibular nuclei play a pivotal role in coordinating eye, head, and body movements, but much remains to be learned about their organization. Signals from the semicircular canals, the otolith organs, and tactile and proprioceptive senses are combined in the central vestibular system with visual and eye-movement-related signals to produce a neural representation of the position and motion of the head, eyes, and body. Activity produced in the neurons related to the semicircular canals has been extensively studied. Less is known of otolith-related activity. Second order otolith neurons respond to changes in head positions with regard to gravity, but how they process activity from the otolith organs in weightlessness is unknown. Preliminary work has shown that neurons receiving otolith activation in the vestibular nuclei are strongly activated by visual inputs, similar to those that would be encountered during translational head movements. The input pathways from the visual system and the dynamics of the response of vestibular neurons to linear field motion are unknown.

Recently, it has become apparent that environmental factors can play an important role in the structural organization of the developing nervous system. For example, if young animals are prevented from experiencing patterned vision in one eye, the input to neurons in the visual cortex does not develop normally. There appears to be a "critical period" for this development, after which patterns of connectivity are established and cannot be substantially altered by further experience. While developmental studies of the vestibular, oculomotor, and body postural systems are relatively limited, there is ample indication that there is significant maturation after birth, which might be sensitive to external conditions. Nothing is known about development in a gravity-free environment, and studies in such conditions might provide unique insights into factors guiding peripheral and central otolith neurons in establishing synaptic contact within the central nervous system. If postural or ocular reflexes were to exhibit a "critical period" during development, it would be of fundamental interest since it could lead to an understanding of how various afferent synaptic inputs are coordinated on target neurons to produce postural and oculomotor responses.

Adaptation and the Vestibulo-Cerebellum

The semicircular canals and otolith organs code a broad range of force levels in responding to angular and linear acceleration associated with head movement. It is essential that mechanisms exist to change the gain, phase, and bias of the input coming from the two ears. Adaptive mechanisms are called into play under conditions in which the visual input is modified or when the input from the labyrinth is altered, as in microgravity. It is likely that these mechanisms play a crucial role adapting oculomotor and skeletal motor performance in the reduced force levels encountered in spaceflight, as well as in disease states where the afferent input from the periphery is altered or central processing is modified. Although the vestibular apparatus is under efferent control of the brainstem, adaptive processes probably operate primarily within the central nervous system, not in the peripheral labyrinth. As yet, there is little information about the neural mechanisms responsible for the adaptation.

No single structure appears to be responsible for producing vestibular adaptation. The vestibulo-cerebellum, which includes the flocculus and paraflocculus and the nodulus and uvula, is well situated to deal with disparities between visual and vestibular information, since it receives visual and vestibular input and projects directly to the vestibular nuclei. There is evidence to suggest that parts of the vestibulo-cerebellum act in concert with inputs from the inferior olive to raise or lower the gain of the VOR and cause it to habituate. Conclusive proof of their involvement is still lacking, however, and must be sought in ground-based studies. How the various parts of the vestibulo-cerebellar cortex interact with the deep cerebellar and vestibular nuclei and what transmitters are utilized in this control are also largely unknown. A better knowledge of the anatomical and physiological substrates of adaptation may lead to strategies that will enable the flight crew to adapt to unusual vestibular stimuli. Such knowledge could also provide a rational basis for the development of drugs that could alleviate the symptoms that are produced by these stimuli.

Scientific Goals

The primary scientific goals for the study of vestibular processing are:

1. *To determine whether the function of the labyrinth is altered during spaceflight.*
2. *To understand how vestibular signals are processed in the central nervous system in microgravity.*
3. *To understand the neural basis of sensorimotor adaptation.*
4. *To understand the role of gravity in the development of sensorimotor functions.*

Scientific Objectives

1. *To determine whether there are structural alterations of the vestibular end organs of mammals during spaceflight.*
2. *To examine the nature of the signals coming from the labyrinth in weightlessness by recording from the vestibular nerve and vestibular nuclei.*
3. *To determine the effects of weightlessness on postnatal development of sensorimotor functions and to establish if there is a "critical period" in development during which the presence of gravity is essential for normal development of these reflexes.*
4. *To investigate the neural basis for adaptation of the vestibular system to weightlessness in earth-based and in-flight research.*

Measurement Requirements

1. Studies are needed of the effects of both short- and long-term exposure to microgravity on the structure of the utricular and saccular maculae and on the formation of otoconia and of otoconial membranes. Interpretation of the flight experiments will require ground-based studies of the detailed structural organization of the vestibular end organs.
2. Alterations in the function of the vestibular end organs should be determined by recording the activity of vestibular nerve fibers in-flight. The methods involved are technically challenging and will require extensive ground-based development. The experiments are best done in chronically implanted animals. Adequate collection of data from individual animals will require missions lasting a month or more.

3. Too little is known about the central processing of otolith information or about the neuronal mechanisms of adaptive plasticity to justify space experiments at the present time. Instead, a vigorous, ground-based program of research, involving the use of modern neurophysiological methods, is called for. Until specific hypotheses can be formulated, space research should be confined to determining the effects of weightlessness on otolith-mediated reflexes, as well as the time course of adaptation to microgravity. Parallel studies in man and animals should be done.

4. The space environment provides a unique opportunity for the study of the role of gravity in the neonatal development of sensorimotor functions. Initial experiments should be descriptive and should correlate behavioral and morphological observations. Young animals should be raised in microgravity. The effects of such nearing of the VOR, postural reflexes, locomotion, and other sensorimotor functions should be assessed. Animals should be flown at various ages and for various durations to see if there are "critical periods" during which neural development is particularly sensitive to the presence or absence of gravity.

Instrumentation/Facility Requirements and Research Subjects

1. Dynamic testing of vestibular processing, of adaptation, and of development in weightlessness requires the variable force centrifuge provided in the OVRF. This facility should include the capability for angular rotation, centripetal acceleration (centrifuge), and linear acceleration (sled) for both animals and humans. Specifications and a more complete description are given in the following section.

2. One-g controls in space are essential for determining structural changes. Facilities for high-quality fixation of the inner ear in space are needed, as well as an on-board centrifuge that can provide variable levels of force.

3. Animal research is fundamental to understanding adaptation of the peripheral end organs and the central vestibular system to space. A vigorous program of morphological and physiological experiments, both ground-based and in-flight, are needed to determine how microgravity affects the function of the end organs. This requires provisions for in-flight recording facilities in an Orbital Neurophysiology Laboratory and for preservation of tissues.

4. The choice of species should be dictated by suitability for the experiments that are proposed and by the applicability of the results to man. Developmental studies can profitably be pursued in fish, amphibian larvae, and small mammals. Morphological experiments on the vestibular end organs are best done in small mammals. Physiological experiments on the VOR and the central vestibular system should be done in monkeys; the results should be compared with those obtained in behavioral studies in monkeys and man.

5. Monkeys are particularly suitable subjects for studies of central adaptation. Their eye movements and brain closely resemble that of man, they can be trained to perform complex tasks, techniques for studying single neurons in the central vestibular system are well developed, and existing quantitative models of the VOR in the monkey provide a theoretical basis for predicting and interpreting the data that will be obtained. In-flight facilities for handling monkeys should be provided.

MOTION SICKNESS

Symptom Complex and Signs

Motion sickness occurs in a variety of transportation modes. It can be elicited by both real or perceived motion of the body and presentation of certain patterns of visual stimulation. With the advent of orbital spaceflight, space motion sickness became a significant operational concern for the Russian and American space programs. Nearly half of U.S. flight personnel have experienced some symptoms of motion sickness and nearly one third have had at least one episode of emesis.

The symptoms most often associated with motion sickness are nausea and vomiting, but the range of symptoms characteristic of motion sickness is actually much broader. It includes pallor, stomach awareness, stomach discomfort, subjective body warmth, sweating, increased salivation, headache, dizziness, dry mouth, drowsiness, and lethargy. The particular symptoms experienced and their order of appearance are influenced by factors such as environmental temperature, exposure duration, and the relative provocativeness of the motion environment. Many of the symptoms are subjective—only pallor, sweating, and vomiting can be easily observed if one cannot communicate with the motion sick subject. This has made it difficult to study motion sickness in animals.

The physiological changes associated with motion sickness tend to be variable or inconsistent both within and across individuals. For example, heart rate, blood pressure, body temperature, and respiration rate appear to show few consistent changes. For this reason, it has been necessary to develop a global scale of motion sickness signs and symptoms to rate severity of involvement. This mandates that large groups of subjects be studied to determine causative factors or efficacy of therapy, a condition that is not easy to attain with limited flight opportunities. Motion sickness also causes changes in gastric motility that could alter the efficacy of antimotion sickness drugs given orally. Biochemical changes associated with motion sickness may be a consequence of vomiting and subsequent fluid loss. Urinary output is diminished in motion sickness, suggesting increased levels of vasopressin. Stress hormones also show increased levels during exposure to provocative motion.

Models of Motion Sickness

The development of methods for predicting and preventing motion sickness has been hindered both by the lack of understanding of its basic causes and the lack of an adequate animal model. One observation appears beyond question: individuals without a functioning labyrinth are not susceptible to motion sickness. In addition, space motion sickness is brought on or exacerbated by head movement and made better by rest. This suggests that activity arising in the labyrinths activates central mechanisms that produce the symptom complex. The most commonly accepted model of motion sickness holds that vestibular input is relayed to an area of the medulla, the area postrema, which has a rich supply of neural transmitters and hormonal receptors. Area postrema is believed to act on a vomiting mechanism located in the medulla, which innervates the gut. The hypothalamus is postulated to be a source of input to the area postrema when motion sickness is produced, either by direct neural connections or through hormonal control. Motion sickness susceptibility is lost in dogs after injury to the nodulus of the vestibulo-cerebellum. It has been proposed that nodular-brainstem connections are important for production of motion sickness.

Critical parts of this hypothesis have been called into question. It has been shown that vomiting can occur when the area postrema is destroyed. Workers were unable to elicit vomiting by electric stimulation of the so-called "vomiting center." Studies of nodular-brainstem connections have not been of value in revealing how this region of the vestibulo-cerebellum might exert its control on the area postrema. At present, therefore, it must be concluded that the basic circuitry responsible for motion sickness, nausea, and vomiting is unknown.

The most widely accepted theory for explaining the sensory input that produces motion sickness is the sensory-conflict perspective. This relates motion sickness to contradictory sensory and motor information in channels carrying activity related to spatial orientation and body configuration. It is difficult with this perspective, however, to account for interindividual threshold differences and the finding that some individuals are highly susceptible to some forms of stimulation but not to others. This is still an important area for research.

Experimental Approaches

No single factor has been identified that predicts susceptibility to motion sickness. Several approaches have been taken in such studies in humans. They include (1) functional capacity tests, (2) ground-based provocative tests, (3) provocative tests administered during parabolic flight in which there are brief periods of weightlessness, and (4) tests of vestibular and sensory motor function before, during, and after orbital flight.

(1) Functional capacity tests include assessment of the VOR and of vestibulo-spinal reflexes. They provide an indication of processing in sensory and motor systems related to balance and orientation. Values obtained on earth before flight may be related to susceptibility to motion sickness in orbital flight, and repetition of the tests after flight can give an indication of the forms of adaptive changes or compensations that have occurred.

(2) Ground-based provocative tests measure susceptibility to different combinations of labyrinth and visual stimulation. They provide a profile of an individual's response to various forms of provocative stimulation and offer insight into adaptive compensations that occur in-flight. Three types of tests have been generally

utilized: off-vertical axis rotation, pitching the head out of the axis of rotation during constant velocity rotation (cross-coupled angular acceleration or pitching while rotating), and sudden-stop rotations. There are several problems with the use of provocative tests. First, they usually challenge the individual's response during short exposures, while microgravity subjects the individual to continuous exposure to free fall. Second, none of the stimuli mimic weightlessness and they have been used primarily because they cause motion sickness. This may account for the finding that none of the tests can predict which subjects will become sick when exposed to weightlessness for extended periods.

(3) Parabolic flight maneuvers have been used to generate brief periods of weightlessness, lasting 20 to 30 s, alternating with 20- to 30-s periods of approximately 2-g force level. Such experiments can provide insight into the sensorimotor alterations that occur during longer exposures to free fall. Some individuals experience motion sickness simply by virtue of exposure to the force fluctuations. One of the most intriguing observations concerning space motion sickness came from the *Skylab M-131* experiment on vestibular function. Astronauts were tested for their susceptibility to motion sickness by having them pitch their heads while rotating. Tests were done before, during, and after flight. Susceptibility to this maneuver was markedly decreased in-flight and for some period after flight. This experiment suggests that the central nervous system had learned to ignore certain types of input from the otolith organs during its exposure to weightlessness. Subsequent parabolic flight experiments have shown that the provocativeness of such head movements during angular rotation decreases immediately on exposure to free fall, relative to its provocativeness on earth or in 2 g. This indicates that the otoliths must provide continuous information for interpreting afferent activity from the semicircular canals and emphasizes the necessity for understanding alterations in otolith activity in free fall.

(4) Finally, in-flight experimental programs are essential for understanding space motion sickness. Valuable information has been obtained from the Skylab missions and the STS missions, including *Spacelab 1*. From these flights, it has become apparent that head movements tend to exacerbate symptom development. Such data support the now generally accepted view that space motion sickness is a form of motion sickness and does not result primarily from the rostral redistribution of body fluid that occurs

in weightlessness. An important aspect of future in-flight experiments will be a systematic analysis of how otolith function and its influence on orientation and sensory motor control are affected during exposure to microgravity and how these alterations are related to space motion sickness.

Symptom Management

Three forms of symptom prevention and management have been or are being explored. These include (1) biofeedback training, (2) preadaptation procedures, and (3) antimotion sickness drugs.

(1) Biofeedback training has been effective in combination with incremental exposure to cross-coupled angular accelerations in preventing motion sickness in airsick flight trainees. The subject monitors various physiological parameters, including heart rate and blood pressure. With the use of appropriate training, some of these individuals are able to maintain control over these variables, and delay or prevent the onset of symptoms of air motion sickness. It would seem reasonable to suppose that biofeedback training could also be used to ameliorate the symptoms of space motion sickness.

(2) To date, preadaptation measures have not been effective in countering space motion sickness. However, procedures involving graded exposure to provocative vestibular stimulation have been effective in preventing air sickness, and adaptation training achieved in slow rotation rooms is known to transfer to aviation conditions. Attempts are currently being made to determine if such training can also prevent the motion sickness elicited by head movements in the microgravity phase of parabolic flight. Effects of prism adaptation on susceptibility to motion sickness and on enhancement of visual over otolith cues are also under investigation.

(3) While effective drug therapy is a major aim of NASA's life sciences program, theoretical insights into how such drugs work do not exist. At present there is no clear rationale for developing such drugs. Drugs used to control space motion sickness are for the most part the same drugs used on earth to treat motion sickness. They include anticholinergic agents, such as scopolamine, that block nuscarinic receptors and antihistaminic drugs such as diphenhydramine or meclizine. These agents are effective in reducing symptoms in some individuals, but why they are ineffective

in others or what part of the amelioration is due to a placebo effect is unknown. Receptors for each of these drugs have been demonstrated in the vestibular nuclei and posterior brainstem. Since these receptors are widely distributed in other regions of the brain, side effects associated with their use makes treatment in high doses or for prolonged periods of time unsatisfactory.

Drug efficacy is usually determined by using provocative testing on earth. The ultimate test, however, is on space travelers as they are exposed to continuous microgravity. Confounding factors in studies are the varying levels of flight crew activity, possible variations in gastric motility affecting absorption, and the findings that many of the crew who experience space motion sickness have had no symptoms under even the most severe test conditions on earth including parabolic flight. In view of the complex operational demands made on the astronauts in-flight, there is a limit to which they can be subjected to provocative testing. Also, the motion environment or administration of antimotion sickness drugs cannot be easily controlled. Research in this area will be facilitated by the use of dedicated payload specialists whose main function is to act as subjects in motion sickness studies.

Scientific Goals

The primary goal for research in space motion sickness is to identify its cause(s). In-flight experimental programs must evaluate the validity of ground-based provocative tests, functional capacity tests, and other psychological and physiological procedures in predicting susceptibility to space motion sickness. In-flight assessments of payload specialists in whom the motion environment and medicine intake are controlled are essential to evaluate the efficacy of various ground-based preadaptation procedures, the possible benefit of autogenic and biofeedback training regimens, and the protective benefit of antimotion sickness drugs.

The identification of the brain region underlying motion sickness should be a primary goal of ground-based research. This end would be facilitated by the development of an animal model of motion sickness that would be amenable to studies of the basic neurophysiology of motion sickness and for testing drugs or other treatment modalities.

Scientific Objectives

1. *To identify in humans the kinds of head movements and visual-vestibular conflicts that are provocative in free fall.*

2. *To develop predictive tests of susceptibility and, thereby, identify individuals requiring medication or preflight adaptation.*

3. *To develop effective symptom management and prevention procedures. In this regard, ground-based parabolic flight and space flight programs designed to understand etiological factors should continue to be supported.*

4. *To define the basic mechanisms of space motion sickness.*

5. *To test classic theories of motion sickness including the possible presence of a chemoreceptor trigger zone and a vomiting center. Circuits that link visual or vestibular inputs to output regions that produce symptoms and signs should be delineated. The role of the vestibulo-cerebellum needs reevaluation.*

6. *To develop a rational basis for pharmaceutical development. The analysis of neurotransmitter and receptor localizations as demonstrated by immunocytochemical, receptor binding and electrophysiological techniques should be the basis for such an effort.*

Facility and Experimental Considerations

For understanding and treating space motion sickness in humans:

1. Aircraft for performing parabolic maneuvers to generate periods of weightlessness.

2. In-flight Orbital Vestibular Research Facility is needed for vestibular and postural testing, study of the VOR, and delivery of provocative in-flight motion.

3. The success of spaceflight experiments depends on having trained individuals (dedicated payload specialists) available with adequate time lines. Experiments on space motion sickness are best carried out with these individuals because it is essential to be able to control the in-flight "exposure history" and use of antimotion sickness drugs. Without such controls it is difficult to obtain reliable information on susceptibility and eliciting factors.

4. A program should be established for ground-based research on basic aspects of the generation of motion sickness, nausea, and vomiting to develop a rational basis for therapy or preconditioning. An important step in this research is to identify an adequate

animal model of motion sickness in which prodromal signs can be recognized, so that effects of motion stimuli or treatment can be studied without the necessity for producing vomiting. Conditioned aversion to food associated with motion sickness experience, or monitoring of autonomic signs may be useful as endpoints if they can be validated.

