Working Group on Problems of Weightlessness in Space Flight

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National Academy of Sciences
National Research Council
2101 Constitution Avenue, N. W.
Washington, D. C.

S P A C E   S C I E N C E   B O A R D

Man in Space Committee

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SUMMARY REPORT

The Space Science Board has undertaken, through its Man in Space Committee, to study several topics of importance to the practical realization of space flight. This report describes the results of discussions of the physiological effects of the weightless state which may be of importance in the development of space flight and contains suggestions for experimental investigations to make good the important deficiencies in present knowledge.

The membership of the Working Group responsible for this paper is given in Appendix A.

In approving this report for distribution, the Space Science Board and the Man in Space Committee gratefully acknowledge the helpful participation of representatives of the National Aeronautics and Space Administration and the Department of Defense.

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I INTRODUCTION

Experience with orbital flight in this country has led to the adoption of spacecraft designs which require the functional services of the astronaut in order to carry out the intended mission. Such automatic devices as may be provided serve principally to relieve and assist the pilot. In these circumstances, preservation of the astronauts' faculties and well-being is as important as the reliable functioning of the spacecraft. The combined experience in this country and the Soviet Union seems to indicate that the astronaut is unlikely to suffer any significant impairment of performance during orbital flights of many hours' duration. Nevertheless, study of the flights which have occurred to date, and consideration of relevant laboratory observations suggest that when long periods of weightlessness are involved, some physiological difficulties may arise which, if not adequately compensated, may produce serious effects on human performance.

This Report represents an attempt to identify some of the more important physiological phenomena which may be associated with the weightless condition and to suggest methods by which a more precise assessment can be made. It should be emphasized that although recent experience gives no grounds for expecting insuperable difficulties, neither the quantity nor quality of the available observations permits the conclusion that long term exposure to weightlessness will not have serious consequences. The critical role to be played by the astronaut demands that every effort be made to identify, in advance, those phenomena which may affect performance and to ascertain the relevant qualitative and quantitative dependences so that proper actions can be taken.

Much of the difficulty in the precise formulation of anticipated problems arises from a prevailing lack of knowledge concerning a wide range of normal mammalian physiological functions. Many of these deficiencies can be remedied straightforwardly in the laboratory. Where spaceflight development is concerned, however, two distinct investigational approaches can be adopted. The first of these may be characterized as empirical and incremental — that is, the capabilities of the astronaut are explored in successive flights involving relatively modest increases in difficulty or severity of the environmental conditions. In this way it is hoped to ascertain the human limitations without running too great a risk. The second approach can be described as fundamental — here one would seek to find, by a series of carefully controlled experiments (or observations), the effects of exposure to spaceflight conditions upon the mammalian physiology generally and that of man in particular. A fundamental understanding of the observed effects would be sought so that predictions for new situations (and ways to control them) could be made with confidence.

It is the conviction of the Working Group that the stakes are too high and the uncertainties too great to warrant exclusive reliance on the first method. It is appreciated, however, that the urgencies of the spaceflight program may not permit a single-minded adherence to the second. The Group believes, therefore, that a judicious combination of these two methods is strongly indicated in the present circumstances.

The achievements of the manned space flight program have rightly earned widespread admiration. No carping criticism is intended, however, when it is pointed out how tentative are these exploratory flights when viewed in relation to the unknowns of the lunar missions. Examination of the data available both from the laboratory and from spaceflight emphasizes the serious lack of that kind of knowledge which would permit extrapolation. We cannot now predict, for example, for flights of 14 days (or more):

a. The effects of sudden reimposition of reentry accelerations and terrestrial gravity

b. Changes in body fluid distribution and composition,

c. The effects of violent physical effort on respiratory and cardiovascular systems in prolonged weightlessness,

d. Central nervous system functions with respect to coordination, skilled motor performance, judgment and sleep-wakefulness cycles.

It can be argued that the degree of success already achieved in flights of short duration gives no grounds for undue apprehension. If the physiological evidence from these flights and from related terrestrial experiments were quite unambiguous, this might be a compelling argument. The Group is persuaded by the evidence, however, that such complacency is not warranted. On the contrary, in several of the above mentioned cases the available data — though meagre and difficult to interpret — suggest quite clearly the need for more thorough investigation.