Orbital Vestibular Research Facility

Investigation of vestibular function in space will require an Orbital Vestibular Research Facility (OVRF) suited for psychophysical and neurophysiological experiments. It should be designed to handle human and animal subjects. The device or devices must be capable of delivering both transient and long-duration, precisely controlled, centrifugal force. Subjects have to be oriented at any desired angle with respect to the force vector and there is also a need for precisely controlled angular accelerations about pitch, roll, and yaw axes, both in isolation and in combination with linear forces. A linear track must also be present to deliver precisely controlled translational accelerations. All motion devices should be provided with full-field visual displays capable of three-dimensional rotations and translations. Horizontal, vertical, and torsional eye movements should be monitored by magnetic search coils. The necessary objectives can be met by constructing a three-axis, high performance rotator that can be placed at the end of a centrifuge or on the linear track. The centrifuge has to be of relatively large dimensions so as to minimize cross-coupled accelerations. The linear track should be sufficiently long to maximize the magnitude of the force that can be delivered at any semisolid frequency. The design of the OVRF should be modular, so that the rotator can be flown separately or mated to the centrifuge or the linear track. The Vestibular Research Facility at Ames Research Center was designed with many of these same objectives in mind and provides a convenient starting place for the design of the OVRF. Whether the OVRF can be integrated into the design of the Variable Force Centrifuge will have to be determined.

In addition to the OVRF, there is a need for animal holding facilities, for in-flight fixation of tissues, and for data processing. A general-purpose neurophysiological module should be designed. It should be capable of recording eye movements, the electrical activity of muscles (electromyography), and the activity of individual neurons. There is also a need for a biomechanics module to analyze the motions of the head and body, as well as the forces acting on them.

5
Bone and Mineral Metabolism

INTRODUCTION

Osteopenia, meaning less bone, as seen on x ray, has been consistently reported as a physiological response to spaceflight. The osteopenia associated with spaceflight has not as yet resulted in the impaired function of bone. There has been only one reported episode of kidney stones. This occurred in a Soviet cosmonaut. Unfortunately, little information is available about the etiological factors surrounding the episode. Despite the relative lack of clinical problems, it seems likely that, as mission duration is prolonged, the osteopenia will result in clinically evident fractures. For this reason it is essential to understand the pathophysiology of the osteopenia caused by space travel and to devise appropriate countermeasures.

Bone Metabolic Processes

Our knowledge of the basic metabolic processes governing bone has increased greatly over the last 10 to 15 years. There are two major systems governing the metabolism of bone in the adult. These are the bone remodeling system and the calcium homeostatic system. The former is responsible for bone formation in adults. The latter regulates the calcium concentration of plasma. These are two independent, but obviously interrelated, processes. Changes originating in the calcium homeostatic system, such as occur during hyperparathyroidism, very rapidly produce changes in bone remodeling. However, changes in the bone remodeling system, e.g., osteoporosis, rarely affect calcium homeostatic processes.

The remodeling process is well-defined in time with bone resorption preceding bone formation. The two processes (resorption and formation) are closely interrelated and must be studied together. Changes in the process started in a one-week spaceflight are not completed for months. Bone loss is not simply due to an increase in the rate of bone resorption. It can also occur with a decrease in the rate of bone formation. The basic function of the bone-formation process in the adult is to replace bone lost by resorption. The process of activation—bone resorption: bone formation—is a sequential unit. Bone loss with age is considered to be a modification of the unit. In fact, bone resorption may in certain cases decrease with age, but the subsequent formation is decreased even more. The result is a gradual net loss of bone.

The Calcium Homeostatic System

Many of the changes in the bone remodeling system may be secondary to changes in calcium homeostasis. This second system functions independently of the bone remodeling system and has as its function the control and maintenance of plasma calcium concentrations. The bone processes controlling plasma calcium are centered at bone/fluid interfaces. They determine the equilibrium between calcium influx into bone and its efflux from bone. These fluxes move in excess of 6 grams of calcium into and out of bone each day in a 70-kg male. This is in contrast to the 300 mg of calcium daily incorporated or released from "formed" bone (i.e., formation and resorption). There are two reasons for suggesting that the homeostatic system may play an important role in the bone loss occurring during spaceflight. (1) Over 25 times as much calcium is moved by this system than by the normal process of bone remodeling in adult humans. (2) Changes in the calcium homeostatic system produce observable effects within hours, whereas changes in bone remodeling generally take weeks to be identified. It would not be surprising, for instance, if the first effect of microgravity was a temporary disequilibrium between these high calcium flux rates and the establishment of new equilibrium levels. This could account for the reports of an early rise in plasma calcium levels and an increased renal excretion of this ion. Changes in bone remodeling occur on a longer time scale.

Past studies of bone loss have tended to focus on the bone remodeling system. This situation is probably due to the fact that the processes governing calcium homeostasis have not as yet been as clearly defined as those involved in bone remodeling. That the homeostatic processes form a metabolic system separate from the bone remodeling process has been established, particularly by recent work. The cellular control of hourly homeostasis probably resides in osteocytes and lining cells rather than in the osteoclasts and osteoblasts, which are responsible for bone remodeling, which occurs over days.

Demineralization and Metabolic Changes During Spaceflight

Since 1969 metabolic balance studies conducted on astronauts in space flight have demonstrated increased excretion of calcium, phosphate, magnesium, and nitrogen. Data available from the Gemini, Apollo, Skylab, and long-term Soviet missions indicate that the osteopenia resulting from microgravity is similar to that occurring during bed rest but may actually be more severe, and may not be completely reversible. Radiographic densitometry measurements have been used to compare the mineral composition of bone before and after spaceflight. There appears to be no bone loss in the radius and ulna but in some cases there was significant loss of calcaneal density. Photon absorption measurements show 19 percent loss of bone in the tibia for the long-term Soviet missions. Recent fragmentary reports of Soviet CAT scans show little or no evidence of vertebral bone loss, and possibly an increase in vertebral density. There have been no histomorphometric measurements of bone done on astronauts. In general, the concentrations in the plasma and urine of some of the hormones involved in calcium metabolism (cortisol, growth hormone, and insulin) tend to increase during spaceflight. On the other hand, the calcitropic hormones (PTH, calcitonin, 25-hydroxycholecalciferol) do not change significantly. Calcium and phosphate concentrations in the plasma do rise in some cases during spaceflight, but remain within the normal range. Several metabolic variables need to be studied more intensively. These include the plasma concentrations of calcitropic hormones, as well as the intestinal absorption of calcium and its subsequent metabolism.

Bed Rest Studies

Bed rest studies have been used as ground-based simulations of weightlessness. These investigations indicate an overall calcium loss of the order of 0.5 percent per month. They show regional bone density differences with vertebral and calcaneal losses, but no losses in the density of the bones of the upper extremities. Bone histomorphometric measurements have not been performed on bed rested volunteers. Such measurements are, however, available from iliac crest biopsies from paraplegics and quadriplegics. Recent work suggests that pathogenesis of the osteopenia of weightlessness differs from that of the osteopenia of paralysis, which may limit the value of such an approach. What is known about histomorphometric changes in bone from paralyzed humans is that the trabecular bone volume is decreased and the cortices are thinned. The volume of osteoid in the cancellous areas is slightly below normal and the rate of calcification is low.

Animal Studies

It would appear, to date, that all of the experiments attempting to study pathogenesis during spaceflights have used rats. In these experiments the parameters associated with bone resorption and bone mineral density showed no significant changes. In some cases, active bone formation was arrested. Proximal tibial and humeral metaphyseal trabecular bone volume decreased. Lumbar vertebral bone turnover appeared to be slow. The mandible, possibly because it is protected by the continued activity of the chewing muscles, did not incur bone loss. Studies of rats suspended in harnesses suggest that the bone loss resulting from the unloading of the skeleton is local, rather than systemic. In studies on restrained monkeys, loss of cancellous bone from the axial skeleton was significantly greater than loss of cortical bone from three appendicular areas, the tibia, radius, and ulna.

Analytical Techniques

There are several studies in progress that attempt to validate computer tomography (CT) measurements of bone density with photon absorption studies. Another project has the goal of improving the sensitivity of dual photon absorptimetry. An improvement of analytic techniques would greatly facilitate future research.

Countermeasures

Dietary supplements have been used to see if they could retard the osteopenia associated with bed rest. A diet high in calcium and phosphates delayed bone loss for the first three months of bed rest, but failed to do so beyond this period. Salmon calcitonin failed as a countermeasure. Diphosphonates, particularly clodronate, prevented the rise in urinary calcium in a majority of bed rested subjects. Unfortunately, clodronate had serious side effects, which resulted in its withdrawal from the market.

Exercise countermeasures were tried in the Skylab missions. These included the use of bicycle ergometers, Cybex machines, treadmills, and spring regimens. The procedure did not decrease urinary calcium loss, nor were they demonstrably effective in preventing the loss of bone mineral. However, the lack of experimental controls precludes a scientific explanation of these failures. The Soviets use an exercise program intended to prevent bone loss and muscle atrophy; few details are available concerning specific exercise regimes or their efficacy. Muscle size and strength decrease significantly in spaceflight, and there may be a negative nitrogen balance. How the changes in bone are affected by changes in muscle has not been investigated in our own space program.

Several physical countermeasures have been tried in bed rested subjects. Lower body negative pressure and intermittent longitudinal compression in the supine position were ineffective in improving calcium balance. Quiet standing produced unreliable results. Heel springs seemed to work but the bicycle ergometer did not. Vigorous exercise in the supine position was ineffective. Impact loads of 25 to 40 lb to the heel also had no effect. In fact, the only procedure that was consistently effective involved extended ambulation for a minimum of 4 h per day. The internal forces exerted on the skeleton during normal walking are quite large and are impulsive in nature. To design a physical regime capable of preventing bone loss in microgravity which does not require the generation of large, impulsive forces over prolonged periods, will not be a trivial task. Basic understanding will be necessary.

It is possible that an effective set of countermeasures could be effected without understanding of the underlying mechanisms responsible for bone loss in microgravity, bed rest, and related situtations. At the same time, an ambitious program of basic research in this area might not only permit the development of countermeasures at the cellular and extracellular level, it would also provide basic information that would contribute to understanding and treating osteopenic diseases. This would be a major contribution to the health of humankind.

MAJOR SCIENTIFIC GOALS

1. *To compile description of the sequential changes that occur in bone as a result of space travel.*

2. *To obtain detailed knowledge concerning the reversibility of bone loss after return to earth.* At this time no adequately validated data exist on this question, from U.S. or Soviet sources, and the urgency of the question will increase with increased flight duration.

3. *To understand the relations between muscular activity and bone function and morphology,i.e., the biomechanics of bone health.*

4. *To develop countermeasures to prevent bone loss.* These should include exercise programs designed to provide known stresses on the musculoskeletal system, particularly the axial and lower appendicular skeleton. Presentation time and dynamics should be considered in this connection.

5. *To understand the cellular and extracellular causes producing basic changes in bone metabolism leading to bone mineral loss.*

6. *More generally, to understand the two major bone metabolism processes in the adult human.* It is of importance that research into the causes of bone loss in zero gravity include studies of both calcium homeostasis and the bone remodeling system, as well as the interaction between the two.

7. *To understand the processes by which urinary calculi are formed and pathological calcification in general.*

8. *To develop analytical biomechanics appropriate to microgravity environments.* Gravity adds great complexity to the study of the mechanics of the musculoskeletal system. Normal gait at the earth's surface involves a series of intricate optimizations for the sake of efficiency, with periodic exchanges of potential and kinetic energy (e.g., as in a pendulum), together with multiaxial rotations of the knee joint and rotations of the pelvis. Redundant muscle groups are active. These serve not only to produce force and motion but also to reduce flexural stresses on the long bones and to stabilize the curvature of the axial skeleton. This situation is in essence a response to gravity. At this time almost nothing is known of the biomechanics of microgravity. The surprising and seemingly inconsistent Soviet reports of large losses in the lower extremities and no loss in the axial skeleton may (if true) indicate a lack of understanding of microgravity biomechanics on the part of the biomedical community. What is certain is that the microgravity environment, with the removal of mechanical constraints that have existed for the entire history of our species, offers dramatic new opportunities for research in biomechanics. Less certain, but highly probable, is that the absence of gravity will greatly simplify certain types of experiments and theoretical analyses. Finally, studies in microgravity may aid our understanding of the nature of musculoskeletal adaptation to altered force environments.

These goals are specific to our problem; their broad implications are obvious. In this connection, it is not possible to separate operational considerations, in particular the health, safety, vitality, and performance of the crew, from the basic scientific question. In order to obtain credible extrapolations for the condition of the skeletons of the crew of a long-duration mission, in order to develop countermeasures to resorption, and in order to understand the functional limitations and hazards that will exist due to resorption, basic knowledge of bone remodeling and its relationship to calcium metabolism and basic knowledge of biomechanics will be necessary. An example of this connection is the question of whether a genetically determined baseline exists for bone mass. The ultimate scientific test of this hypothesis exists in the microgravity environment; the answer also represents an asymptote for the crew of a long-duration mission. There is in fact an ethical imperative to acquire the necessary basic knowledge in order to meet the operational demands of such missions.

ARCHITECTURE OF BONE

Bone Mass and Bone Structure

The mass of a bone reflects its mechanical and chemical environment. There is a need for research directed specifically at what is happening to the skeleton. Measurement of calcium absorption and depletion, however carefully done, cannot provide a pathophysiological understanding since a variety of possible mechanisms can account for any calcium balance observation. Densitometric studies cannot differentiate between osteomalacic changes (having to do with inadequate usable calcium in the system) and osteoporosis (having to do with loss of bone volume). The mineral content of bone varies with age and condition. A larger volume of bone with low calcium concentration may appear similar in densitometric studies to a smaller volume of bone with normal calcium concentrations. Newly formed, unmineralized bone matrix is virtually invisible to densitometry. What is sorely needed are measurements of unmineralized matrix to determine whether the problem is one of diminished bone density or decreased calcification of the organic matrix. Such measurements require histomorphometry from a bone biopsy.

Bone Quality

The issue of quality is most obvious for trabecular bone, where the largest early changes due to microgravity are known to occur. Changes in trabecular bone are almost without exception architectural, involving the shape, size, number, and especially connectivity of the trabeculae. The properties of the bone, particularly its mechanical strength, are very sensitive to these geometrical parameters. Such changes can have a profound effect on the viability of the axial skeleton and the articulations of the long bones. The development of osteoporosis (less bone volume) largely determines the strength of bone. To understand the pathogenesis of osteoporosis, there is a need to assess the quality, macroarchitecture, and degree of calcification of bone. This requires direct examination, which, although invasive, is also essential for understanding.

Scientific Objective

To obtain accurate histomorphological and architectural descriptions of the changes that occur in bone due to space travel.

Measurement Requirements

1. Histomorphometry, in an appropriate animal model, on the axial skeleton and upper and lower appendages, regularly over time periods of at least several months. Trabecular bone architecture needs to be examined, especially in the axial skeleton.
2. Bone should be studied microscopically in its calcified state.
3. Vital stains, such as tetracycline and its derivatives, should be used to mark the mineralized bone formed at various times during the study.
4. Quantitative evaluation should be made of volume fractions (i.e., fraction of space occupied by calcified bone), using stereological or geographic techniques, by examining trabecular structure quantitatively and by examination of the macroarchitecture and microarchitecture of the cortical bone being studied. Included in the latter should be ultrastructural and biochemical characterization including identification of possible changes in the collagenous, amorphous, and mineral phases.
5. Molecular and histomorphometric studies of ground-based models appropriate to microgravity studies should be done. Extension of these studies to human volunteers is highly desirable, but it will require the availability of noninvasive procedures to measure bone density and architecture. CT scanning promises to be a more reliable index, particularly of metaphyseal bone density. The development of nondestructive measurement of bone elasticity and anelasticity would be an especially valuable tool, even if its use is confined to the bones of the arms and legs.

ANIMAL MODELS

Relevance of Animal Models

Most of the available data on microgravity osteopenia comes from studies on rats. Unfortunately, the rat is not a particularly good model for bone remodeling in adult humans. Mature monkeys, dogs, and miniature pigs are known to have remodeling systems similar to that of man. The rat does not. The rat maintains an immature skeleton. It is difficult to separate remodeling (adaptive change) and modeling (growth change) from each other in any immature animal, or in the rat, at any time. Moreover, the primary bone of the rat is physiologically and metabolically different from human bone. These facts alone would severely limit the relevance of research with rats. The great advantage of rat experimentation is its cost, small size, and ease of handling. Efforts must be made to identify those parts of the rat skeleton that can serve as models of mature bone. The use of other species has to be considered.

Duration of Experiment

In animal models as well as humans, experiments of short duration will provide misleading data. Each experiment must continue until there is substantial evidence that the remodeling system has returned to equilibrium; lesser time periods will provide "transients," which will be difficult to interpret. A rapidly produced bone loss (or gain) may be only temporary; following equilibrium, the lasting rate of bone loss may be quite different. Determining changes in bone remodeling will require histomorphometric analysis of bone samples. Changes that began at zero gravity (or other experimental conditions) continue until equilibrium even if the conditions are changed. Thus carefully planned and executed experiments covering suitably long periods of time will be necessary if an accurate picture of the effect of microgravity on bone remodeling is to be obtained.

Although rats are not particularly suitable for studies of bone remodeling processes in humans, this may not be true for studies seeking information concerning calcium interactions between fluid and bone surfaces. The major problem in this area is that the best research tools are radioactive isotopes. Such data are difficult to interpret because the results are influenced by the previous calcium intake as well as the relationship of administration of the tag to current oral calcium intake.

Scientific Objective

1. *To develop improved animal models for the changes in bone that occur in microgravity.*

Measurement Requirements

1. A centrifuge with 1-g capability, large enough for humans or at least medium-sized primates. As discussed above, various elements of the systems for calcium metabolism and bone metabolism appear to have distinctly different response times. The ability to turn gravity on and off, and correlate hormonal, biochemical, and cellular responses confers a unique opportunity to identify the elements and the role(s) they play.
2. An animal holding facility suitable for primates as well as smaller animals. As stated above, some of the research will require primates.
3. Instrumentation for stress and strain.
4. Refrigeration and fast sample return for tissue and fluid specimens.
5. Gravity requirements are probably best determined by the minimum effective signal (MES) for bone remodeling, which is not, at this time, precisely known. However we expect that no measurements should be compromised by the expected operational accelerations.

LOCAL AND SYSTEMIC EFFECTS

Localization

Both space-based and ground-based studies amply demonstrate the regional nature of the changes that occur in bone during exposure to microgravity or bed rest. It seems likely that mechanical factors are responsible for this regionalization, since there are large differences in the mechanical forces acting on the upper extremities, axial skeleton, and lower extremities, both in space and in various model situations. An understanding of mechanical factors requires the direct measurement of bone strains and muscle forces.

The Relationship Between Disuse Osteopenia and Microgravity Osteopenia

That microgravity osteopenia is a variation of disuse osteopenia is an unproven assumption that may be incorrect. Effort must be directed at trying to differentiate between the osteopenia of disuse due to paralysis and that due to microgravity. For instance, paralysis may have a greater effect on muscle mass and bone circulation than does microgravity. Circulatory changes may well have a profound effect on bone mass.

Bone As an Organ

Bone has to be viewed as an organ. Studies of cellular mechanics and tissue cultures are unlikely to demonstrate how bone, the organ, will behave. Bones of different architectures can respond very differently in any particular circumstance. With regard to microgravity, cancellous bone will respond first. There must be adequate study of the differences in response between trabecular and cortical bone. Again, it is necessary to emphasize that rats are a remarkably poor experimental model.