Attempts have been made and will, no doubt, continue to be made during future flights to conduct observations to illuminate these questions. This deserves every encouragement, but the results to date serve mainly to emphasize the difficulty of performing physiological research simultaneously with a flight development program. Moreover, although the techniques and results can certainly be improved, many types of measurements are difficult or impossible to perform on an astronaut without increasing personal risk or discomfort. A complementary program of animal experiments avoids this difficulty.

The Working Group therefore recommends:

1. That physiological research be recognized as a fundamental part of future manned spaceflight programs. Success of these programs is dependent on data, much of which is obtainable only through experiments in space. They cannot be safeguarded by theoretical analyses which, by themselves, have little quantitative predictive value in biological systems.

2. Terrestrial experiments relevant to the weightless state should receive high priority and be planned toward the conduct of flight studies on both animals and man.

3. In view of the difficulty of adequate internal instrumentation of human subjects under the rigors of space flight, immediate attention should be given to experiments involving extensive internal monitoring in animals. A program limited to observations conducted

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on a non-interference basis in current manned flight programs has little merit in contributing to advanced vehicular design.

4. As in other fields, periodic review and revision of programs for investigating the physiological effects of weightlessness are most important. The need to forestall difficulties which may arise in the manned flight development programs lends additional urgency to this task.

II FUNDAMENTAL STUDIES OF WEIGHTLESSNESS: NASA PROGRAMS.

The Working Group was informed of plans for investigating the effects of prolonged weightlessness on animals for periods of 14 days and longer. The Offices of Space Sciences and Advanced Research and Technology in the NASA are both interested in such studies. In particular, the Office of Space Sciences is undertaking to procure and launch for biological experimentation a series of 6 recoverable satellites. The details of design and operation of these satellites are at present under study and about sixty proposals have been received for experimental investigations. Many of these concern the physiological effects of weightlessness. It is anticipated that the first flight would occur 18 months after the commencement of the program. Additional flight experiments may be performed in Gemini spacecraft but their life support systems would not be adequate for a 14 day flight including both a man and a subhuman primate. For economic reasons, Mercury capsules now held in excess of current requirements will not be used for this kind of work.

NASA representatives emphasized that current planning for manned space programs involves a systematic extension from physiological observations in animals to the management of comparable problems in man, and finally, with the establishment of man as part of the man-vehicle system design. Moreover, these studies require the separate and combined evaluation of central nervous, cardio-vascular, respiratory, gastro-intestinal and other systems, to be considered as a matrix in mutual interdependence. Particular interest hinges on the effects of weightlessness in flights exceeding 14 days.

The Working Group suggests that preparation for mammalian flights of the order of 30 days duration also merits early and close attention, including the development of satisfactory solutions to problems in life support and other systems which must precede such a program. It is possible that many important long-term experiments could be performed only in a manned orbiting laboratory. Development of such a facility equipped for biological experiments may well be an important requirement for studies in anticipation of manned flights of longer duration than Apollo. Unless the biological satellite programs of the type mentioned above are successful in providing the necessary data, such a manned laboratory may also be important in studies of shorter range.

III EVALUATION OF INTEGRATED PHYSIOLOGICAL ORGANIZATION IN THE WEIGHTLESS MAMMAL; GENERAL STUDIES OF BIOLOGICAL RHYTHMICITY.

The effects of weightlessness on the organism as a whole may be manifest by important changes in integrated behavioral patterns having an inherently rhythmic character. Modifications in basic behavioral patterns and performance may occur as disruptions of rhythmic physiological phenomena which are themselves the end product of interrelated functional activity in a number of physiological systems, such as the neuroendocrine, cardiovascular and central nervous system.

Monitoring of some quite simple physiological and behavioral parameters over prolonged periods of weightlessness can yield highly important information. Measurement of body temperature and daily motor activity cycles and assessment of their relationship to artificially imposed daylight-darkness schedules, and measurement of sleep-wakefulness cycles with varying schedules of required task performance, exemplify fields in which lack of knowledge inhibits prediction for the conditions of space flight, but which may be of vital importance to missions in the near future. Since performance is quickly disrupted by fatigue, ability to adapt to schedules artificially imposed in space flight may be an important factor in astronaut selection.