Calcium balance studies and bone densitometry studies provide, respectively, measures of skeletal retention or loss of calcium, and how dense, to a given standard, the measured regions of the bone are. Both techniques are advantageous in being noninvasive and are thus attractive to the researcher in bone metabolism. Unfortunately, neither technique provides information as to bone strength or to the underlying mechanisms responsible for the density changes. Bone strength is directly related not only to the degree of calcification but also to the quality of the bone and to its macroarchitecture. Bone density measurements cannot differentiate between the loss of mass (osteoporosis) and deficiencies of bone matrix calcification (osteomalacia). Calcium balance studies and bone densitometry measurements give no indication of where the bone is being lost or gained, i.e., endosteal, periosteal, or intracortical, and no information as to the rate of change; both techniques are essentially "black box" approaches.

With regard to measurement of blood parathyroid hormone and vitamin D metabolite levels, we note that the control of the level of blood serum calcium involves these substances, but the control mechanisms are complex and highly multivariate.

Scientific Objectives

1. *To obtain accurate descriptions of the changes in the bone on a local basis, including changes in stresses, strains, and strain rates.*

2. *To delineate the relationship between microgravity osteopenia and the other types of osteopenia.*

3. *To describe bone as an organ, with organisms and operating systems on higher and more complex levels than studies on the molecular and cellular scales would indicate.*

Measurement Requirements

1. Significantly improved methods for measurement of the levels of calcitropic hormones in serum. Studies of calcium homeostasis are currently limited by the reliability and availability of analytical capability.

2. Direct measurement of strain and strain rate. Because such measurements are invasive, the use of human volunteers is probably not justifiable. Similarly, the volunteer bed rest program is not appropriate to this end. Appropriate animal models should be used. Restrained monkeys would appear to be a suitable model as they can be taught sophisticated exercise programs. In vivo longitudinal modeling of strain and strain rate must be carried out. There is considerable evidence at this time to suggest that impulsive loading has the most profound effect, relatively speaking, on the formation of bone.

3. Histomorphometric measurements, when made, should be accompanied by measurements of strain and strain rates on the bones studied.

4. Radiographic facility, including quantitative imaging for bone loss. At this time such a facility is a scientific objective as much as it is a requirement.

COUNTERMEASURES

Background

Medical history contains many examples of diseases for which successful treatment predates understanding of the pathophysiology. On the other hand, treatment regimens based on an understanding of the disease process tend to be safer and more reliable. It must be understood that microgravity osteopenia is not a disease but rather a functional adaptation that is driven by the changes in skeletal forces that occur when the musculoskeletal system is no longer subject to gravitationally induced loading. The involvement of other factors, such as vascular changes, is not strongly supported by available evidence. Since appropriate countermeasures are vital to a continuation of the NASA space program, it is reasonable to seek countermeasures at the same time that the research on pathogenesis is being carried out.

As implied above, the central and major assumption that should be made is that mechanical factors are responsible for microgravity osteopenia. The extreme variability of effectiveness of mechanical countermeasures, which have been attempted on an ad hoc basis, strongly suggests the necessity of biomechanical analysis. Only certain types of exercise will be effective in increasing bone formation or decreasing turnover. By way of example, the arms of tennis players have increased bone density, but not the legs of joggers. Different exercise creates different strains at different rates and different strain histories, and the unreliability of the countermeasures thus far attempted is, in this connection, not unexpected. If in fact the osteopenia is due to the reduction in strain on the bones due to the reduction in gravitational forces on the skeleton, then it is necessary to measure the alteration in strain parameters. Only in this way will it be known what exercise regimens replace the missing mechanical stimuli and duplicate the missing strains. In addition, recent developments in sports medicine and related fields indicate that the strain rate is also a critical variable. Certainly, it is important to note that jogging on a treadmill in microgravity is very different, in terms of skeletal forces, than, for example, walking in normal gravity, and there is no reason to expect the effects on bone metabolism to be similar.

Scientific Objective

To obtain the biomechanical data necessary to develop adequate mechanical countermeasures to microgravity osteopenia.

Measurement Requirements

1. Initial countermeasure studies should be limited to ground-based experiments, as there is probably a significant alteration in degree of mechanical factors acting on various crew members of a space mission, each of whom have differing responsibilities while in space. The reason some astronauts/cosmonauts respond to spring resistance exercises may be the result of how vigorously (and at what strain rate) they perform them. Ground-based studies will

permit the investigators to be sure that all subjects have significant bone loss before beginning an exercise program; this would be an impractical constraint on flight crews.

2. Once it has become apparent which exercise programs create the missing mechanical input to the bones, bed rest volunteer study subjects could be used to determine whether such exercise programs do, in fact, prevent bone loss. Validation of CT measurements of bone density with histomorphometric measurements in the monkeys should permit the study, using noninvasive CT measurements, of bone loss in human volunteers subjected to particular exercise programs, thus obviating the need for bone biopsy in humans. The noninvasive approach also allows serial determinations in the same subject.

3. For microgravity environments, the equivalent of what is called, at the earth's surface, gait analysis, must be developed. At this time the forces on the skeleton in microgravity environments are not known. Instrumentation must be developed to measure such forces. In all likelihood, the necessary instrumentation (typically, goniometers and LEDs) can be easily built into space suits and would probably be useful in other types of research as well. Besides the importance in understanding bone loss, such instrumentation should be very useful in analyzing, e.g., the biomechanics of EVA, which should be very important in planning the construction of space stations. Specifically, the need will exist for:

a. Instrumentation for the biomechanical measurement of force and displacement.

b. Instrumentation (e.g., video, with goniometers) for motion analysis and corresponding computational capabilities.

THE ROLE OF MUSCLE

Given the central assumption of the previous section, it is important to note that skeletal stresses and strains are dominated by muscle forces; very large muscle forces are used to counteract gravity during normal locomotion. Muscle forces, even those exerted just to maintain equilibria of some sort, are always several times greater than the external loads associated with such forces, since muscles always act on the shorter lever arm in the skeleton. Although the situation is sometimes complicated by the action of antagonistic muscle groups, it is clear, for example, that in ordinary walking the abductor muscles of the hip exert forces that are several times the weight of the body. An instructive therapeutic example may be found in the literature on poliomyelitis rehabilitation. In general, disuse osteopenia was not corrected by manipulation of a passive patient. Only when muscle forces were exerted did the recovery process begin.

Some muscles lose 50 percent of their mass within 5 days of being subjected to reduced activity, and the forces they exert on the bone will be correspondingly reduced. Thus, although countermeasures based on activity rather than force have not been effective, the loss of muscle mass due to inactivity may eventually result in a reduction of skeletal strain. In any case, the well-being of muscle and bone are clearly intertwined and this should be reflected in the planned research.

Scientific Objective

1. *To obtain a description of the changes in the muscular system in sufficient detail to support the objectives abovementioned in bone and mineral metabolism.*

Measurement Requirements

1. Clearly, the biomechanical instrumentation, discussed above in the section on Countermeasures (p. 123), will be important in this connection as well. The intra-articular forces and stresses and strains on the skeletal system will be produced largely by the muscles.
2. Electromyographic instrumentation.

GROUND-BASED AND SPACE-BASED STRATEGIES

A substantial well-correlated ground-based component is necessary, including histomorphological molecular studies, and the baseline countermeasures studies. Noninvasive ground-based validations on human volunteers will be necessary for the results of the in-flight experiments on animal models involving invasive methods. A considerable ground-based effort will be required to develop and refine analytical tools, e.g., noninvasive measurement of mechanical properties of bone and improved calcitropic hormone assay. Some components are uniquely space-based, e.g., the animal experiments and, more particularly, microgravity biomechanics. With regard to personnel, the various experiments will require training at least on the level of laboratory technician in biomechanics and associated instrumentation, primate handling, EMG, radiography, and possibly pathology.

In the matter of musculoskeletal biomechanics the ground-based approaches will be limited by the complexity of the response of the musculoskeletal system to gravitational forces and to external forces in general. By way of example, the shape of the axial skeleton is controlled by hundreds of muscles, all in response to gravitational forces, with a degree of complication that has to this day defied detailed analysis. Normal ambulation, involving multi-axial rotations for the sake of energy efficiency, is, on the earth's surface, deceptively complex. In many respects the microgravity environment represents a simplification of almost Newtonian proportions. Musculoskeletal biomechanics should be substantially and fundamentally advanced by space experimentation, as well as being necessary to the mission itself in terms of the demineralization problem, EVA, and sensorimotor research. The shape towards which the mammalian skeleton adapts in microgravity and the mechanisms of adaption involve fundamental questions. Resolution of such questions, even in part, would add greatly to our knowledge of skeletal development and metabolism.

ON IMPLEMENTATION

It is clear that space travel presents the opportunity and the necessity to advance the understanding of bone and mineral metabolism. Here, a unified approach has much to recommend it. A complete understanding of bone remodeling would include descriptions of the biomechanical stimuli, the skeletal signals (e.g., bioelectrical) that are evoked, the systemic and cellular entities that respond to the signals, the nature of the systemic and cellular responses, and the final result (i.e., the architecture) from the macroscopic to the ultrastructural scales, and the mechanical properties that correspond to these structures. This chapter focused the very beginning and ending of the process, to the nature of the initial stimulus and the final result, as understanding of these steps must underlie any progress in understanding causality and mechanism. Such understanding does not at present exist. However, it would be wasteful and even imprudent to undertake such studies in isolation. Unification is necessary.

6
Cardiovascular and Pulmonary Systems

INTRODUCTION

The cardiovascular system guarantees the flow of metabolites, heat, and hormonal substances to and from all cells in the body, and it is also involved in the exchange of materials and energy between the body and the external environment. The external exchanges occur in the kidney, lungs, and skin. The system consists of pumps—the right and left hearts—and of tubes—the vascular system. The vascular part of the system is subdivided into the systemic and pulmonary circulations, each with arteries, capillary and lymphatic vessels, and venous returns. The system is regulated by autonomic reflexes and by neurohormonal controls. In addition, the blood flow through capillaries is under the local control of such factors as the availability of oxygen and the accumulation of carbon dioxide, hydrogen ions, various metabolites, and locally generated control factors. The local and more global controls serve to regulate blood pressure, blood volume, cardiac output, and local blood flows. The regulatory systems are called into play by a variety of perturbations. One such perturbation occurs when the effect of gravity on the cardiovascular system is altered. This happens when a subject moves from an erect to a recumbent position or when a subject is placed in the microgravity environment of orbital flight. This chapter considers the adaptation to altered gravity and the regulatory mechanisms that may be involved.

CARDIOVASCULAR ADAPTATION TO ALTERED GRAVITATIONAL STIMULATION

In a standing human being, gravity acts to increase the pressure in blood vessels below the heart above intracardiac pressures and to decrease the pressure in vessels above the heart. Blood flow to the lower extremities is favored, while that to the upper limbs and head is impeded. Rapidly acting baroceptive reflexes involving the autonomic nervous system provide the major means of adjusting to these gravitational effects, especially to assure an adequate blood flow to the brain.

Now consider what happens when a subject moves into a recumbent position or is placed into a microgravity environment. In either case, the hydrostatic effects of gravity are reduced and the blood is redistributed. Approximately 0.6 to 2.0 liters of blood leave the lower body and move to the torso, neck, and head. As a result of this redistribution, legs become thinner and faces become puffy. Blood accumulates at the level of the heart, causing distention of the right and left atria. The walls of the atria contain mechanoreceptors that are sensitive to variations in stretch or local volume. Atrial distention is interpreted as a real blood overload and, through a variety of neuroendocrine reflexes, there is a diuresis, i.e., an increased urinary output. The result of the diuresis is a rapid loss of 2 to 4 liters of fluid. The process continues until the atrial distention returns to normal. According to current information, the fluid loss that occurs in space is completed in four days.

Possible Sites of the Adaptation to Altered Gravity

Microcirculation

The cardiovascular system is a follower that responds to the demands set by the metabolic needs of tissues, by the needs for thermoregulation, and by mental states such as excitement of the anticipation of exercise. The metabolic needs of tissues usually determine cardiovascular state by controlling the local flow of blood through capillaries. The regulation is accomplished by the adjustment of the tension of smooth muscles in small arteries and arterioles and the regulation of the permeability of capillary walls, both of which can be influenced by the action of regional chemicals such as kinins, histamines, paracrines, metabolites, or even growth factors from peripheral nerve nets. The local controls are sufficiently powerful that the microcirculation normally operates in a gravity-compensated fashion. In an erect, slowly walking person, the hands may be transiently above the heart, below the heart, or at heart level. In any of these positions, the tissue needs of the hands will be met by controls that provide a rapid, powerful and automatic regulation of capillary blood flow. The principles of microvascular exchange have been extensively studied. The conclusion is that postural shifts of vascular and interstitial fluid volume. should have little, if any, influence on microcirculatory function and that capillary exchanges will be normal in microgravity.

In considering the global adaptations to altered gravity stimulation, including microgravity, we have to look elsewhere—at the heart, at the macrovasculature (arteries and veins), and at neuroendocrine regulatory mechanisms.

Macrovasculature

The macrovasculature has variable resistances (particularly on the arterial side) and variable compliances (particularly on the venous side). The distribution of pressures, volumes, and flows in the circulatory system is determined by the cardiac output and the patterns of these resistances and compliances. To understand the state of the macrocirculation in, say, microgravity, it is necessary to conduct experiments that can measure the cardiac output and the settings of these resistances and compliances. The limited evidence available suggests that venous compliance is decreased and peripheral resistance is increased in microgravity, but the data are far from certain. Large vessels contain receptors for monitoring and regulating the circulation by way of nervous reflexes. The role of these reflexes in the adaptation to microgravity is, as yet, unclear.

Heart

The state of the heart is influenced by many factors:

- The diastolic volume, i.e., the amount of blood contained in the heart just before the start of each heart beat (Frank-Starling law). This volume will be increased by the headward shift of fluids that occurs in microgravity or during recumbency.

- The hydraulic resistance of the peripheral circulation. This resistance largely determines the work of the heart at any stroke volume.
- Catecholamines released from the sympathetic nerves innervating the heart and from the adrenal medulla. During excitement especially, these hormones increase both the heart rate and the strength of cardiac contractions.

In space travel, the early excitement of lift-off and the headward fluid shifts act in a direction that stimulates cardiac activity. Furthermore, the metabolism of the heart is raised when the peripheral resistance increases. But there is also, as noted previously, a net loss of blood volume will serve to decrease cardiac work and metabolism by lowering blood volume. Because these various influences oppose one another and the relative magnitudes of their effects are uncertain, we do not know the exact status of the heart (and circulation) during exposure to the space environment. Echocardiographic observations in Skylab astronauts postflight indicated small decreases in stroke volume, left ventricular end-diastolic volume and estimated left ventricular mass. Similar measurements in cosmonauts showed a more substantial decrease in cardiac muscle. There is simply too little information to decide whether the heart is in a normal condition, hypodynamic and undergoing atrophy, or hyperdynamic and becoming hypertrophic. These are fundamental issues that can only be settled by further research.

The focus of the next round of cardiovascular studies should be on establishing the status of the venous side of the systemic circulation, the status of the heart, and the overall integration of the cardiovascular system by neuroendocrine and other regulatory mechanisms.

Neuroendocrine and Neural Regulation

Studies of the neuroendocrine regulation of the cardiovascular system are important in understanding the adaptation to microgravity and may also provide a basis for pharmacological intervention to enhance the adaptation to space and, perhaps more importantly, the readaptation that occurs on return to earth. The neuroendocrine control arrangements include at least the following features.

(1) Fluid volume regulation by the kidney is under the control of various hormones. Those that act rather specifically on the kidney are aldosterone from the adrenal cortex, antidiuretic hormone (ADH) from the posterior pituitary, and atrial natriuretic peptide (ANP) from the heart. ANP is released into the general circulators and inhibits sodium reabsorption by renal tubules. No neural pathway is involved. In contrast, ADH is inhibited by stretch of the right atrium through a neural pathway that eventually reaches the posterior pituitary. The rate of release of ADH into the general circulation is decreased so that the kidney excretes more water whenever there is an increase in central blood volume. Aldosterone is part of a so-called renin-angiotensin-aldosterone system. Hydraulic and neural signals within the kidney produce renin, which converts angiotensin, a circulating polypeptide, into an active form that stimulates aldosterone release from the adrenal cortex. Aldosterone, in turn, stimulates sodium reabsorption in the kidney. An increase in central blood volume increases ANF and decreases ADH and aldosterone. The result, as illustrated in Figure 6.1, is a diuresis and a decrease in circulating blood volume.

(2) Increases in central venous pressure cardiac chamber size and stroke volume influence the activity of the autonomic nervous system, which acts on the heart, blood vessels, and the renin-angiotensin-aldosterone system. In addition, the adrenal medulla can release epinephrine and norpinephrine into the general circulation, where they reach cardiac and vascular receptors of various kinds.

(3) In addition to the specific neuroendocrine mechanisms described above, there is a more general effect exerted by cortisol, another adrenal cortical hormone. Cortisol modulates the sensitivity of vascular receptors to catecholamine hormones and possibly influences receptors to other factors. The cortisol effects usually take minutes to hours, whereas the other neuroendocrine effects are more immediate, often occurring within seconds to minutes.

Although the influence of each of the described mechanisms on cardiovascular regulation has been amply documented, their integration into a single, adaptive response is far from understood. Furthermore, many of the mechanisms have been discovered in animals, but have not yet been demonstrated in humans. For these reasons, the scheme presented in Figure 6.1 must be considered provisional with respect to human physiology in space.

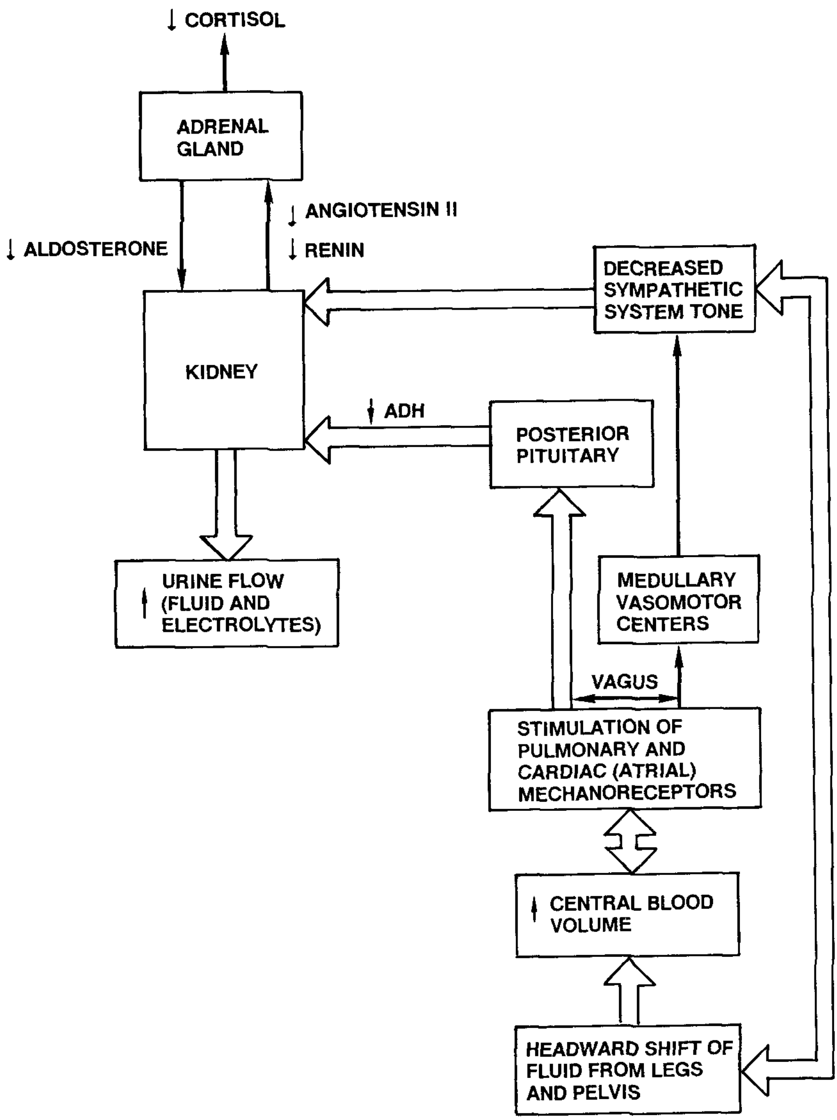

FIGURE 6.1 Circulatory events accompanying a change in posture (standing to lying) and possibly weightlessness.

There are many opportunities for the study of the neuroendocrine states achieved by man in microgravity. These can be compared with his endocrine status on earth. There are many inhibitors or antagonists, as well as agonists that can adjust neuroendocrine responses. Detailed studies of cardiovascular neuroendocrine control, both on earth and in microgravity, may provide a basis for pharmacological interventions to alter the operating point of the cardiovascular system should that prove desirable. In order to understand the actions of hormones, one has to take into account changes in receptors, since these may undergo variations in their numbers per cell—"up or down regulations"—which change the gain of the system.

EARTH-BASED MODELS OF VARYING GRAVITATIONAL FORCES

The usual effects of gravity on the distribution of blood in the upright position can be exaggerated in at least four ways:

(1) During quiet standing, the muscular contractions in the lower extremities, which aid venous return, are reduced. The result is a gravity-induced pooling of blood in the legs.

(2) Placing a subject on a tilt table further reduces the muscular contributions to venous return.

(3) Application of lower-body negative pressure traps blood in the legs.

(4) The gravitational force can be increased by placing the subject with legs out on a centrifuge.

Conversely, the microgravity effects of orbital flight can be simulated, in part, by whole-body water immersion or by prolonged bedrest, usually with slight head-down tilt. These procedures simulate microgravity by reducing hydrostatic gradients. Yet, there is no exact terrestial equivalent for the microgravity conditions of orbital flight. Ultimately, we must conduct experiments in orbital flight to test man's cardiovascular adaptability for prolonged duty in space. This does not mean that terrestial studies on subjects at bed rest are useless; quite the contrary, such studies have taught us much of what we know about the probable state of the circulation under microgravity conditions.

In earth-based simulation studies, the headward fluid shift with bed rest creates changes in stroke volume and cardiac output that occur in at least three stages. Initially an enlarged central circulating blood volume leads to an increase in both ventricular filling pressure and heart volume. These changes augment stroke volume and cardiac output. The various neurohumoral mechanisms that regulate central blood volume operate over the next 24 h or so to ameliorate the detected central volume overload. A diuresis occurs. This fluid excretion reduces blood volume, venous pressure, end-diastolic cardiac volume, and cardiac output. Later, a third stage of adaptation is reached. During this phase, cardiac output and stroke volume continue to decrease and eventually stabilize at significantly lower levels as compared with pre-bed rest values. These changes are consistent with decreased circulating blood volume, a decrease in oxygen demand, loss of muscle mass, and decreases in circulation to specific muscle beds such as those in the leg. We might expect, although it has never been shown, that similar changes are occurring during prolonged spaceflights.

PULMONARY SYSTEM, VENTILATION AND CIRCULATION

At the earth's surface, lung function is affected by gravity. During standing, as compared to recumbency, there is a reduction in pulmonary blood flow due to pooling in the lower body, and regional blood flow within the lung is greatest towards the bottom. There is a gradient in pleural pressure and of lung gas volume due to the weight of the lung in the thorax. Additional gradients down the lung exist for ventilation and blood flow. The result is that at the end of a normal breath, the lungs are more expanded near the top, where there is a maximum in the ratio of ventilation-to-blood perfusion. Recumbency shifts the maximum to lower locations. Despite this, posture has little effect on oxygen and carbon dioxide transfer. Pulmonary function is considerably altered by increased gravitational forces.

Although microgravity-induced changes in regional lung distention, ventilation perfusion, and ventilation-to-perfusion ratio are likely to improve pulmonary gas exchange during rest, we do not know the maximum working oxygen consumption possible in a microgravity-conditioned astronaut, his capacity for arm work, and whether these will be adequate for his assigned tasks. This is an important area for investigation since the lungs may become sensitive to alterations in gravity during exercise. Changes in the gas exchange and the mechanical properties of the lung and their consequences on arterial blood gas and on acid-base status need to be established in space for basal conditions, normal workloads, and maximal exertion. In addition, we do not know how the respiratory control mechanisms, the diaphragm and other respiratory muscles, and gas exchange will be affected by reentry into the 1-g environment of earth.

READAPTATION TO THE EARTH'S ENVIRONMENT

After return to earth, all astronauts and cosmonauts have exhibited some degree of cardiovascular deconditioning. There is an orthostatic (postural) intolerance, reflected by blood pressure (a tendency to subnormal) and only partially compensated for by exaggerated heart rate and blood pressure responses to standing, head-up tilting, or the application of lower-body negative pressure (LBNP). The measured responses include tachycardia, a drop in systolic pressure, and a decrease of the pulse pressure. Fatigue, light-headedness, and reduced exercise tolerance have also been reported. The postflight duration of cardiovascular symptoms have typically ranged from 2 to 5 days. There has, however, been considerable variation in the time required for readaptation. *Skylab 3* and *4* crewmembers returned to preflight cardiovascular status within 5 days, while the *Skylab 2* crew required 21 days. Increased in-flight exercise was thought to be a factor in the improved recovery rate experienced in the later Skylab missions. In one Soviet mission, full recovery required 30 days.

COUNTERMEASURES

Various measures have been tried to enhance the postflight recovery of cardiovascular function. These have included in-flight exercises and repeated application of LBNP, venous occlusion, pre-reentry oral consumption of fluids and electrolytes, and postflight supportive measures including use of antigravity suits, which increase the pressure on the lower body and prevent pooling of blood in the legs upon return to earth. In addition, drugs and hormones have been tried experimentally. Among the more promising countermeasures, as measured by postflight recovery rates, are in-flight exercises, repeated in-flight application of LBNP, replacement of fluids and electrolytes, and antigravity suits. None of these measures has been evaluated in controlled experiments, so their efficacy is uncertain. The one clear finding is that, following flights of short durations, postflight symptoms can be reduced to a few days, even if the precise reasons for the reduction are not entirely understood. This suggests that a systematic study of countermeasures could provide considerable operational dividends. While postflight recovery has apparently not depended on mission duration, it is unclear that this conclusion would hold for missions lasting several years.

COMMENTS

Below are five comments on the present state of our knowledge about the human cardiovascular and pulmonary systems as they operate under conditions of microgravity.

(1) In the current literature, there is a confounding of the effects of cardiovascular deconditioning from a state of high athletic training, with those of primary adaptations to microgravity. Even in ground-based bed rest studies, changes in cardiovascular status occur more rapidly and dramatically in athletically trained than in sedentary subjects. Most astronauts have been in athletic training prior to spaceflight. Some of the acute changes in their cardiovascular systems may not have been specific to the space environment, but may merely have represented the ordinary changes that occur when a person in athletic training becomes sedentary.

(2) Many of the acute cardiovascular changes that accompany the headward shift of fluid may represent an appropriate adaptation to microgravity. If this is so, then introducing countermeasures early in flights of long duration may be counterproductive. It might, for example, make sense to promote the adaptation to microgravity at the start of flight and, then, near the end of the mission to begin regimens that facilitate the readaptation that will occur upon return to earth.

(3) Many things do not happen in spaceflight—at least as far as is known. In general, the cardiovascular system functions well in spaceflight. On the other hand, the successful adaptation may be viewed as directly responsible for the cardiovascular dysfunction that is apparent upon return to normal gravity. There is an alternative view—that the normal regulatory mechanisms are unable

to deal with the fluid shift that occurs upon entry into microgravity, so that there is a sustained hyperdynamic circulatory state that has the potential of causing myocardial dysfunction even in space. Although all of the evidence collected to date supports the former view, more research is required to settle the issue. So far, it appears that pulmonary function is normal in space, and those astronauts who have participated in extravehicular activity have delivered transient, high power outputs that have been successfully supported by their cardiovascular and pulmonary systems. The quantification of such power outputs should be made so that realistic estimates can be made of man's maximum performance in space.

(4) Although bed rest or water immersion are not perfect simulations of the microgravity effects on the human cardiovascular and pulmonary systems, they have value in suggesting possible adaptations and mechanisms pertinent to space physiology.

(5) Because of his erect posture, man's adaptations to gravity are qualitatively different from those of most animals, which have a quadripedal posture. For that reason, man is the most suitable subject for studies relating to his adaptation to normal or altered gravity.

SCIENTIFIC GOALS

1. *To understand the cardiovascular and pulmonary adaptation to microgravity.* The adaptation is best studied by recognizing three time frames, each with its own phenomena. *Acute* (0-2 weeks): What are the initial adaptive processes and what are their mechanisms? *Medium-term* (2 weeks to 3 months): Does the initial adaptation progress, stop, or reverse? *Long-term* (from 3 months to several years): Does man reach a steady state and, if so, what are its characteristics? Are all of the responses to long-term spaceflight beneficial? If some of the changes are deleterious, are their consequences sufficiently serious to warrant in-flight intervention?

2. *To determine the relation between the cardiovascular and pulmonary adaptations of spaceflight and those occurring in earth-based models such as bed rest and, so, to ascertain if the space environment offers any unique advantages for the study of man's cardiovascular and pulmonary adaptations to variations in gravitational stimulation.*

3. *To develop adequate measures that will hasten man's adaptation to microgravity and to his reentry to earth.*

Measurement Requirements

Acute and Medium-Term Measurements

The measurement requirements for the acute and medium-term periods are identical. Experimental schedules are based on the experience arising from bed rest studies and data from space-flight experiments.

1. Central venous pressure should be measured by an in-dwelling catheter placed as close to the superior vena cava as is safe. Measurements should be done before and during flight through a catheter inserted preflight. Cardiac output, stroke volume, and left ventricular chamber and wall dimensions and contractile performance need to be estimated by echocardiography. Standard measures of cardiovascular function, including heart rate, systolic and diastolic pressures, and electrocardiography should be obtained. The measurements should start as early as possible after reaching orbit and should be made continuously, especially during the first few days of the mission. All of the measuring devices should be designed to permit easy movement both in the space vehicle and on earth.
2. There should be daily measures of lung volumes, airflow, gas distribution, diffusing capacity, respiratory dead space, and breathing patterns.
3. Measures of water and salt intake and of total daily urinary output should be done for at least two weeks to determine the magnitude and time course of the expected fluid losses and diuresis.
4. Measurements are required of plasma and urinary concentrations of various hormones, including ADH, catecholamines, renin, angiotensin, aldosterone, prostaglandins, and perhaps ANF. These should be done hourly during the first mission day, every six hours during the next three days, daily for the next two weeks and twice weekly for the remainder of the mission. The pattern of hormonal changes should be compared with the time course of changes in the physiological responses that underlie the adaptation to microgravity.

5. The frequency of testing during the early part of the mission will require dedicated subjects and dedicated payload and mission specialists to conduct the experiments.

6. In-flight measures of neuroendocrine reflex competence need to be done on a weekly basis. Tests should include the ability to excrete volume loads and to resist orthostatic hypotension, such as might be produced by LBNP or on a 1-g centrifuge. Tests of the physiological responses to the administration of particular hormones should be considered in an attempt to determine receptor sensitivity.

7. Postflight cardiovascular and pulmonary function should be assessed by a battery of tests, including tilt-table and LBNP measures of orthostatic competence; treadmill exercise; and arm and leg exercises with the subjects in both upright and supine positions. These latter studies will require a specially constructed bicycle ergometer.

8. All of the above observations should be compared in two groups of individuals: those who have and those who have not been in athletic conditioning preflight. This is necessary to eliminate the confusion between the effects of athletic deconditioning and those of microgravity per se. If such comparisons are not possible, it would be better to use subjects that are not in a state of high athletic conditioning preflight.

9. In-flight or postflight countermeasures will have to be strictly controlled if we are to determine their efficiency. In short- and medium-duration flights, some subjects should not receive any in-flight countermeasures. This is the only way to assess the full impact of microgravity on cardiovascular and pulmonary function. The effect of postflight countermeasures should be evaluated by dividing subjects into two groups: (1) a control group allowed to do as it pleases with respect to getting up and lying down, eating and drinking, and exercising and (2) a comparision group on whom selected countermeasures would be strictly imposed. To investigate in-flight countermeasures would also require two sets of subjects: (1) crewmembers going about their daily activities and (2) a group subjected to a well-defined countermeasure regime. The various countermeasures that warrant investigation include active in-flight exercise or stressing with LBNP, oral fluid and electrolyte replacement just before reentry, and the use of antigravity suits after return to earth. The cardiovascular and pulmonary states preflight and postflight should be compared by a battery

of tests involving measurements of cardiovascular and pulmonary function during quiet standing and during various stresses—tilt table, LBNP, and graded exercises involving the arms, the legs, or both. The exercise tests should be done on the aforementioned bicycle ergometer.

10. The controlled experiments on countermeasures should be supplemented by more informal, operational studies. Detailed logs should be kept on crewmembers concerning their state of preflight athletic conditioning and their general medical, cardiovascular, and pulmonary status; their activities during flight, including exercise regimens and medication; and countermeasures used inflight, just before and during reentry, and postflight. Tests of cardiovascular competence involving the use of LBNP and the response to various levels of exercise, should be conducted preflight, biweekly in-flight, and daily in the immediate postflight period. The aim of these studies is to identify factors responsible for the fact that postflight cardiovascular readaptation to return to earth has ranged from a few days to several weeks.

11. The results of spaceflight experiments should be compared with those obtained in various ground-based models of microgravity, including prolonged bed rest and water immersion.

Long-Term Measurements

1. One goal of these studies is to determine whether or not man reaches a cardiovascular steady state during prolonged spaceflight. For this reason, the experimental protocols listed above, especially measurement requirements 1 through 6, should be repeated, although not so frequently after long sojourns in space. The results should be compared with those obtained in short- and medium-duration missions.

2. Emphasis should be placed on measuring the cardiovascular, metabolic, and pulmonary responses to exercise challenges. It would be important to know the levels of maximum transient work output that are possible after long periods in space in subjects in which countermeasures are or are not employed. Standard bicycle ergometry with monitoring of the electrocardiogram and of respiratory function would be sufficient to analyze exercise tolerance.

3. Studies of countermeasures should be designed with the following questions in mind. (1) When should countermeasures

be started, or must countermeasures be used throughout long-duration missions? (2) Which combination of in-flight and post-flight countermeasures are most efficacious—in-flight exercise, in-flight exposure to LBNP, fluid and electrolyte replacement, anti-gravity suits, or other procedures. (3) Are there any new measures, including drug treatments, that offer advantages?

Instrumentation Requirements

The instrumentation required to meet the measurement requirements described above includes:

1. Physiologic monitoring devices to measure multiple pressures and electrocardiographic signals.
2. Basic respiratory function laboratory equipment including a small mass spectrometer to measure blood gasses.
3. Radionuclide counting facilities for isotope studies in man.
4. A state-of-the-art echocardiographic system including advanced Doppler facilities.
5. Image analysis workstation.
6. Multichannel recording devices (with redundancy).
7. A specially constructed bicycle ergometer.
8. On-board computer facilities to analyze, integrate, display, and store data in real time.

7
Muscle Remodeling

GENERAL CONSIDERATIONS

Muscle accounts for a substantial fraction of the nutritional and metabolic needs of the entire body. Muscle contributes an increasing proportion of the body's weight during growth and development, reaching a peak of 45 percent in young adulthood and then declining with age. Approximately 1 percent of the muscle protein in adults turns over each day, and this accounts for some 20 to 30 percent of the body's entire synthesis and breakdown of protein. The nutrient protein requirements of muscle are high. So are its energy requirements. Even light muscular exercise, such as occurs during daily activities, can increase the metabolic rate 30 to 40 percent over basal levels, and heavy exercise can transiently increase caloric requirements severalfold. The metabolic status of muscle is also regulated by dietary intake, exercise, and hormones. The resulting changes in muscle physiology can have a major impact on an individual's energy and protein balance.

Muscle is capable of being remodeled to meet new functional requirements, such as those that occur during exercise. The effect of exercise on muscle is dramatically shown by the fact that even the muscles of a severely fasted animal can be made to hypertrophy by increasing their workload. The exercise effects are complex and depend on both the kind of exercise regimen and the type of muscle fiber. Endurance training, such as that involved in long-distance running, is characterized by activity over long periods of time against loads that are similar to those occurring during everyday life. Such exercise results in only a modest increase in muscle mass. The main change is an increase in mitochondria, the organelles responsible for oxidative metabolism, and in mitochondrial enzymes, as well as in the vascularization of the muscle. Changes are largely confined to so-called Type I muscle fibers, red muscle fibers of the slow, oxidative type. The result is an increase in muscular endurance, without a marked increase in maximal muscle force. Strength training, as in weightlifting, requires brief activity against heavy loads. The result is muscle hypertrophy, largely the result of an increase in the abundance of the contractile proteins that are organized into myofibrils. The changes occur not only in Type I muscle fibers, but also in Type II fibers, including fast pale muscles of both the glycolytic and oxidative types. Glycolytic fibers, among other characteristics, have relatively few mitochondria and, so, most of their metabolism is nonoxidative. Such fibers, while they can generate great force, can do so only briefly since they are easily fatigued. It is this last kind of change, one involving an increase in mass and in myofibrillar protein that is of particular interest in view of the changes that take place during spaceflight, that involves a decrease in muscle mass or disuse atrophy.

The mechanisms responsible for an exercise-induced change in muscle protein have been studied in animals. Among the factors involved are the transport of amino acids into the muscle cell and their synthesis into protein. Exercise increases transport and synthesis; disuse decreases them. The role of protein degradation is less clear. Some studies report an increase in degradation with exercise; others report a decrease. Some protein degradation involves lysosomes, intracellular organelles that specialize in the breakdown of molecules, and to some extent this portion of protein degradation is sensitive to growth factors such as insulin. Lysosomal degradation of protein may be involved in the regulation of actin and myosin, the contractile proteins of the myofibrils. Another possibility is that lysosomes degrade membrane receptors and other macromolecules. The resulting products of hydrolysis could then regulate the synthesis and degradation of contractile proteins within the cytosol. There are two other problems that are of fundamental importance. One involves the processes responsible for the assembly of the contractile proteins into the precise configuration of the myofibril and their disassembly during atrophy and normal protein turnover. The other concerns the transduction signals that allow muscular exercise to influence protein synthesis. There is evidence that the signals include neurotrophic factors, passive stretch, active contraction, and increased tension. The relative roles of the various signals need to be studied. The mechanisms by which such signals can influence the molecular machinery of the cell are largely unknown.