In the last half century, the advantage of a multivariate approach to the assessment of the physiological condition of the whole organism has been amply demonstrated. Little value attaches to isolated readings of a single physiological parameter — without reference to data from interrelated physiological systems.

Measurements of interdependent components of biological rhythmicity lend themselves readily to analysis by methods well established in physics — including correlation and spectral analyses, and sensitive techniques revealing phase modulation and variance in rhythmic processes. A wide variety of physiological functions can themselves be treated as periodic variables in the analysis, including rhythmicities in cardiac output and blood pressure, respiration, brain waves, and the slower tides of appetite, sleep-wakefulness, etc. The importance of such investigations argues for their inclusion in forthcoming flight programs. Their relative simplicity from an experimental point of view is an additional advantage.

A short bibliography of selected references on biological rhythms and their analysis is given in Appendix B.

IV EFFECTS OF WEIGHTLESSNESS ON THE CARDIOVASCULAR SYSTEM.

Although flight data are at present scanty, certain suggestive aspects of the experimental evidence currently available for animals and man indicate the urgent need for further extensive, carefully controlled investigations, on the cardiovascular system. There is, for example, evidence that orbital flight in animals and man may be associated with hypertension involving both systemic and pulmonary circulations, and that this persists at least into the initial hours of weightlessness. Significant improvement is needed and achievable in the simple monitoring of blood pressure in man, and the possibility of certain catheterization procedures in man should not be ruled out.

Many highly significant circulatory parameters are inaccessible to any techniques of surface monitoring currently available. In view of the inconvenience of using deeply implanted transducers in man, the desired information can be secured only by comprehensive implantations of experimental animals (primates) for collection of data suitable for extrapolation to the human.

The immature chimpanzee may not be the most suitable animal for this purpose, since its vascular reflex pattern resembles that of the human child rather than the adult. For this reason, animals such as the adult pig-tailed macaque monkey (M. nemestrina) may be more suitable. Adequate assessment of cardiovascular status requires catheterization of right atrium and pulmonary arterial system, as well as implantation of one or more electromagnetic flowmeters in major systemic arteries, such as the aorta, the common carotid or the femoral arteries.

Current developments in cardiovascular instrumentation were reviewed, in relation to acquisition of data in man. The Group believes that, with appropriate support, many promising experimental methods in this area may be developed to take their place in the physiological monitoring systems for manned space flight. For example, ear lobe oximetry, indirect measurements of blood flow and of blood pressure by finger plethysmography or impedance plethysmography, and ballistocardiographic techniques may be cited as examples of methods having sufficient potential value to warrant consideration of their ultimate application to manned space flight. Difficulties of interpretation appear to make vibrocardiographic and phonocardiographic measurements of less certain value.

Further highly significant baseline data should be sought from animal experiments in the laboratory aimed at determining threshold conditions for irreversible cardiovascular changes associated with high environmental temperatures in conditions of preexisting debilities, such as dehydration.

Adaptation to prolonged exposure to weightlessness or to lunar gravity may cause difficulties when the astronaut is exposed again to re-entry forces and terrestrial gravity. It is possible that these adaptive changes may thus produce unacceptable effects on performance or cause risk to life. It is important to obtain experimental evidence on this subject.

V. METABOLIC EFFECTS OF WEIGHTLESSNESS.

a. Observations on basal metabolism.

In flights currently planned in the Gemini and Apollo programs, it is hoped that attempts will be made to secure data on modifications in basal metabolic rates under conditions of weightlessness. It is to be expected that diminished expenditure of muscular energy will be required for both tonic postural mechanisms and for the execution of motor tasks. The controlled environment and self contained life support systems should, in principle, make quantitative metabolic measurements relatively easy.

It is feasible to make accurate indirect measurements of metabolic rates, as, for example, by the injection of doubly labeled water (D_2O^{18}). Such methods can be applied to small mammals, such as rats and mice, and require no instrumentation on the animals in the course of the actual weightless phase. Estimations can be made on blood samples secured before and after flight. The great importance of metabolic information to long flight plans warrants its early collection. Without such information, accurate planning of environmental systems is difficult and likely to be wasteful.

b. Effects on body fluid equilibria.

Importance also attaches to early evaluation of weightlessness effects on body fluid equilibria. The results of Earth orbital flights and of terrestrial water-immersion experiments suggest the occurrence of undesirable changes — although no effects leading to operational incapacity have yet arisen in the relatively short' durations so far encountered. In both situations, a profound diuresis of sufficient severity to produce hemoconcentration with a facial plethora and polydipsia has been described. Data from the second U. S. orbital flight, although not accurately defined by preflight controls, including measurements of fluid intake, indicated certain trends. The astronaut experienced a substantial decrease in body weight during the mission, associated with the excretion of a large amount of very dilute urine, despite problems of suit overheating and sweating.

These effects require much more study in future orbital flights. There may be a connection between the increased pulse pressure observed in orbital flight and the water diuresis. The mechanisms responsible are incompletely understood and the conditions producing it can only partially be simulated on Earth. In both recumbency and immersion, a similarly significant redistribution and release of body fluids occur. It has been suggested that recumbency may affect an extracellular fluid volume receptor mechanism which, by decreasing aldosterone secretion by the adrenal, would decrease sodium reabsorption by the renal tubules. Aldosterone excretion decreases during recumbency and during standing in water but increases while standing in air. There is also evidence for cardiac atrial volume receptor mechanisms, with reflex inhibition of release of the pituitary antidiuretic hormone (ADH) by increased filling of the left atrium with a resulting diuresis (Henry-Gauer reflex). A simple flight experiment would involve careful timing of fluid intake and output with a known preflight water loading. Such an experiment would provide a measure of hypothalamic functions and assist in resolving problems of renin-angiotensin interrelations. It would also aid in the evaluation of functional interrelations between aldosterone and other steroid substances.

Available evidence indicates that the profound diuresis incurred in the weightless condition may be far from transient, and that adaptive mechanisms, if any, may arise relatively slowly. It undoubtedly contributed to Glenn's dehydration and fatigue in the capsule after water landing and may have serious implication for prolonged flights. In any event, the condition itself and appropriate combative measures can only be evaluated by careful mammalian investigations in the space environment, and possibly only in man and in adult primates characterized by an erect posture in the terrestrial environment.

c. Changes in electrolyte balance attributable to weightlessness.

Altered fluid equilibria in buoyant states are accompanied by shifts in intra- and extracellular electrolyte distribution, including sodium and potassium. Evidence from recumbency studies indicates a strong correlation between loss of erect posture or weight bearing and excretion of calcium stores in bone. This matter is discussed in detail in Appendix C to this report and will be summarized here. Excretion of calcium in the urine is accompanied by risk of its deposition as calculi or "kidney stones" in the urinary tract. Changes in calcium metabolism resulting from weightlessness over periods up to two weeks do not appear to represent a hazard requiring precautionary measures.

Flights in excess of two weeks constitute a more serious problem of sufficient significance to warrant obtaining comprehensive data in the planned 14 day orbital flights. Therapeutic immobilization, post-poliomyelitis immobility, and experimental restraint in normal subjects clearly lead to a negative calcium balance, with some hypercalcemia and hypercalcuria. Unless other circulatory or renal factors completely alter the picture, skeletal losses of calcium over a period of two weeks would be 10 gm or less from a total skeletal depot exceeding 1000 gm. In normal man, this loss is reversible and may be ignored.

The hypercalcemias and hypercalcuria accompanying this negative calcium balance raise questions of possible renal damage or renal calculi or both. Although clinical experience has indicated an incidence as high as 40 per cent of renal calculi in immobilized patients, these data are complicated by factors such as urinary stasis and infections from catheterization. Although acute and massive hypercalcemias can cause renal damage, disorders of calcium metabolism probably do not rank as a serious hazard in manned space flights of two weeks' duration.

In longer flights, problems associated with skeletal development and maintenance appear of sufficient magnitude and are characterized by such a lack of basic information as to warrant high priorities in space research.

d. Muscle wasting.