Hormones thought to be involved in muscle protein regulation include insulin, growth hormone (and the somatomedins), glucocorticoids, iodothyronines, and testosterone. Changes in the concentration of circulating growth hormone and insulin are not essential for exercise-induced hypertrophy of muscle. Rather, the hormones appear to influence the absolute change in muscle size. There are interactions among hormones; they are subject to local control; and some of them, glucocorticoids to cite an example, may act on protein synthesis only at unphysiological concentrations. These basic problems in hormone action require clarification before the role of various hormones in work-related changes in muscle can be understood.

MUSCLE ATROPHY IN SPACE

In weightlessness, the legs no longer experience the loads required on earth for the maintenance of an erect posture or for locomotion, while the arms may take on additional responsibilities for locomotion and body stabilization. Given the altered force-motion environment of spaceflight, it would be expected that the activity of muscles of the lower extremities, particularly the antigravity or extensor muscles, would be decreased, and this, in turn, should lead to disuse atrophy. Data on muscle function are available from Skylab missions and, to a lesser extent, from Salyut missions. There is considerable evidence that humans experience atrophy in leg muscles, but not in arm muscles. Biochemical studies show that there are in-flight increases in plasma and urinary concentrations of several substances that point to the degradation of muscle protein. Metabolic studies indicate an alteration in nitrogen balance and, hence, of net protein metabolism. Postflight measurements have been made of limb dimensions, of muscle strength, and of the electrical activity of muscles (electromyography or EMG). After missions of several weeks duration, there was a loss in the volume of the legs, particularly the calves, only part of which could be attributed to the loss of body fluids that takes place in space. Loss in arm volume was negligible. Loss of muscle strength, amounting to 10 to 20 percent, occurred in the legs, but not the arms. Surprisingly, the strength of leg flexors and leg extensors were affected to almost the same extent. EMG data indicated reduced muscular efficiency and increased susceptibility to fatigue. Recovery of muscle function, particularly of strength, required several days to weeks following missions lasting weeks to months. Whether there is a complete restoration of muscle mass after long-duration flights has not been systematically studied. Ground-based clinical experience shows that humans can regain normal muscle function and mass even after years of disuse and so there is some reason to suppose that the same would occur following prolonged space occupancy. The fact that the muscular changes associated with spaceflight are confined to the legs would implicate mechanical factors as being of major etiological importance in the production of space muscle atrophy. A subsidiary influence of diet or hormonal regulation is also possible.

The data, although providing convincing evidence of muscle atrophy, are not optimal for several reasons. First, most crew members have been in a state of high athletic conditioning before flight, and, hence, there is a confounding of the effects of athletic deconditioning with those of weightlessness per se. Second, the subjects in most studies have pursued exercise regimens in-flight. There is evidence from Skylab missions that in-flight exercise can reduce muscle atrophy. Unfortunately, the influence of exercise has not been systematically studied. For this reason, it is difficult to evaluate the muscle atrophy that has occurred or the efficacy of the various exercise countermeasures that have been tried. Methods used to evaluate muscle physiology have been rudimentary and have only been employed postflight. There have been no measures in space of typical muscle forces that occur as a result of active contraction or passive stretch. Because of these limitations, we do not know the end point of space disuse atrophy or the time course with which it is reached. Nor do we know the forces that various muscles experience in weightlessness, either during everyday activities or during many of the exercises that have been used to counteract muscle atrophy. Without such knowledge, it will be impossible to determine the relation of the disuse atrophy of space to the various kinds of exercise-related changes in muscular function that take place on earth or to evaluate various countermeasures. There is no evidence that the muscle atrophy that occurs in missions lasting several weeks to months has led to serious clinical problems either in-flight or postflight. The data are insufficient to permit extrapolation to missions of several years duration.

Recent animal experiments flown during the 7-day mission of *Spacelab-3*, although limited in scope and duration, have confirmed and extended some of the human studies. Mass and protein content were decreased in leg muscles, especially the extensors. In general, muscle metabolism shifted in a glycolytic direction. Many of the results were similar to ground-based controls in which the hindlimbs were unloaded by tail suspension.

SCIENTIFIC GOAL

To understand the basic mechanisms of activity-related muscle remodeling as they occur on earth and in space.

SCIENTIFIC OBJECTIVES

1. *To determine the physiological and biochemical factors that control muscle function on earth.*
2. *To determine the causes of muscle atrophy in space and, so, provide a basis for the evaluation of countermeasures.*
3. *To ascertain if the changes in muscular function that occur during spaceflight are similar to those occurring on earth and if spaceflight offers any unique opportunity for the study of muscle remodeling.*

Measurement Requirements

1. A rigorous ground-based program is needed to determine the mechanical, biochemical, molecular, hormonal, neuronal, and nutritional factors that control muscle function. This is best carried out in animal models of muscle remodeling. The functions of muscles that require study include their metabolic status, their morphology and histochemistry, and their contractile properties and electrophysiological status. The influence of various kinds of exercise, including regimens that simulate endurance and strength training, need to be investigated. The effects on various types of muscle fibers should be compared. There is a need to improve ground-based biochemical techniques, especially those involved in

measurements of the absolute rates of protein synthesis and degradation, and to adapt standard physiological, morphological, and biochemical methods for use in spaceflight.

2. Various ground-based animal preparations of muscle remodeling should be investigated. It is equally important to study models of muscle hypertrophy and muscle atrophy, since both presumably involve the same cellular and molecular mechanisms. For similar reasons, the reversion from these states is also of interest. Models of atrophy include immobilization by casting, hindlimb unloading accomplished by tail suspension or body harnessing, paraplegia, denervation of specific muscle groups either by surgical transection or by local pharmacological nerve block, and cutting the tendon (tenotomy) of the muscle of interest or of its antagonists. Hypertrophy can be studied by forced exercise or by tenotomy or denervation of synergists. The rat has been the favorite animal for this research and remains a suitable choice of species. Human models that should continue to be studied include paraplegic patients, bed-rested subjects, or people in various exercise regimens.

3. Muscle function in space-flown animals needs to be measured as a function of mission duration and exercise regime. Such space experiments are needed to compare the characteristics of disuse atrophy in space and on the ground. An important problem concerns whether space atrophy involves a conversion of muscle fibers from one type to another. Biochemical and morphological effects have to be studied as a function of mission duration and, in most cases, without the complications of returning the animals to earth. Biochemical studies can be done postflight on specimens that are frozen in-flight. Morphological analysis will require in-flight fixation. Provisions should be made for in-flight physiological measurements on intact animals, on isolated muscles, and on individual muscle fibers obtained from animals at various times during missions.

4. Muscular performance in humans should be determined in-flight, as a function of mission duration, and compared to results obtained preflight and, as performance improves, postflight. Measures are needed of the maximum force. Force-velocity curves, length-tension relations, and fatigability of various muscle groups should be studied during both maximal and submaximal activity. The recruitment of motor units should change as a muscle atrophies. This can be studied by recording electromyographic activity

from representative muscles as the strength of voluntary muscular contractions is varied.

5. An in-flight biomechanical analysis in humans is needed that correlates EMG activity, the forces acting on the musculoskeletal system, and the movements of joints. The measurements should be obtained during both routine and strenuous activity and have to be compared with those obtained on earth.

6. Countermeasures are best judged in terms of the aforementioned biomechanical studies. Various exercise protocols and the use of motion-resisting devices need evaluation.

7. As in the case of nutritional research in space, it will be important to study the influence of preflight athletic conditioning, as well as the affects of in-flight exercise. The design of all experiments should include four groups of subjects, including all combinations of preflight conditioning versus no preflight conditioning and in-flight exercise versus no in-flight exercise. Such 2×2 balanced design is required if we are to understand the effects of weightlessness per se on muscle function, of preflight conditioning, and of various in-flight exercise programs.

8
The Anemia of Spaceflight

INTRODUCTION

Description of Symptoms

Anemia was first noticed in Gemini missions in which astronauts were breathing pure oxygen at low ambient pressures. This presumably caused oxidation of red blood cell (RBC) membranes and a destruction of the RBCs themselves, a so-called hemolysis. In the Apollo program normal ambient air was provided at launch but was gradually enriched so that astronauts were eventually breathing pure oxygen. When they were found anemic, it was thought to be due to the same oxidative RBC damage. A similar anemia, however, has also been seen in Shuttle missions, where the cabin air is identical in pressure and composition to that found at sea level and, so, cannot be attibuted to high oxygen levels.

There are only limited in-flight data on the time course over which the anemia develops and on its persistence during long-duration missions. Available information suggests that the anemia appears as early as four days after launch and reaches a maximum at 30 to 60 days when the decrement in RBC mass is typically 15 percent. After that, the anemia may stabilize or slightly recede. The etiology of the anemia is not yet clear. It has not, as yet, led to clinical complications in-flight, although it has the potential for doing so. In particular, were a serious accident or illness to occur during a mission, a diminished RBC mass could contribute to morbidity or possibly even to mortality. Following missions of long duration, RBC mass begins to recover after a delay of two weeks and may take as long as six weeks to return to normal. Undoubtedly, the anemia contributes to the cardiovascular difficulties, including the orthostatic intolerance, seen in the immediate postflight period.

Etiology of the Anemia

Most anemias in man involve more than one cause. The same is likely to be true for space anemia. Here, there would appear to be at least three potential contributing factors: (1) a reduction in RBC production that is a consequence of the headward redistribution of blood occurring upon orbital entry, (2) a shortened lifespan of circulating RBCs, and (3) a direct effect of microgravity on bone marrow that reduces RBC production. The three factors are not mutually exclusive; they are considered in turn.

Normal RBC homeostasis is determined by a feedback system that includes an oxygen sensor in the kidneys. The sensor regulates the production by the kidney of a hormone, erythropoietin (EPO), which in turn controls the rate of RBC production by the bone marrows (Table 8.1). Suppose that the concentration of RBCs in the blood, the so-called hematocrit, is reduced. This will lead to a reduction in the oxygen delivered to all of the organs of the body. In the case of the kidney, the oxygen sensor is triggered, and there is an increase in EPO production and eventually an increase in the number of circulating RBCs. If, on the other hand, the hematocrit rises slightly, the oxygen supply to the oxygen sensor is increased, and EPO production is stopped. At even higher hematocrits, there is an increase in blood viscosity with the result that the rate of blood flow and oxygen transport may actually decrease. This may cause a relative hypoxia in most tissues, but not the kidney. Here, there will be an automatic decrease in oxygen consumption, which is determined by glomerular filtration and blood flow. Consequently the feedback control depicted in Table 8.1 is effective at all RBC concentrations. We can now consider how this feedback system will operate during exposure to weightlessness.

Under terrestrial conditions, a considerable amount of blood and other fluids (approximately 2 liters) is kept in the legs under the influence of gravity. In space, some of these fluids will be redistributed to the upper body. This is interpreted by sensors in the torso and the brain as an increase in blood volume. A variety of neurohumoral mechanisms are called into play, and

TABLE 8.1 Baseline Data for Analysis of Erythrokinetics of Spaceflight[a]

Parameter	Settings and Subjects			
	Ground-based[b]		In-flight[c]	
	Animal	Human	Animal	Human
Red cell count	+	+	+	+
Hemoglobin	+	+	+	+
Hematocrit	+	+	+	+
Red cell mass	+	+	+	+
Blood volume	+	+	+	+
Plasma volume	+	+	+	+
Reticulocyte count	+	+	+	+
Erythropoietin	+	+	+	+
Plasma or serum haptoglobin	+	+	+	+
Platelets	+	+	+	+
Red cell shape	+	+	+	+
Red cell size	+	+	+	+
Blood P_{50}	+	+	+	+
Blood PCO_2	+	+	+	+
Red cell 2,3-DPG	+	+	+	+
Red cell ATP	+	+	+	+
Red cell sodium	+	+	+	+
Skin petechiae	-	-	+	+
Subcutaneous, subserosal oozing of RBC	-	-	+	-
Bone marrow smear	+	-	+	-

[a]When feasible, measure sequentially for temporal aspects.
[b]Examples: biological laboratories, hospitals, space simulation facilities (bed rest, water immersion, etc.), spacecraft simulators.
[c]Include preflight, in-flight, and postflight phases.

there will be a diuresis, a loss of blood plasma volume, and an increased hematocrit. The latter causes a suppression of EPO production until the RBC mass is decreased to the point where the hematocrit and blood's viscosity return to normal. This is an entirely appropriate physiological adjustment as long as the subject remains in space. Upon return to earth, however, some fluids are redistributed to the legs. This is interpreted by the sensors in the upper body as a decreased blood volume, and the same mechanisms now lead to a decreased urinary output and thirst. Once the astronauts have quenched their thirst, the plasma volume is restored to normal, but the RBC mass is diluted. The astronauts will have a reduced hematocrit and are recognized as anemic. Over time, the EPO feedback system will result in an accelerated RBC production, and the anemia should disappear.

The production of RBCs from stem or precursor cells in the bone marrow takes approximately 72 h. EPO is thought to exert its influence early in this process. The first signs of a reduced RBC mass has been observed four days into flight. It is thus conceivable that the EPO feedback system could be responsible for even the early stages of space anemia. At the same time, the neurohumoral mechanisms responsible for the diuresis, the increased hematocrit, and the presumed suppression of EPO require time to work. This has led to the suggestion that there is a hemolysis or shortened RBC lifespan that may help to explain the early onset of the space anemia. An increased hemolysis was in fact observed in flight experiments done on rats. The origin of the hemolysis is not entirely clear, but it could be due to an increase in the sequestering and destruction of RBCs in the reticuloendothelial system, particularly the spleen. The changes in RBC shape noted in Skylab and Soviet missions, should facilitate hemolysis by the reticuloendothelial system.

Microgravity may have a direct effect on marrow structure and function. This is suggested by an observation made by Soviet scientists. There was a depletion of stem cells of the femoral marrow of rats carried on an 18-day mission. It is reasonable to suppose that marrow, as is the case for bone in general, can be influenced by local mechanical forces (see Chapter 5).

SCIENTIFIC GOAL AND OBJECTIVE

To characterize the anemia that occurs in spaceflight and to determine the relative importance of various factors that may contribute to the loss of red-blood cell (RBC) mass.

Measurement Requirements

1. There is a need for more detailed studies of the time course and magnitude of the anemia. RBC mass should be estimated from blood samples drawn at least twice daily during the first two weeks of the mission and twice weekly thereafter. Of particular interest are the time of onset of the anemia, its maximum magnitude, and whether it reaches a steady state for missions of several months duration.

2. Erythropoietin (EPO) levels in blood. The bioassays that have been used to date are not sufficiently sensitive to detect expected changes in EPO levels, particularly those that might occur during the early stages of space anemia. The radioimmunoassay being developed in a few academic laboratories has the requisite sensitivity and uses less than 1 ml of plasma. The frequency of testing will depend on studies currently being done in normal animals and humans. The results suggest considerable variation in EPO levels. At the time of launch and for several ensuing days, EPO levels may have to be determined from multiple samples collected every few hours, or possibly even more frequently. Daily collections may miss peaks and troughs and may not be representative. Similar measurements should be made preflight and postflight.

There is also a need for physiological studies of the relationship between altered hematocrit, renal function, and EPO levels. Such studies need to be carried out first at sea level on animals where changes in hematocrit are caused by dehydration or by systemic blood dilution, later on patients with these syndromes, and last on animals and humans in the microgravity environment.

3. Red blood cell survival studies. In order to determine the hemolytic component of space anemia, red blood cell kinetics should be measured in humans immediately preflight at launch, daily during the first week of flight, and weekly thereafter. Similar measurements in the immediate postflight period would also be of interest. A simple measure of hemolysis, the determination of

serum bilirubin concentrations, should be done on the same time schedule as the kinetic measurements. Both kinds of measurements have to be corrected for alterations in total plasma volume, which should also be determined.

Changes in RBC shape have been reported in previous missions. Studies are needed to describe the changes in more detail and to determine the underlying etiology, which is at present unclear.

4. Bone marrow studies. Marrow function should be evaluated histologically in an appropriate animal model subjected to microgravity. The specimens can be obtained in the same morphological experiments in which the bone demineralization is studied (see Chapter 5).

5. Clinical implications. As far as is known, the loss of RBC mass is an appropriate adaptation to the cardiovascular changes that occur during spaceflight. At the same time, it is important to evaluate the clinical implications of the anemia should a serious illness or accident occur, especially during long-duration missions.

9
Human Nutrition

INTRODUCTION

It might be expected that the energy requirements of posture and motion should be less in space than on earth since the body does not have to work against the force of gravity. This would suggest that caloric requirements would be lower in space. Yet, man typically exhibits a small loss in weight during spaceflight even though the diet appears to have a nearly normal caloric content. Much of the weight loss occurs during the first three days of a mission and is rapidly recovered postflight. The rapid weight changes are almost certainly due to the changes in body fluids that are part of the cardiovascular adaptation to weightlessness and the readaptation occurring upon return to earth. There can also be slower changes in body mass during long-duration flights. Skylab astronauts usually showed a slow weight loss that was correlated with the caloric intake of the individual crewmembers. In two Soviet missions of six-month duration, three of four cosmonauts gained weight. This was attributed to an increase in adipose tissue that more than offsets losses in lean body mass and in body fluids. From energetic considerations, a change in body mass must be explainable in terms of four processes: (1) loss or retention of fluid, (2) caloric intake, (3) alterations in energy metabolism or storage, and (4) changes in the efficiency with which metabolic energy is utilized. The two consistent findings are a rapid weight loss, ascribable to a fluid loss, and a slower decrease in lean body mass. The latter is probably the result of the muscle atrophy that accompanies prolonged spaceflight and, as such, represents an alteration in energy metabolism and storage. Several questions remain to be answered. This information can be used to evaluate the effects of the transient digestive disturbances associated with space sickness, as well as of long-term changes in gastrointestinal absorption and in gut flora. Are there changes in energy metabolism and storage other than those due to muscle changes? Is spaceflight associated with a change in energy expenditure? What, in fact, are the energetic requirements of work in the space environment?

Biochemical analyses of plasma and urine samples collected in-flight during Skylab missions are consistent with a muscle atrophy. These include increases in plasma concentrations of potassium and creatinine and increased urinary excretion of potassium, creatinine, total hydroxylysine, N^+-methylhistidine, and almost all amino acids. Metabolic balance studies were also done during the Skylab missions. There was a shift in nitrogen balance in a negative direction, as would be expected from a breakdown of muscle protein. The data are somewhat difficult to interpret, however, since the preflight baseline measurements indicated a positive balance. While the negative shift was a consistent finding, the absolute magnitude of the nitrogen balance that occurs in-flight warrants reexamination.

There is a need for detailed and precise studies to characterize the energy and nitrogen metabolism of prolonged space occupancy. It is essential in the planning of long-duration missions to know caloric needs and to determine an appropriate diet in terms of carbohydrate, fat, protein, and trace nutrients. Without such information, the health and well-being of crew members cannot be guaranteed. Furthermore, inadequate human nutrition during long-duration missions could have a serious impact on the overall science strategy, since studies on humans form an integral part of any comprehensive program in human space biology and medicine.