Long exposure to low gravity environments, as on the Moon, and to weightlessness is likely to produce muscle wasting unless compensating measures can be applied. Study of this phenomenon both in simulation (immobilization; water immersion) and in space flight should be encouraged.

Muscle bulk should be estimated before and after flight, with evaluation of the nature of mechanisms underlying fluid displacements. Since most of the body content of potassium is distributed in muscular tissue, such studies might conveniently use the estimations of potassium by measurement of K^{40} in the whole-body counter. It is estimated that this method can give total body potassium with an error of about $\pm 3\ \%$ in absolute measurements and appreciably higher precision in relative measurements. The convenience of the technique is an additional recommendation. Selected references on this subject will be found in Appendix B to this report.

VI CENTRAL NERVOUS SYSTEM FUNCTIONS IN WEIGHTLESSNESS.

Exposure to the weightless environment will powerfully affect integrative nervous mechanisms, probably to a greater degree than any other physiological system. This report directs attention only to those aspects where experience in terrestrial experiments suggests that important practical problems may arise in the space environment.

Human performance may be evaluated as a whole, rather than on the basis of performance capability in separate physiological systems. Such a point of view may, however, overlook the great value of separate identification of system components in which abnormal functioning has value for prediction of the performance of the organism as a whole, and for the chances of survival.

a. Vestibular mechanisms.

The wide range of individual tolerance to disruptive effects of vestibular stimulation has emphasized the importance of this factor in astronaut selection. At the same time, vestibular functions require consideration jointly with visual task performance, since both have special significance in vehicle docking procedures (such as those proposed in the Gemini and Apollo programs). Vestibular functions in the weightless state remain almost completely unknown. Limited evidence from animal and manned space flights suggests that head turning, through the associated vestibular stimulation, may seriously interfere with concurrent visuo-motor performance , but that these disturbances show significant differences in individual susceptibility, and that at least partial adaptation occurs relatively quickly.

There are two main questions to be answered about vestibular functions in weightlessness: (1) Whether vestibular functions will be significantly modified, and (2) whether there will be failure of integration of vestibulovisual and proprioceptive information from muscular and other deep structures with the effect of limiting skilled motor performance. The following experimental approaches are suggested for investigation of these phenomena and adaptation to them:

(i) Repeated performance of specific visuomotor tasks of limited duration during head turning, with recording of eye movements optically or electrically.

(ii) Measurement of the magnitude of head movements in relation to an arbitrary horizontal line.

(iii) Using controlled rates of angular acceleration of the vehicle as a test stimulus.

Such tests would cover present major gaps in knowledge of the effects of small amounts of added acceleration in a weightless or low gravity environment. Much interest centers in this important area, and appropriately instrumented animals can provide further useful evidence. It is suggested that such animals be subjected to compound accelerations in 0, 1, 2 and 3 g environments, and that, in the Gemini program, man and animal should be subjected to similar accelerations. Research is proceeding in behavioral testing of animals sensitive to small increments in g forces, both to establish thresholds necessary to induce behavioral change, and to give animals an opportunity to select preferred g levels. Animal experiments also offer an opportunity for exploration of selective, temporary, pharmacological interference with functions of either semicircular canals or vestibular organs on a reversible basis.

(iv) A carefully designed motor task (e.g. skilled finger movements during reaching), could provide information in a single test about the relative significance of proprioceptive, visual and vestibular systems in skilled performance in zero-g. Such a test would provide information on total performance capability, and, in event of demonstrated deficit, could provide information on individual system defects.

b. Psychophysiological testing of weightlessness effects in man.

There is need for development of a psychophysiological assay system beyond current minimal requirements of dial reading or listening to radio instructions. For example, a careful appraisal of visual acuity in prolonged weightlessness is of vital importance, and might include parameters, such as flicker fusion frequency, which are useful for short-term extrapolation. Visual acuity is dependent on plasma protein levels and body fluid distribution, which may be modified in prolonged weightlessness Stereopsis and depth perception may be affected to a degree requiring adaptive training of the individual for preservation of full performance.

The observation of significant decrements in any major task performance would require appropriate training schedules for the maintenance of skills. Use of substituted sensory influxes may play an increasing role in long flights.

Surface contact forces (as through magnetic boots) could perhaps be a substitute for gravity, and experimental study of the role of such stimuli in perception may yield useful results. In orbital rendezvous, small forces on the subject's back could provide a local vertical, and in approach to the Moon's surface, deceleration in retrorocket firing will lead to immediate orientation in relation to that vector. (Possible visual field distortions which may accompany acceleration e.g. rotation, used as a substitute for gravity may also be worth investigation.)

In the monitoring of central nervous functions in the space environment it would be useful to record electroencephalograms, electromyograms, galvanic skin response and eye movements (with, perhaps, other observations). By providing continuous measures without disturbance in the required task performances, their value lies in assessment of states of alertness, fatigue, drowsiness and sleep, and in providing a measure of physiological states related to performance capability. Use of the electroencephalogram, with computational analysis of the data, appears to have great value in this regard. The NASA currently plans collection of extensive baseline EEG under controlled conditions in a form suitable for mathematical analysis. Data will be taken from about 200 subjects in major national and overseas centers. It is intended that this study will assist in astronaut selection, and subject monitoring in the space environment.

Many effects of weightlessness on nervous functions require monitoring of the autonomic nervous system, including gastrointestinal activity, secretory functions, lacrimation, salivation, sweating and the central control of respiration. Urinary estimations of catecholamines and aromatic substances, such as 5-hydroxyindoleacetic acid, would provide important data, if collected in appropriate fractions and assessed in relation to appropriate pre- and post-flight controls.

c. Long-term effects of weightlessness on central nervous functions.

It is expected that exposure to

weightlessness or to the relatively low lunar gravity will be accompanied by adaptive changes in motor performance capability, and that these changes may be detrimental to subsequent performance at 1 g or more, particularly when exposure to low gravity has been of very long duration.

The Moon's gravitational field is a special case and may be particularly suitable for study of the possible physiological effects of acclerations in a low gravity environment. Simulation of a continuous spectrum of gravitational levels would be easy in an orbiting laboratory. By such means, data could be obtained on the levels of exercise required in prolonged weightless states for preventing detrimental adaptive changes. Animal experiments in such a laboratory could be designed to allow subjects to select optimal g levels. They would also permit assessment of weightlessness as a contributing factor to problems of isolation, with its risk of decreased attention span and altered judgment capability.

It goes without saying that valuable psychophysiological data will be obtained as the astronauts make their routine reports, follow instructions, and perform their assigned tasks while in the weightless state. Errors in their performance should be sought and analyzed by ground-based observers skilled in recognizing and evaluating behavior of men under stress. It may even be desirable to devise a set of performance tasks which from time to time will deliberately test their ability to perform complex mental computations and motor acts. If the astronaut encounters difficulties from any cause an early sign of breakdown is likely to be a change in verbal behavior and subtle decline in coordination of other motor acts.

VII PRIMARY REQUIREMENTS FOR AN EFFECTIVE RESEARCH PROGRAM ON ALTERED GRAVITATIONAL ENVIRONMENTS IN MAMMALIAN PHYSIOLOGY.

Most effects of prolonged exposure to weightlessness or low gravity states remain unknown at present, and it is therefore of great importance that a logical sequence of carefully planned experiments be initiated as soon as possible. The experiments should take advantage of current manned flight programs, unmanned research spacecraft and terrestrial laboratories, as appropriate.

These experiments would necessarily involve an integrated evaluation of data gathered both in man and animals. The highest importance attaches to a broadly organized, carefully conceived program of experiments in subhuman primates and other mammals. The requirements in experimental design and data evaluation demand the talents of the best investigators in the academic community, and cannot be delegated to lesser echelons or to interests concerned only with limited, applied aspects of biological research.

Highest priority would attach to experiments likely to reveal fundamental changes in the physiological systems of the mammalian organism in prolonged weightlessness, since these experiments would probably provide both baseline data and predictive capability in future flight planning. The importance of animal experiments is also emphasized in this connection, since in many instances complex bioinstrumentation can be more readily adapted to animals than man.