SCIENTIFIC GOAL

To understand and describe the nutritional needs of human space travel.

SCIENTIFIC OBJECTIVES

1. *To characterize the caloric needs of man in the space environment.*

2. *To determine the nitrogen balance during spaceflight and, if it is negative, to determine its source and possible interventions.*

3. *To ascertain if the microgravity environment requires nutritional supplements of vitamins, minerals, or other nutrients not required on earth.*

Measurement Requirements

1. Metabolic studies require the careful evaluation of food and fluid intake by the use of a diet rigorously controlled in its caloric and nutrient composition. Accurate collection of excreta is also essential. What has been the food and fluid intake during spaceflight? To what extent are nutritional requirements modified by transient digestive disturbances, such as the anorexia, nausea, and vomiting associated with space sickness? Do the conditions of spaceflight alter gastrointestinal physiology, including the absorption of essential nutrients and the functioning of gut flora?

2. Measure energy expenditure by intermittent gas exchange methods or by the use of isotopic water ($^2H_2{}^{18}O_2$). These should be done under a variety of situations, including basal conditions, normal workloads, and during strenuous exercise. In-flight and preflight values should be compared.

3. Measure body composition by indirect methods periodically in-flight and compare with preflight date. The isotopic body-water method can be used for in-flight measurements. For preflight and postflight determinations, several other methods, such as underwater weighting and total body electric conductance, should be considered.

4. Nutritional data should be collected for all individuals as a matter of record, as well as for study. The rigors of adherence to the strict regime required for metabolic studies must be recognized, even to the point of requiring formula diets for precise balance data. Reliable studies require dedicated subjects and have to be conducted by highly trained flight personnel.

5. Develop requirements for essential nutrients by reviewing the literature and conducting research.

6. Study the biomechanics of motor performance in space to gain insights into the energetic requirements of working in this environment.

7. An important variable is the state of prior athletic conditioning. In particular, it will be important to fly some individuals

who are athletically unconditioned. This is neccessary to evaluate the separate effects of athletic deconditioning and microgravity on nutritional requirements and on protein and energy metabolism.

10
Human Reproductive Biology in Space

INTRODUCTION

Studies on the effects of space travel and the physiological adaptation to zero gravity have not yet addressed alterations in the reproductive system in either man or woman. This chapter will review current knowledge and some issues that appear to emerge from it as they apply to the human reproductive system. Current experiments on mammalian reproduction in space have been limited to rats. The first study involved animals carried in flight by the Russians for 19 days (*Cosmos 1129*). These were to mate in space and give birth on return. None delivered, and the Soviets hypothesized that stress caused fetal absorption. A more recent flight (*Cosmos 1167*) contained rats that successfully delivered in space, and simulated flight research at the Ames Research Center also did not corroborate the original Russian observation of reproductive failure.

Three broad processes in space travel can affect reproductive function: these are stress, the microgravity environment, and radiation. Stress and training in preparation for spaceflight may have important effects on the reproductive system, particularly in females. This may represent an appropriate adaptive change analogous to the reproductive disorders, including amenorrhea, which have been documented in female recruits at the United States Military Academy where emphasis is placed on heavy physical training. The same phenomenon is also seen in female athletes and ballet dancers. The mechanism is thought to be an altered hypothalamic gonadotropin-releasing hormone (GnRH) secretion. Normally GnRH pulses stimulate the secretion of LH (luteinizing hormone) and FSH (follicle stimulating hormone) from the anterior pituitary, and these in turn regulate ovarian function. Thus alterations of neuroendocrine regulation of the hypothalamic-pituitary axis may produce changes in trained female astronauts similar to athletes undergoing intensive physical or emotional training. The frequency of GnRH pulses also appears to be important; slow frequencies are associated with hypogonadotropic anovulation while faster frequencies produce elevated LH levels as seen in clinical aberrations like the polycystic-anovulatory syndromes. Data on the effects of training on the male reproductive system are less clear. Some results have suggested that heavy endurance training may affect testosterone secretion.

Stress

Since there is considerable evidence that stress can produce short-term effects in women, the impact of these hormonal changes on other organ systems should be considered. One of the most serious might be an augmentation of loss of bone mineral which would be accelerated by hypoestrogenism, even in the short term. Estrogen has very significant effects on bone turnover, and the hypoestrogenism seen even in young active athletes is known to be asssociated with accelerated calcium loss and decreased bone density. Thus the osteopenia of spaceflight would definitely be compounded by hypoestrogenism and, more importantly, may not be completely reversible. It is not known if equivalent decreases in gonadal hormones in men would have similar effects. The importance of hypoestrogenism has not been addressed in previous reports on bone demineralization in spaceflight. Replacement therapy should be considered, especially in those females who have previously shown a low threshold to stress-produced amenorrhea.

Microgravity

Microgravity may also present other problems for the female reproductive system. The normal egress of menstrual fluid may be impeded, and tubal reflux, an accepted mechanism in the development of endometriosis, may be more frequent. Fluid shifts seen in space may be altered by the normal menstrual cycle. One

TABLE 10.1 Implications of Spaceflight on Male and Female Reproduction

Variables of Concern	
Hypogravity	Dietary modifications
Radiation	Environmental factors (i.e., noise)
Altered light/dark cycles	Altered oxygenation (EVA)
Confinement	Stress (training & flight)
Sexual abstinence	Testicular temperature (males)
Limited sensory input	
Potential Effects	
Germ cell damage or loss	Depression
Teratogenicity	Abnormal fertilization
Mutagenicity	Abnormal implantation (females)
Altered endocrine rhythms	Endometriosis (females)
Impotence (males)	Estrogen-deficient osteopenia (females)
Altered menses (females)	

study using bed rest as a model analogous to the weightless environment showed that the reduction in plasma volume seen in bed rest is neutralized by the preovulatory estrogen peak at midcycle. The bed rest model has also shown that women develop inadequate luteal phases, and this is also likely to develop in the weightlessness of spaceflight.

In pregnancy, the fluid and electrolyte shifts associated with microgravity, particularly the drop in plasma potassium, may affect growth of the developing blastocyst, particularly the inner cell mass, which develops into the embryo. If cleavage is delayed and a critical 16 cells are not present at the time of cavitation, an embryo will not develop. These specific developmental processes, discussed in greater detail in Chapter 2, would be applicable to women should a pregnancy be in process.

Radiation

Space travel entails exposure to radiation. Although there are descriptions of the type of radiation encountered in space and gonadal doses have been calculated, direct determinations have not been made. Crewmembers encounter chronic, low level radiation which is qualitatively different from the radiation used in ground studies. The latter has consisted mainly of gamma and x rays whose relative biological effectiveness (RBE) is equivalent to one. Space radiation is mixed, and some consists of elements that have RBEs substantially higher than one.

The effect of space radiation on male and female reproduction has not been characterized and even experimental animal work, although of significant importance, may not be applicable to man because of the marked decreases in sensitivity from not only one species to another but even between strains of the same species.

Radiation could affect gametogenesis as well as the developing embryo. Male gametogenesis is particularly susceptible with an increase in genetic risk due to chromosome damage as well as depressed spermatogenesis. It has been calculated that linear energy transfer (LET) high radiation with an RBE of around 20 would double the chance of producing a genetically defective offspring in males from 15 per 1000 live births to 30. At the present time, there are no experiments on developing embryos of any species with the mixed radiation exposure encountered in space.

SCIENTIFIC GOAL

To study the effects of the space environment on human reproductive function.

SCIENTIFIC OBJECTIVES

1. *To characterize the effects of stress and the microgravity environment of spaceflight on reproductive function as evidenced by hormonal and physiological alterations, including the contribution of hypoestrogenism to bone loss.*
2. *To study the effects of the microgravity environment on eggs and sperm directly, and on the fertilized ovum and its subsequent development.*
3. *To characterize the radiation effects in spaceflight on male and female reproduction and the possible pathological effects of this to eggs, sperm, and developing embryos.*

Measurement Requirements

1. Data collection. Female crewmembers should collect basal body temperatures for at least three months prior to launch as

well as having on file a reproductive history including menses, pregnancies, and other pertinent data. A complete reproductive history of male crewmembers should likewise be documented relative to normal and abnormal pregnancies and fetal wastage. Such histories should be continued for several years postflight to determine the effect of prolonged space travel on human reproductive competency. The incidence of birth defects in the pregnancy of crewmembers is of particular concern.

2. Many of the potential alterations in female reproductive function are likely to be the result of the stress asociated with preflight training and with spaceflight itself. Since the symptoms are not peculiar to the space environment, a specific program of space research is not warranted. There are two exceptions to this general conclusion. (1) Hypoestrogenism may exacerbate the osteopenia of spaceflight. Hence, women crewmembers should be included in studies of human bone function (see Chapter 5) to determine whether there is a correlation between the occurrence of amenorrhea and the severity of space osteopenia. If there is, the efficacy of estrogen-replacement therapy should be investigated. (2) Microgravity may result in endometriosis as a consequence of tubal reflux. Since recumbency should reproduce the physical conditions leading to tubal reflux, a study should be conducted in bed rested female volunteers to determine the incidence of this problem before spaceflight experiments are contemplated.

3. Direct sperm analysis. A new technology, the characterization of human sperm using zona-free hamster eggs, permits the direct analysis of human sperm chromosomes for structural abnormalities. Normals have about 20 percent recognizable aberrations. Preflight, in-flight, and postflight analysis in parallel with other determinations such as direct and calculated gonadal radiation should be done to assess the effects of the space environment on the human gamete. In parallel with these should be other standard assays such as motility and electron microscopic examination. Depending on these and other studies, frozen semen for future reproduction may be indicated for male crewmembers. Direct analysis of human eggs or of the human fertilized ovum are unwarranted. Here it will be necessary to rely on animal models. The experiments described in Chapter 2, Developmental Biology, including those involving mammalian development and radiation effects, provide an appropriate starting point.

11
Human Behavior

INTRODUCTION

Behavior involves the interaction of individuals with their environments. Many important functions depend in some way on such behavioral interactions. A partial list of these functions would include sleep and wakefulness; maintenance of nutrition, fluid balance, personal hygiene, and health; work and the response to emergencies; and organizational, social, and recreational activities. Clearly, adaptive behavior is essential to the success of any human endeavor. The conditions under which adaptive behavioral interactions must be effectively maintained vary widely. Unusual and demanding spaceflight environments can adversely influence such adaptations especially if intensive and highly skilled performances are required on the part of individuals and groups. Despite this, there have been few official reports in the U.S. or Soviet space programs of serious behavioral disruptions or of behavioral problems that have impeded crew performance or threatened completion of a mission.

There is some indication, however, that official reports on the behavioral adaptation to space are not completely accurate. Moreover, there is reason to believe that behavioral and social problems will become more frequent as missions become longer and more complex, and as crews become larger and more heterogeneous in their makeup. This chapter begins with a review of the stressful conditions imposed by spaceflight and the behavioral problems that have been observed. It then presents other situations that resemble spaceflight in that personnel are placed in isolated, confined microsocieties with demands for high performance; experience in these other situations illustrates the kinds of behavioral disturbances that can arise in such an environment.

CURRENT KNOWLEDGE

Spaceflight

Several aspects of the space environment can be expected to have an impact on behavioral adaptation. Living space is confined, food is restricted in quality and diversity, there is a lack of privacy, and there are limited facilities for personal hygiene. Artificial life support systems do not provide an environment comparable in quality to that found on earth. Noise levels can be high and unpleasant odors abound. The weightless environment requires a readjustment of motor and perceptual skills. Disorientation and space sickness are common during the first week of flight. Social interactions are limited to other crew members. The only contact with family and friends is by radio-telephone communication, and sexual activity is constrained. Demanding workloads can be stressful as can the everpresent danger of a major life-threatening system malfunction. Added to all of this, there is no escape from the environment during the mission.

Despite all of these discomforts and stressful conditions, there have been no official reports of major behavioral disturbances in U.S. missions lasting as long as 84 days or in Soviet missions of up to 237 days duration. Decrements in performance have usually been transient, occurring early in the mission. Many of these can be related to the need of learning new perceptual and motor skills in weightlessness, as well as to the spatial disorientation and space sickness that occur during the first few days of a mission. Others are due to abrupt, scheduled changes in sleep-wakefulness cycles from those occurring on earth. The symptoms of such rescheduling have been sleep loss, poor quality of sleep, fatigue, and a decrement in performance. A form of functional myopia, similar to that experienced by submariners, has been reported. While this may be an appropriate adaptation to being confined to cramped quarters, it can impair distant judgment and spatial vision for far-away objects. There are examples of a distortion of the sense of time, a so-called time compression, that may reflect overly crowded task scheduling.

The apparent lack of performance decrements may be due as much to the reluctance of astronauts to render official reports of what they fear may be regarded as "aberrations" and to the reticence of space program directors to publicly acknowledge behavioral disturbances. In contrast, the picture that emerges from less formal reviews of mission reports and interviews with space crews and ground personnel reveals that both Soviet cosmonauts and American astronauts have experienced performance decrements in the form of experimental errors, lost data, and equipment mishandling. In addition, a long list of symptoms has been described including sleep disturbances, fatigue, irritability, depression, anxiety, mood fluctuations, boredom, tension, social withdrawal, and motivational changes. Reported instances of interpersonal hostility between crewmembers in flight have appeared, and occasional hostile and uncooperative exchanges between space and ground crews have been publicized. There are indications, however, that fatigue factors may have been involved in the instances cited, and differences were quickly and amicably resolved. Significantly, there are unpublished accounts of the Soviet space program that suggest the occurrence of episodes of mental depression during some long-duration missions.

The validity and reliability of such anecdotal accounts are difficult to evaluate, but no more so than official reports in the same regard. There has been an unfortunate lack of direct access to flight and ground crews by behavioral scientists. Related to this is a lack of systematic assessment of individual performance both in training and during missions. The absence of such data makes evaluation of factors that may influence human performance difficult. Under the circumstances, it must be concluded that there is insufficient objective information to determine the incidence and severity of behavioral disturbances in spaceflight programs. To some extent, however, insights into the possible behavioral consequences of prolonged isolation and confinement in space may be derived from studies of ground-based environments that bear some similarity to spaceflight conditions.

Confined Microsocieties on Earth

Undersea habitats, submarines, and polar stations in the Arctic and Antarctic share several features with spaceflight. These include confinement, isolation, personal discomfort, and potential danger. Adverse effects have ranged from boredom and listlessness, through heightened anxiety with psychosomatic symptoms, sleep disturbances, fatigue, and impaired cognition to irritability, hostility, depression, and deterioration of individual behavioral adjustment. These observations have to be placed in context. For one thing, psychological disturbances were not a universal feature of such habitats. Furthermore, despite the stressful nature of the environments, most groups were able to adapt and perform effectively. Perhaps most importantly, studies have helped to identify some of the factors that enhanced or impaired group performance. Positive factors were gregariousness, role-sharing, privacy, and good leadership. Negative factors were lack of privacy, of social stimulation, and of objective rewards; inability to communicate with outsiders; unchanging environment; family concerns; group adjustment problems; and absence of customary sources of emotional satisfaction. The results of spaceflight simulations show the importance of crew selection and pre-mission training that emphasizes group coherence and group performance.

Summary

There is not enough objective data to determine the seriousness of behavioral impairments in past spaceflight missions. Nevertheless, there is reason to suppose that psychological problems have already occurred in spaceflights and that these will increase in frequency and severity as missions become longer and more complex, as crews become larger and more heterogeneous, and as the dangers of spaceflight become more fully appreciated. Behavioral studies in ground-based situations demonstrate that, with proper methodology, the factors contributing to enhanced performance, as well as to individual and group satisfaction, can be identified.

METHODOLOGICAL CONSIDERATIONS

The greatest single requirement in this field is access to crews by trained behavioral scientists. Such access is needed to observe, test, and evaluate behavior, including sensory and motor capabilities, cognitive and perceptual processing, and the motivational and emotional factors that influence the operational performance of individuals and of entire crews. Flight personnel must be available for study starting from selection and preflight training through the mission and into the postflight period. The data obtained from mission-related activities can be supplemented by studies of other confined microsocieties and of mission simulations. Many research opportunities are provided by these other situations. At the same time, it must be emphasized that they are not a substitute for the study of the spaceflight environment.

The information obtained from spaceflight and from similar ground-based situations can be used to define and understand the factors that influence behavior in both space environments and other microsocieties. Systematic observation and controlled experimentation can aid in determining the characteristics and conditions that maximize human achievement and satisfaction. A well-planned research program is essential to determine the environmental, individual, group, and organizational requirements for the long-term occupancy of space by humans. In addition, the knowledge obtained should be applicable to all human activities that involve the cooperative and productive interactions of small groups operating in a larger organizational context.

MAJOR SCIENTIFIC GOAL

The overall goal for the study of human behavior in space is the development of empirically based scientific principles that identify the environmental, individual, group, and organizational requirements for the long-term occupancy of space by humans. Although the evidence is fragmentary, it seems likely that behavioral and social problems have already occurred during long-term missions and that such problems will be exacerbated as missions becomes more complex, as mission duration is increased, and as the composition of crews become more heterogeneous. An understanding of the problems and their amelioration is essential if man desires to occupy space for extended periods of time. Even more important from a scientific perspective, it seems likely that significant advances in our basic knowledge of human interaction and group processes will emerge from the research needed to ensure effective performance and adjustment in space.

ENVIRONMENTAL FACTORS

There are many research questions associated with the design of space habitats and their influence on individual and group behavior. Of necessity, the physical characteristics of spacecrafts impose limitations on general living conditions and performance levels. Life in a spacecraft imposes constraints on physical mobility and the variety and nature of social interactions. The challenge is to design an environment that maximizes personal satisfaction in the face of these constraints.

One of the more significant aspects of spaceflight is weightlessness. There is a need for individuals to adapt their sensory and motor skills to an altered force-motion environment. There is spatial disorientation. Space sickness is a common, if not universal, consequence. In most descriptive accounts, space sickness is described as an episodic process marked by vomiting that occurs perhaps a few times a day. This is a far from accurate picture. Space sickness has the same symptoms as does terrestrial motion sickness. The symptoms include nausea, pallor, sweating, malaise, and a general feeling of discomfort and uneasiness, as well as vomiting. Continuous monitoring of subjective feelings was done on *Spacelab-1*. Vomiting occurred episodically, but feelings of malaise and discomfort were more or less continuously present during the first several days of the mission.

Fortunately, the space sickness syndrome disappears within a few days to a week. Nevertheless, space sickness has a serious impact on operational efficiency early in the mission, when many important duties are to be performed. The design of the spacecraft can be of considerable importance. Many astronauts have found that the sense of disorientation and space sickness are exacerbated by the lack of clear and consistent visual cues that would reinforce a sense of verticality. An increased contact force of the feet with support surfaces might also be investigated. In addition, there are intrusive noises, objectionable odors, and uncomfortable temperatures. Again the discomfort from these sources usually habituates within a few days. Properly designed studies of the spacecraft environment could provide insights into the conditions that enhance orientation to the vertical and minimize irritation by external stimuli. (See Chapter 4 for a further discussion of space motion sickness.)

Two aspects of spaceflight have the potential of being particularly troublesome. These are likely to take on increasing importance as a mission progresses. Environmental design research involving back-to-back workstations and designated private quarters for each crewmember not under video surveillance could provide an approach to reducing these problems. The psychological adjustment of cosmonauts has reportedly been enhanced by the opportunity to maintain personal diaries as well as the provision of space-ground radio links for crewmembers to communicate with their families. The role of such environmental design features in maintaining morale, solving personal problems, and reducing emotionally stressful conditions requires systematic study.

There are a number of research leads that need to be pursued in developing countermeasures to the boredom, which can be expected to occur when mission tasks become routine. The Soviet practice of permitting crewmembers some personal latitude in the design of their environments, and of allowing them to select personal items for recreational purposes and to request favorite foods delivered by resupply flights has reportedly helped to maintain morale and productivity. So, too, has the Soviet practice of frequent radio conversations between the cosmonauts and interesting civilians on earth. These practices should be studied systematically with a particular focus upon investigations of the extent to which crew-initiated changes in living habitats and work environments (within the limits of operational constraints) can alleviate boredom and enhance performance.

Fairly sophisticated models have been developed for use in workplace design. The parameters included in the models are those that promote ease of operation—reach, physical clearance, removal of encumbrances, and the effective design of visual displays. There are, as well, extensively developed principles of manual control that reflect the complex nature of human motor performance. Application of these principles to the altered force-motion environment of spaceflight requires research, but could have an important salutary influence on the design of space habitats.

A prominent feature of space environments is the presence of computers and other automatic devices. As computer technology develops, we can anticipate that automatic controls will increasingly dominate both the physical and behavioral features of space environments. Research is needed to determine the optimal integration of the human operator into a highly automated environment that controls the entire range of life supports, the organization of work tasks, and general performance functions. Optimization will require that careful attention be paid not only to task efficiency, but also to the overall impact of automation on effectiveness as well as the motivational and emotional stability of the crew. These latter concerns are part of the more general issue of the influence of individual and group autonomy on performance and psychological adjustment, an issue of special concern in the planning of long-duration space missions.

The possibility of long-term occupancy of space by humans will depend on the effective design of space habitats. As a starting point, it will be necessary to determine in a scientifically sound manner the effects of environmental factors on human behavior in space.

Scientific Goal

To analyze the environmental factors, including the architectural design of the spacecraft, that affect behavioral adjustment as well as both individual and group performance effectiveness.

Scientific Objectives

1. *To measure the effect of an artificial vertical, supplied by visual and contact cues, on spatial disorientation, on the incidence of motion sickness, on human performance, and on behavioral adjustment during spaceflight.* Are the effects prominent only during the initial phases of spaceflight or do they last throughout missions of long duration?

2. *To determine the influence of various combinations of external stimuli—for example, lights, sounds, odors, and ambient temperature—on the health, welfare, and productivity of humans in space.* The effects should be studied as a function of time from the start of the mission.

3. *To measure the impact of systematically varied degrees of individual privacy on human performance and psychological adjustment in space.*

4. *To understand how variations of spacecraft architecture during space missions influence human behavior.* How do the effects differ when the changes are under the control of the flight crew as compared to when they are programmed by others?

5. *To examine the influence of alternative designs of workstations and living quarters on human behavior in space.*

6. *To measure the effects of various degrees of automation and its integration with the human operator on human behavior in space.*

INDIVIDUAL FACTORS

The success of a space mission depends on the adaptation of individual crewmembers. To assure such adaptation, research is required in several areas. These include screening and selection procedures; the effects of the space environment on sensorimotor and more complex functions; the influence of daily schedules of work, relaxation, and sleep on performance and adaptation; the stressful nature of spaceflight, its measurement, and effective ways to ameliorate it; and the impact of various factors on the motivational and emotional stability of individual crewmembers.

Screening and Selection

There has been much research on the screening and selection of individuals for situations that resemble spaceflight in requiring both high technical competence and the ability to work well in small, highly interactive groups. For the most part, selection procedures have emphasized the identification and elimination of disruptive individuals combined with the selection of people possessing the capability for high performance. The twin goals of achievement and interpersonal harmony are especially important in the isolated and confined microsociety of spaceflight, where there are great demands for productivity but where serious interpersonal conflict can have disastrous consequences. Recent research has identified two areas of personality that influence individual and group performance. The first relates to the motivation to achieve and includes at least three components: a desire for the mastery of new and challenging tasks, a need to work hard and effectively, and interpersonal competitiveness. The second involves social skills and interpersonal attributes, including concern for others, empathy, and emotional reactivity. Individuals high on the interpersonal dimension have a greater potential for working and adjusting in a group setting. The influence of the achievement motives is more complex. For example, in air transport crews, the mastery needs of individuals were positively related to crew performance, whereas the motivational aspects of work were not a predictor of group success, and competitiveness was negatively related. Much research needs to be done to identify other factors that may be important in group performance and to determine the validity of such criteria in other situations, including long-duration spaceflight. The need to identify individual behavioral factors that enhance effectiveness in responding to crises and to stressful situations is especially important. It is also essential to continue the identification of personality factors that may be associated with physical symptoms—for example, sleep disturbances, headaches, and gastrointestinal disturbances.

Cognitive and Sensorimotor Functions

Research on the determinants of group and individual decision making is a central concern of contemporary psychology. Among the factors known to influence decision making are psychological stress, subtle and overt group and organizational pressures, fatigue, and intergroup tensions. Concern about decision making extends beyond the crew to include ground-based managers and collaborators, as well as the processes involved in reaching joint decisions between ground crew and space crew, and between higher and lower levels of the organization. Also of relevance is the investigation of how complex and conflicting information from diverse sources is processed, organized, and used. Both basic, laboratory investigation and systematic observational studies are needed to provide guidance for operational procedures and organization. Full mission simulations, both of spaceflight and in aviation, can provide a valuable source of data.

There is a so-called time compression, a distortion in the subject's ability to estimate the passage of time. The etiology is unknown but may involve excessive workload, information overload, and changes in cognitive processes. Effective performance requires the processes involved in learning and memory, perception, the development of new skills, problem solving, and verbal behavior. The times to complete a set of motor tasks practiced preflight were measured in Skylab missions. Crewmembers completed the tasks within normal times, except during the first in-flight performance. The initial decrement in performance was attributed to the stressful conditions association with last-minute flight preparations, change to a microgravity environment, greater care and caution in in-flight performance, and some degree of work overload.

It is important to measure the performance of unpracticed tasks, including those requiring complicated perceptual-motor abilities, as well as general cognitive abilities at various times after the start of a mission.

The effects of microgravity on sensory systems involved in spatial orientation were discussed in Chapter 4, Sensorimotor Integration, as was the necessity for the restructuring of motor programs. Suggestions for the study of these effects can also be found in that chapter. Spacecraft are noisy, there are unpleasant odors, and the level of illumination is somewhat higher than experienced on the ground. Possible changes in hearing thresholds and in the sensitivity of the gustatory (taste) and olfactory (smell) systems, especially early in flight, should be measured. There is a defect in visual accommodation, somewhat akin to submariners' myopia. The Soviets report a reduction in visual discriminative functions during the early phases of missions, but these recover as the mission progresses. There should be alterations in proprioceptive sensory inputs from joints and muscles, and this might be expected to alter the ability, in the absence of vision, to determine the position of a limb with respect to the torso, to detect the movement of a limb or finger, or to point a finger at another part of the body or at the memorized location of an external object.

Daily Schedules

Work, recreation, and sleep have to be scheduled so as to maximize the performance and adaptation of flight crews. Overly long or crowded work schedules can be counterproductive. Research analysis will be required to determine the optimal variety and temporal distribution of relaxation and recreational opportunities to minimize the potentially stressful and boring effects of prolonged spaceflight. The extent to which the scheduling of sleep and waking activities should be synchronized for all crewmembers and follow the patterns established on earth in the immediate preflight period requires further investigation. Most importantly, research is needed to devise optimal schedules that are sufficiently flexible to accommodate unanticipated complications that occur during missions.

The obviously stressful aspects of spaceflight associated with crowded work schedules, lack of privacy, novel sensory experience, friction between crewmembers, and concerns about family and other earthly matters need to be investigated from the perspective of their effects on flight personnel. In the first instance, selection and training procedures will require continuous research-based refinements to improve identification and definition of those individual characteristics and environmental conditions that provide the necessary resistance and/or tolerance to such stressful conditions. It is also important to recognize the early warning signs of stressful interactions. Ground-based observations suggest that such detection can be improved by research focusing upon the monitoring of work performances and autonomic responses, of the intention tremor accompanying voluntary movements, and of changes in voice quality. Most importantly, systematic studies are required to determine the effectiveness and optimal application of such environmental interventions as workload changes and social support from flight and ground crews in counteracting the effects of stressful spaceflight conditions. In addition, self-management procedures involving relaxation methodologies and biofeedback control of muscle and autonomic responses should be studied to determine their potential utility under such circumstances. It will also be necessary to continue systematic research on the role of pharmacological agents in the management of stress.

Extrinsic Motivational Factors

Until the recent *Challenger* disaster, there was a tendency to view recent manned spaceflight as becoming routine and lacking the glamour, pioneering interest, and stimulation of earlier missions. One goal of the U.S. space program is to make manned spaceflight as routine as possible, at least in terms of crew safety and flight frequency. Under such conditions, it may be difficult to maintain individual motivational support essential to ensure performance effectiveness, especially during long-duration flights. There is thus a need for research directed toward the identification and definition of such motivational factors as they may involve space system organization, command and control, crew autonomy, role sharing, personal support, career development, growth potential, and external incentives. While much of the required research must, of necessity, involve actual spaceflight, there is also a need for basic research involving small work groups in both natural and experimental laboratory settings.

Scientific Goal

To understand the individual factors that determine personal well-being and accomplishment during space missions.

Scientific Objectives

1. *To develop effective screening, selection, and training procedures for flight crews that emphasize individual and group achievement, group compatibility, and the ability to cope with stressful conditions and to respond to crisis situations.*
2. *To measure the influence of the space environment on cognitive functions, including information processing and decision making, and on sensorimotor capacity.*
3. *To determine the schedules of work, recreation, and sleep that optimize human performance and adaptation in space.*
4. *To evaluate the factors that contribute to behaviorally stressful interactions involving individual crewmembers and to develop procedures that facilitate early detection and effective intervention in such stressful situations.*
5. *To determine the extrinsic motivational factors that contribute to the development and maintenance of human performance during manned missions of various durations.* There is a need for basic research on human motivational issues. This research can be conducted both in natural and in controlled laboratory settings.

GROUP AND ORGANIZATIONAL FACTORS

There is an extensive literature on the effects that the structure of small groups have on overall performance, group solidarity, and individual well-being. Knowledge in this area is deficient in several regards. Findings reported for groups in one setting are not always applicable in other settings. Empirical results are typically of such limited scope that they are of little practical utility in guiding the selection and management of operational groups. The traditional approach to the study of small group dynamics has been to isolate individual factors that influence the interactions between group members and, thus, that may affect group productivity and individual adjustment. A more appropriate model may involve the recognition that groups are small social systems that are shaped by multiple determinants, no one of which, when considered in isolation, can account for variations in group and individual function. Viewed within the context of a multifactorial social systems model, there are four major topics to be considered in the development and maintenance of semiautonomous groups that can function effectively during extended space missions. These are (1) the division of authority between the space crew and the ground-based mission control; (2) the initial composition of the space crew and the development over time of group interactions; (3) the function of leaders in determining group performance; and (4) the effective delivery of support from the ground crews to flight crews.

Division of Authority

Much remains to be learned about the partitioning of authority and autonomy among ground managers at mission control centers, designated leaders of the space crew (mission commanders), and individual crewmembers. Existing research shows that the delineation of a clear set of objectives that challenges a group provides a powerful incentive for individuals to help meet overall organizational goals. The precise means of setting goals and controlling overall mission direction have to be ascertained for groups, such as space crews, that are physically remote from the central base of operations for extended periods of time. Research is also needed to determine the appropriate exercise of authority in solving interpersonal disputes that threaten the integrity of the group and the success of the mission.

Group Selection and Group Development

Research on issues of group composition has been relatively limited in scope. Recent studies, cited above, show that individuals that combine the characteristics of achievement motivation and social sensitivity work well in groups. There is less information on how to choose the members of a group so that they complement one another in their technical skills and personal attributes or how group dynamics develop over time. There is some evidence that events that occur when groups are first put together or at the midpoint of a group's life can have a profound influence on subsequent performance and group interactions. It is important to assign responsibilities in a clear manner in order to avoid conflicts between space crews and ground personnel and between individual members of the crew. At the same time, the crew has to be given the flexibility to redefine tasks as the need arises. Allowing individuals to share tasks adds to group cohesiveness and the sense of individual accomplishment. Although these considerations may seem obvious, research is needed to determine methods of selection and training that will facilitate the development of group cohesiveness and optimize group performance.

Leadership

Competent leadership is essential to group performance. There is an extensive literature on the attributes of leaders, but much of the research lacks validity. More progress might be made by studying the functions that leaders perform in helping groups to meet their objectives, as well as continuing research on the personal attributes and situational influences that help to determine leadership. Some of the functions can be identified: setting directions and establishing authority within the group, creating a well-composed group with clearly defined tasks, and providing organizational and behavioral support for a group as it carries out its work. Research on this functional approach to leadership is essential.

Research is also needed to determine how leadership functions are best allocated. Which functions are best performed by ground-based managers who are charged with the responsibility for group formation and mission organization? By other ground-based managers who work with the spacecrews during the actual missions? By designated leaders within the crew? The answers to these questions are required both for the characterization of leadership roles and for the selection and training of individuals to fill these roles.

Group Decision Making

The processes involved in reaching group decisions are a natural complement of those occurring in individuals. There is much research that, nevertheless, demonstrates that decisions reached by a group are not directly predictable from a knowledge about the individual members of the group. This is an important principle in understanding group behavior in all settings. In space operations, the situation is further complicated by the fact that decisions must frequently be reached by the interactions of several small groups that can be geographically separated and can have diverse needs and immediate goals.

Organizational Support

Effective functioning of space crews depends on the support they receive from the ground-based organization. Such support can be divided into three broad areas: (1) the reward system of the organization that determines the consequences of performance for the crew and its members, (2) the information system that provides the crew with essential data and advice needed to fulfill mission objectives, and (3) the material resources system that ensures the adequacy of equipment and supplies. Each of these areas can have a major impact on the success of a mission. Research is needed on the effective design of delivery systems for making these supports available to crews. Essential features of the design are to keep the support facilities flexible enough to meet the ever-changing needs of the crew and the mission and to integrate the various facets of support to maximize crew performance and well-being, as well as ensuring the attainment of overall organizational goals.

Scientific Goal

To characterize the group and organizational factors that influence the performance and behavioral stability of individuals and the entire crew in the space environment.

Scientific Objectives

1. *To determine the allocation of authority and autonomy between ground-based mission managers, leaders of space crews, and individual crewmembers.* Research is needed not only to determine the general principles that govern such allocation, but also to suggest how the allocation should be modified to take into consideration group composition and the goals and duration of particular missions.

2. *To understand the critical elements and processes involved in complex decision making by groups operating independently or in combination.* Knowledge in this area is needed to ensure that

available information is used effectively and that the various alternative regarding program and mission organization are properly weighed.

3. *To study the principles governing the optimal composition of groups, task design, and task assignment.* Selection and training methods, as well as in-flight procedures have to be developed to implement these goals.

4. *To identify the functions performed by leaders in assuring successful group performance and the optimal assignment of authority and responsibility between space-based and ground-based leaders.*

5. *To determine the principles underlying the design of delivery systems that assure the effective support of the crew by the ground-based organization.* Here the study of aircraft crews and their organizational support would be particularly informative.

GROUND-BASED MODELS

The overall goal, the understanding of the social system including its critical components and their interactions, will require the integration of the results of research on environmental, individual, group, and organizational factors into a coherent body of knowledge that can be used in the design and operation of flight programs and individual missions. Spaceflight research should be supplemented by comparable studies of various earth-based models, including small groups working in isolation and confinement. In addition, there is much research to be done on more general issues related to the functioning of small groups operating in a larger organizational context. Findings from these other situations can enlarge the data base that will lead to an understanding of how human behavior in the space environment is determined. It should also be possible to identify those behavioral features that are unique to spaceflight, those that occur in most confined, isolated microsocieties, and those that occur in all groups, whether these are or are not confined and isolated. Such a comparative approach provides a powerful means of developing a general theory of human group behavior.

Scientific Goal

To supplement spaceflight research with studies of the effects of environmental, individual, group, and organizational factors on the behavior of humans in earth-based microsocieties, including simulations and other controlled research settings, as well as such fully operational situations as undersea habitats, submarines, and polar stations.

Many of the behavioral topics of particular concern in spaceflight can be profitably explored in ground-based situations involving groups that are confined and isolated, as well as groups functioning in more typical social contexts.

Specific research areas with high priority include:

1. Environmental factors: the impact of various degrees of individual privacy on human performance and behavioral adjustment; the influence of variations of architecture during extended occupancy; alternative designs of workstations and living quarters; and the effects of automation and their integration with the human operator.
2. Individual factors: screening and selection procedures; the effects of sensory deprivation on sensorimotor capacity and cognitive functions; schedules of work, recreation, and sleep; stressful conditions and their amelioration; and the development and maintenance of human motivation support and enhancement.
3. Group and organizational factors: allocation of authority and autonomy between organizational leaders, group leaders, and individual crewmembers; the optimal composition of groups, task design, and task assignment; the function of leaders; and the design of organizational support for the group.

Summary

The study of human behavior in space is best accomplished by an integrated program involving study of a wide variety of ground-based settings. These include simulations, other controlled environments, as well as fully operational situations. Ground-based research will be especially important in the immediate future, since there will be relatively few manned missions. At the same time, it has to be emphasized that there is a need for research in the space environment. Such an integrated research program is needed to ensure the effective design and conduct of individual missions and of entire flight programs. While the research is dictated by the needs of the U.S. space program, it can make important contributions to our understanding of the behavior of individuals, groups, and large organizations.

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Science Program and Policy Issues

In this chapter, the committee discusses what is required to achieve the scientific goals described in this report. Proposals are made concerning the use of scientific panels to oversee the implementation of the strategy, life sciences' need for continuous access to spaceflight opportunities, the advantages of a focused mission strategy, certain design features that will enhance spaceflight experimentation, and general facilities. Other topics that are considered include mission planning, crew selection and training, and interagency and international cooperation. Many of our recommendations represent departures from the current operating procedures used by NASA in implementing its Space Biology and Medicine Program. Wherever appropriate, the committee reviews current practices and indicates its reasons for wanting them changed.

SCIENCE PROGRAM ISSUES

Overall Research Plans

In most of the subdisciplines of space biology and medicine, there are a small number of essential questions that require answers in the next 10 to 20 years. To answer these questions requires a comprehensive research strategy in each area that integrates space and ground-based research. In clinically relevant areas, there has to be a further coordination of clinical and basic research. The present strategy can be viewed as a first step in this process. The next step will involve the implementation of the strategy for each area. Biology, like most other sciences, is dynamic. Hence, the strategies will have to change in the light of new results and of new technical developments. There is a continuing need to ensure that the strategies for the various areas are coordinated into a coherent plan for the entire life sciences. Planning is best done by scientific panels, working in close cooperation with the NASA Life Sciences Office.