This research program would necessarily involve adequate ground-based experiments prior to actual space flight. In such programs special attention should be directed to the development of new and improved bioinstrumentation techniques in such fields as sensors and monitors, including data processing and computation as an in-flight requirement. No major program of flight research appears possible without full participation of accomplished life science investigators in the development of appropriate engineering systems.

The detection of potentially hazardous trends in any of the physiological systems of the mammalian organism will probably be reflected in the integrated performance of the individual, and will also diversify the requirements for special research projects in selected areas. Information of this type may only be available in comprehensive form with the advent of a manned orbital space station. It is considered that steps to secure such an investigative platform would be of great importance in later phases of life science research.

This report has outlined major areas in which prolonged weightlessness may be expected to interfere with performance, judgment, and ultimately, with chances of survival. These include cardiovascular, metabolic, central nervous, psychophysiological and biorhythmic effects. They have been dealt with separately and in sequence, but it is not intended that they should be viewed as hierarchic. The relative scarcity of control data necessarily precludes such an evaluation.

VIII CONCLUSIONS AND RECOMMENDATIONS.

1. Physiological research on the effects of exposure to weightlessness — especially of long duration — must be recognized as a fundamental part of manned flight development.
2. Terrestrial laboratory experiments relevant to weightlessness deserve high priority.
3. Comprehensively instrumented animal experiments merit immediate attention in view of the difficulty or impossibility of using human subjects in the conditions of space flight.
4. Periodic review and revision of physiological research programs is necessary.
5. Although immediate interest attaches to durations of weightlessness of about 14 days, preparation also should be made for the following additional steps:
    (a) Instrumented mammalian experiments in space of about 30 days' duration.

(b) Development of manned orbiting laboratory facilities for studies of indefinite length.

6. Appropriate physiological and behavioral parameters should be monitored and analyzed from the point of view of biological rhythms.

7. The behavior of the cardio-vascular system should be carefully investigated in weightlessness using appropriately instrumented animal subjects and human subjects where feasible.

8. Instrumental techniques for measurement of cardio-vascular functions deserve additional support in order to improve precision, reliability and convenience in conducting measurements.

9. Experimental evidence is required on the effects of adaptation or exposure to prolonged low or zero gravity:

   (a) on reimposition of higher accelerations;

   (b) basal metabolic rates;

   (c) body fluid distribution;

   (d) changes in intra and extracellular electrolyte distribution;

   (e) skeletal maintenance;

   (f) muscle bulk.

10. Experimental evidence should be sought on the effects on human performance of vestibular functions and possible failure of integration of vestibulo-visual and proprioceptive information (experimental procedures are suggested).

11. Investigations of psychophysiological phenomena in weightlessness deserve support. Examples include: studies, of perception, sensory stimuli which may serve as substitutes for gravity in orientation; assessment and monitoring of alertness and fatigue with reference to performance capabilities.

National Academy of Sciences
2101 Constitution Avenue
Washington 25, D. C.

APPENDIX A

S P A C E   S C I E N C E   B O A R D

Man in Space Committee

Members:

C. J. Lambertsen, M.D., University of Pennsylvania - Chairman
W. R. Adey, M.D., University of California
L. D. Carlson, Ph.D., University of Kentucky
C. O. Chichester, Ph.D., University of California
H. J. Curtis, Ph.D., Brookhaven National Laboratory
J. D. Hardy, Ph.D., John B. Pierce Foundation
J. P. Henry, M.D., University of Southern California
W. R. Lovelace, M.D., Lovelace Foundation for Medical Education and Research
N. Nelson, Ph.D., New York University
R. W. Porter, Ph.D., General Electric Company
J. W. Senders, Bolt, Beranek & Newman, Inc.