Specialty Panels

There is a continuing need to refine, update, and implement the research strategy in each subdiscipline or specialty area. *It is recommended that a standing panel of 5 to 10 qualified scientists in each specialty area be appointed to help NASA's Life Sciences Office in this task.* The areas represented on the specialty panels should include: developmental biology, plant gravitropism, sensorimotor integration, bone and mineral metabolism, cardiovascular and pulmonary gunction, muscle biology, endocrinology, nutrition and hematology, and human behavior.

The specialty panels would have several functions. They would serve as peer-review panels, evaluating research proposals in terms of their scientific merit and their impact on the overall strategy. Each panel would review all of the activities sponsored by the Life Sciences Office in its respective specialty area and provide advice as to how the various research programs—basic, clinical, ground-based, and space research—can best be integrated to meet research objectives. The panels would also seek to identify promising, but neglected, research topics. Work on these topics could then be encouraged by any of several approaches.

Currently, NASA uses many advisory panels of extramural scientists. Some are specialty groups that are asked to advise on research strategies. These are usually ad hoc panels and, so, are unable to provide the continuity required to refine and implement the strategies they propose. There are several standing committees, but these do not fill the roles envisioned here. Some of them lack the concentration of scientists to oversee progress and define strategies in particular areas. Others are charged with the evaluation of research proposals, but lack the responsibility to formulate strategy. Still others combine planning and evaluation, but are concerned with only a limited sphere of activities, rather than with all of the relevant activities in the life sciences program related to the area of specialization. In contrast, each of the proposed specialty panels would provide continuing help in both the planning and implementation of a research strategy and would have as its purview the entire research effort in a particular area.

To oversee the implementation and coordination of the programs in the various disciplines is the responsibility of the Director of Life Sciences, who should seek advice from various more generally constituted panels, including NASA's Life Sciences Advisory Committee (LSAC), and the Space Science Board's Committee on Space Biology and Medicine. A major function of these multidisciplinary panels should be to frame the overall goals of the life sciences program and to work toward ensuring a proper balance in terms of research funds and flight opportunities among the several specialty areas.

Dedicated Life Sciences Laboratory

One of the major reasons for the slow progress in space biology and medicine over the last decade has been the lack of flight opportunities, especially in the U.S. space program. There were no initiatives in human biology in the time between the Skylab missions and the start of the Space Shuttle flights. In the same period, there were only a handful of biological experiments. To date, large numbers of life sciences payloads have been carried on only two Shuttle missions, *Spacelabs 1* and *3*, both of which were designed as verification tests. The lack of flight opportunities is all the more unfortunate because biology is largely an empirical science. Replication is needed to verify results. Progress usually comes only when experiments can be modified in the light of past results. The research program outlined in this strategy requires the collection of large amounts of data and the gradual improvement of research protocols and techniques. If significant progress is to be made by the end of the century, then the space biology and medicine scientists will need continuous access to spaceflight opportunities. Most of the experiments require manned intervention. *Based on the dual requirements of continuous access and manned intervention, the committee recommends that there be a dedicated Life Sciences Laboratory (LSL) on the Space Station. Until the Space Station becomes a reality, the ground-based research program in each specialty area must be vigorously pursued with various* *model systems of the adaptation to microgravity conditions. Once operations are resumed in the Space Shuttle, it should be used at every available opportunity to sharpen hypotheses and techniques.* Scientists must work closely with designers and engineers at every stage in the development of the LSL and of the equipment that is to be used within it. The laboratory must have the flexibility to be rapidly converted to accommodate the needs of different types and combinations of experiments. The existence of a dedicated LSL, serving many different functions, requires that provision be made to insert, remove, or reconfigure equipment, racks, and dividing walls. The need for flexibility in the architecture of the LSL can be illustrated by example. Many types of research can best be accommodated in a facility consisting of numerous, discrete units of space. This arrangement allows the simultaneous conduct of experiments requiring different conditions of ambient temperature and illumination. Other research, the use of a linear sled in vestibular studies being one example, requires an open configuration.

Focused Missions

Most flight missions involving the life sciences have carried experiments from several research areas. There is, however, a better way to meet our research goals. *It is recommended that the space biology and medicine research time on the Space Station be divided into 3-to 6-month blocks, with each block largely devoted to a single research area. Missions in each subdiscipline should occur at least three times each decade.* Such focused missions offer several advantages.

Payload specialists can be intensively trained in a particular discipline. It must be emphasized that many of the experiments in space biology and medicine will critically depend on the training and understanding of the individuals conducting them. One reason involves the manual skills required. Another, more important reason is that it is often important to innovate, either to modify experiments and, so, take full advantage of recently acquired data, or else to get around malfunctions of the equipment or the preparation. Innovation is best carried out by highly trained individuals, who are familiar with the techniques and concepts in a discipline and who can converse fluently with the ground-based team. *The* *committee recommends that two or more payload specialists on each flight be practicing laboratory scientists in the particular discipline.*

Mission planning and implementation are simplified. The same equipment and, in some instances, the same biological specimens can be used in several experiments. The scientific working group participating in the mission have a common orientation and, presumably, a common set of goals. This should facilitate task integration. The mutual understanding within the working group, as well as longer mission durations should enhance flexibility in the scheduling of individual experiments.

Flexibility and innovation are both important in successful biological experimentation. There is a greater chance that the results obtained will have a major impact on the particular discipline involved. This is especially so if all the experiments flown during the 3- to 6-month mission are focused on the few essential questions in each research area that need to be answered in the next 10 to 20 years. The success of such a mission may depend on recruiting a team of the very best scientists in the particular area. Three things could help to attract more of the best scientists to participate. One is the promise of important results. Another is the opportunity of joining in a team effort with other first-rate scientists. The third is that there can be a sharing of the administrative and organizational burdens entailed in mission planning and implementation.

The style of research in space biology and medicine has been to do experiments of small scope. Replication and modification of the experiments would have been desirable, but could seldom be done. The proposed mode of research resembles that which is carried out in the other space sciences. Each mission is devoted to a single, broadly conceived goal. Sufficient flight time is given to collect reliable results, to replicate experiments when necessary, and to change protocols as data are gathered and interpreted. At the same time, sufficient time is given between experiments to analyze data in detail, to come up with new hypotheses, to test these on the ground, and to plan for the next major mission. There is a promise of important results, a prospect that is enhanced by having the best scientists participate. If such a strategy is adopted, space biology and medicine can become a mature science within one to two decades.

The only research area that might not profit from such an approach is human behavior, where much of the research requires that the crew go about its normal activities and the major research strategies involve the use of embedded tasks and inobtrusive observation. Because of its nature, research on human behavior should be included as part of every mission. Those aspects of human behavior involving psychophysical measurements form a natural extension of sensorimotor research.

Flexibility in Spaceflight Experiments

Space biology and medical research, as conducted on earth, is usually done by a single principle investigator working with his or her graduate students, postdoctoral fellows, and technicians in a laboratory designed for the specific research program. As suggested above, the complexity and cost of space experiments may require team research, whereby groups of scientists collaborate in large experiments, with individuals contributing their special skills, but sharing observations and facilities. The engineering and scheduling requirements of spaceflight have usually meant that experimental protocols have to be approved years in advance and strictly adhered to during the mission. On the other hand, scientific productivity will be greatly enhanced if missions can be planned with sufficient flexibility so that the design of individual experiments can be modified in the light of the latest research findings, including those obtained on the flight. The challenge will be to mount large-scale experiments and to meet engineering and scheduling requirements, yet retain the flexibility of experimental design and execution crucial to biological research.

There are several ways in which experimental flexibility can be enhanced. The first requirement is the rapid feedback of results during the mission. This, in turn, implies an increase in on-board analytical capabilities and the ability to communicate the results in an understandable manner to both the crew doing the experiment and their ground-based colleagues. Second, it is important that the two groups be able to exchange data, information, and ideas. Third, there has to be flexibility in the availability of equipment and experimental organisms, as well as in the scheduling of experiments.

Rapid Feedback of Results

The LSL has to be provided with a workstation designed for rapid analysis of biological samples. Such an increase in on-board analytic capabilities would enhance research productivity greatly. Still, some biological samples are best analyzed on the ground. In many cases, this requires in-flight preservation of samples, either by fixation or freezing, until they can be returned by an STS resupply vehicle. In other instances, for example when analysis is needed to guide ongoing experiments, rapid sample return could be accomplished by small passive reentry vehicles.

Adequate Data Links to Earth

Because many life sciences deal with dynamic, rapid changes and highly interactive systems, there is a need to modify procedures not only to take advantage of recently acquired data, but also to accommodate unanticipated changes in experimental conditions. It is for this reason that chemical, morphological, and physiological data must be made available to the crew and to the ground-based research team in close to real time. Communication between the two groups is especially important when protocols have to be modified. Since the information that has to be exchanged has a large qualitative component, voice communication can be particularly effective. Visual data links are needed for the transferring of morphological and behavioral data. The use of a "blackboard", possibly implemented by computer pen tracing screens, to communicate between spacecraft and the ground should be explored. A sketch of a graph or conceptual model in real time on such a screen, when coupled with a voice link, might prove a powerful mode of communication. A video manual of various procedures should be stored on-board so that they can be reviewed by payload specialists before or during the experiment. There may be a need to enlarge the manual by transmitting information from earth.

Experimental Flexibility

In many instances, new pieces of equipment or additional experimental subjects may be required. The LSL should be provided with a stockroom of flight-qualified hardware, consisting of commonly used material, tools, and equipment. A stockroom will allow not only repair and replacement of defective parts, but the fabrication of new parts as well. There needs to be an adequate supply of experimental animals and plants to allow for the demands of predeveloped protocols and of new protocols that may be developed during the mission. The present style of doing space research requires that specific configurations of equipment and specific protocols be approved for spaceflight. The new style requires the approval of a whole repertoire of configurations that falls within an agreed upon design envelope. Similarly, in-flight time schedules have to be kept sufficiently flexible to allow for unanticipated experimental difficulties and/or for the replication of unexpected but important results.

One attribute of a good scientist is the ability to anticipate the unanticipated. The scientific team must foresee the repertoire of parts and protocols that will maximize the scientific productivity of the mission, and they must work closely with engineers and managers to see that the parts and protocols are available when needed. As is true in ground-based research, the repertoires should grow with time and experience.

Perhaps the most important ingredient in a flexible style of research is the presence of payload specialists who are practicing laboratory scientists and, hence, are fully conversant in the techniques and concepts of the particular area being studied.

General Facilities

This section deals with facilities that would be of general use in space biology and medicine research. Facilities specifically needed by the individual disciplines are described in the chapters concerning those disciplines. Remarks here are confined to research in space.

Variable Force Centrifuge

Such a device is an essential component of any space biology and medicine program. It has three, equally important functions.

(1) The first and most obvious of these is that it provides an on-board 1-g control that can separate the influences of weightlessness from the other effects of spaceflight, including the effects of launch, reentry, and radiation. At present, such controls require the conduct of full-blown ground simulations. The use of simulated controls, while valuable, is seldom a compelling exercise because of the difficulty of ensuring that the simulations reproduce all of the salient conditions of spaceflight.

(2) A second use of the VFC is to provide transient stimuli to test the responses of biological systems to gravitational forces at various stages of adaptation to weightlessness. Conversely, subjects can be held at 1-g and briefly exposed to microgravity. The latter allows for detailed study of the initial stages of adaptation. More generally, alternations in gravitational force can be expected to have both immediate and long-term adaptational effects on biological systems. A VFC enormously increases experimental opportunities by allowing the study of the two kinds of effects, either separately or in combination. To cite a simple use of the VFC in this regard, animals can be held in a nonadapted, 1-g state until such time as adaptation experiments are ready to be done. Individual experimental protocols can be repeated several times during a mission of 90 days duration. This will allow for replication of results. As important, the protocols can be changed to reflect the results already obtained on a mission. The increase in experimental flexibility and scientific payoff could be enormous.

(3) The third use of VFC is to provide fractional g forces. We already know that the absence of gravity can have profound effects on biological systems. Important insights into underlying mechanisms can be obtained by determining the shape of the force-response function, including the presence of threshold effects. Another use of fractional g forces is to remove or reduce some of the complications of doing experiments in microgravity. A specific example can be cited. An area of particular interest relates to the role of gravity in neonatal development. The success of such experiments will depend on the ability of newborn animals to suckle or, otherwise, be nourished. The presence of fractional g forces may simplify the nutrition problems and, at the same time, allow the animals to be reared under reduced forces that still challenge normal development.

The VFC should be capable of supporting a wide variety of species and must run for several months without stopping. Specimens will have to be placed on the VFC or removed from it while it is spinning. This could be accomplished by building a second, man-rated centrifuge that can be brought up to speed with the crewmember positioned immediately opposite the point on the VFC requiring access. The second centrifuge could also function as a Spaceflight Vestibular Research Facility (SVRF) to test vestibular function in man and animals and as a means to test other physiological responses of human subjects to linear forces. The VFC and its mate should be of the maximum possible dimension to maximize capacity and to minimize force gradients.

We have been apprised of the engineering problems involved in the inclusion of a large centrifuge in a freely floating Space Station. *The committee still recommends that a Variable Force Centrifuge (VFC) of the largest possible dimensions be designed, built, and included in the initial operating configuration of the Life Sciences Laboratory. It does so because a VFC is an essential instrument for the future of space biology and medicine.*

Specimen Facilities

Humans are the subjects of choice in many areas of space research. A system for the collection and preservation of specimens, including blood, urine, and stool samples, is essential. Animal research will be required in several areas, including sensorimotor adaptation, muscle atrophy, bone and mineral metabolism, and developmental biology. *A Research Animals Holding Facility (RAHF) should be included in the initial operating configuration of the Life Sciences Laboratory.* The RAHF should be modular and flexible and should accommodate both large and small animals. Advances in biology have often been based on the use of comparative methods, and space biology would benefit similarly from the availability of a wide range of animals. The individual units of the RAHF should be easily mated to the VFC and to other equipment. *Plant research requires a chamber in which specimens can be grown in space from seed-to-seed under conditions of controlled temperature, light, humidity, and nutrition.*

On-board Handling and Analysis of Cell and Tissue Specimens

There need to be on-board facilities for analytical biochemistry, automated radioimmunoassays, and radioactive tracer studies. In-flight histological examination requires facilities for the fixation and sectioning of specimens and a light microscope with direct and phase contrast optics. The microscope should have an attached video camera that interfaces with a computer-based image processor. A sterile tissue culture facility should include provisions for media preparation, a preparative centrifuge, incubators, 1-g rotating discs for control cultures, a glove box, and freezer and cooler units. Freezers are needed for sample and carcass storage. As already mentioned, rapid sample return to earth is desirable.

Computational Facilities

Many experiments will run best with dedicated microprocessors used for process control, data storage, or both. There should also be a common facility that can be used for general purpose computations, as well as data management, analysis, and display. The need for rapid access to data by the crew and ground-based scientists and for rapid communication between the two groups has already been mentioned.

SCIENCE POLICY ISSUES

Mission Planning

The selection process for a spaceflight opportunity usually begins with an Announcement of Opportunity (AO). In the past, the AOs in the life sciences have stated NASA's intention to fly experiments on a certain mission and have indicated the fields of biology that were of particular interest. The AOs in the future should be more specific. To the extent that missions will be focused, the AOs should be confined to the particular research area and should explicitly state the major research questions that the mission is intended to answer. The specialty panels should be consulted in the framing of the AOs and they should be the primary peer-review panel in the selection of proposals.

A serious problem in previous missions has been an original commitment to fly too many experiments followed by a long period during which the time and resources for each experiment were reduced as launch approached. The result was a watered down version of every experiment and this severely compromised scientific yield. A preferable plan would be to start with a more realistic assessment of the number of experiments that can be accommodated. At the present time, NASA usually uses an investigators' working group (IWG) in mediating these decisions. The IWG does not provide an effective forum for discussions of this type. The reasons are that it is large, its composition is heterogeneous, and its meetings are infrequent. There is also a conflict of interests as principal investigators seek to protect their own experiments.

Some, but not all, of these problems will be alleviated with the advent of focused missions and more cohesive IWGs. The specialty panels could play an important advisory role in making these decisions. The data should be analyzed quickly, the findings should be published in a refereed journal, and, if at all possible, the data should be placed in archives that are accessible to the general scientific community.

Crew Selection and Training

Space biology and medicine research in space, perhaps more than any other discipline, requires that the experiments be done by skilled scientists. The qualifications of such scientists should generally include a Ph.D. or equivalent, extensive laboratory experience in the relevant discipline or disciplines, and evidence of independent research abilities. It would be well to have two such scientists on each mission. Training of scientists who are not members of the astronaut corps must be sufficient to ensure maximum scientific return without being of such length as to discourage the best individuals from applying. A training period of 1 to 2 years should suffice. During this time, candidates will have to keep a close collaboration with the science team involved in the mission. This will facilitate mission implementation and will also maintain the crewmembers' ties to the scientific community. The crewmembers should be encouraged to participate in all phases of the project, and their contributions should be recognized in terms of authorship on published research. Participation as a flight scientist should be so structured that it will enhance, rather than jeopardize the individual's career in research, whether this be at a NASA Research Center, private industy, or a university.

Interagency Cooperation

While the responsibility for a coordinated program in space biology and medicine clearly rests with NASA, some aspects of the research will also be of interest to other agencies, including NIH and NSF. It would be wise for NASA to maintain a liaison with these agencies. One mechanism might be to appoint representatives from other agencies as ex officio members of the specialty-oriented panels.

International Cooperation

Other countries, most notably Canada and the countries that are members of the European Space Agency (ESA), have active research programs in the life sciences. There are many outstanding scientists and research teams in these other countries. They have made important contibutions to past space ventures. Their continued participation should be encouraged. One mechanism of collaboration between ESA and NASA has worked well in the past and may provide a model for the future. ESA has concentrated on the development of both general-purpose and special-purpose facilities that can be used by both agencies. Examples are the Spacelab, which has been essential to life sciences research on the Space Shuttle and the ESA sled, which promises to be a major facility for vestibular testing. ESA currently plans to develop two general-purpose facilities: Biorack, a workstation for cell biology; and Anthrorack, a facility for human physiological monitoring. Both facilities should be important assets to an overall space biology and medicine program.

The Soviet Union has made a larger investment in space biology and medicine than we have. Much of their effort has gone to guaranteeing a permanent manned presence in space. They also have an active program of basic biological research. In many areas, the Soviets are more accomplished than we are, and their lead continues to grow during the hiatus in our manned space program. Scientific interchanges, especially during the past decade, have been sporadic. This has, in part, reflected differences in publication style and changes in the political relations between the two nations. There are indications that the problems have lessened. More of the results of the Soviet's experiments have been published in the open literature. There has been increased cultural and scientific communication. The free and open exchange of scientific results and ideas would be of enormous benefit to both countries since we share a common interest in the understanding of life's processes and in the manned exploration of space.

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