Liaison Representatives:

Col. J. Bollerud, MC, USAF; Headquarters, USAF
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C. S. Pittendrigh, Ph.D., SSB Environmental Biology Committee
Capt. J. P. Pollard, MC, USN; Office of Naval Research
Brig. Gen. C. H. Roadman, MC, USAF; Aerospace Medicine, NASA Office of Manned Space Flight
Capt. V. E. Senter, MC, USN; Navy Bureau of Medicine & Surgery
Brig. Gen. B. A. Strickland, Jr., MC, USAF; Assistant for Bioastronautics, AFSC
Lt. Col. S. C. White, MC, USAF; Life Systems Division, Manned Spacecraft Center, NASA

Consultant:

H. K. Hartline, M.D., The Rockefeller Institute

Secretariat:

G. A. Derbyshire
T. Gikas
J. P. T. Pearman
H. G. Shepler, M.D.

Working Group on Problems of Weightlessness in Space Flight

Members:

W. R. Adey, University of California - Chairman
R. Galambos, Yale University
A. Graybiel, U.S. Naval School of Aviation Medicine
F. Halberg, University of Minnesota
R. W. Lawton, General Electric Company
R. B. Livingston, National Institutes of Health
W. F. Neuman, University of Rochester
N. Pace, University of California

Liaison Representatives:

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R. R. Hessberg, Air Force Systems Command
E. B. Konecci, NASA Office of Advanced Research & Technology
E. J. McLaughlin, NASA Office of Manned Space Flight
G. Smith, NASA Manned Spacecraft Center
F. Voris, NASA Office of Advanced Research & Technology

Invited Participants:

O. Reynolds, NASA Office of Space Sciences
J. W. Senders, Bolt, Beranek & Newman, Inc.

Secretariat:

J. P. T. Pearman

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POSSIBLE EFFECTS OF WEIGHTLESSNESS ON CALCIUM METABOLISM IN MAN

By

William F. Neuman
The University of Rochester

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ABSTRACT

In the Man in Space Program, manned flights of two weeks' duration are projected for the immediate future. Such periods of immobilization under gravity-free conditions are likely to produce mobilization of skeletal calcium, hypercalcemia, and hypercalcuria. Data on fracture-patients, polio-patients, and immobilized normal "volunteers" are reviewed to provide a basis for a tentative evaluation of the immediate problem and to delineate those data needed for an evaluation of the problem in more protracted flights scheduled for the more distant future.

This is a brief report on the possible effects of weightlessness on calcium metabolism. Interest in this topic is based on common, clinical experience: immobilization from any cause is accompanied by skeletal rarefaction and hypercalcuria.

HISTORICAL

Probably the earliest experimental study of disuse atropny of bone was reported in 1921 (1). One of the earliest studies of inactivity in human beings was reported in 1929 (2). Bone rarefaction was experimentally induced by nerve section in 1945 (3) and about this time clinical interest was aroused by dramatic reports from Albright. In one instance a fracture-patient's hypercalcemia and hypercalcuria led to an unsuccessful exploration for a parathyroid adenoma (4) ! World War II with its attendant problems of convalescence further stimulated clinical interest. Later, patients suffering from paralytic polio kept this interest alive, but with the success of polio vaccines, the importance of the problem has waned somewhat. However, the anticipation of prolonged space flights places the problem in an entirely new perspective.

THE PROBLEM

For reasons not yet clear (the interplay of nervous supply, muscle tone, blood supply, hormonal levels, mechanical forces, etc.), immobilization, from any cause, leads to an excess of osteoclastic over osteoblastic activity in the affected part or parts. There seems nothing abnormal in the processes themselves. Rather, it is the inbalance of bone removal and its replacement which gives rise to the following sequelae: low-grade hypercalcemia, hypercalcuria, and an increased incidence of renal calculi and renal malfunction.

UNCERTAINTIES IN EVALUATION

There exists very little experimental work on animal species other than the rat. As an animal-model referrable to man the rat leaves much to be desired. Unlike man the rat can survive without vitamin D and without parathyroid function. Normal rat serum exhibits an ion product $(Ca^{++}) \times (P_i)$ three to four times that of human serum. Finally, the rat does not close its epiphyses at puberty and this fact alone renders most comparisons in atrophy studies (atrophying vs. growing limb) open to question.

This forces one to draw on clinical experience almost entirely. Here, there are complicating factors. Most clinical material is derived from three sources: paraplegics, polio patients, and fracture-patients. From animal research, it is clear that nervous supply is an important factor in the effects of immobilization. Thus, it can be questioned whether the response of a normal patient can be accurately predicted from non-normal patients. Even fracture-patients are somewhat doubtful. Some of these patients may harbor a low-grade skeletal problem which contributed to the occurrence of fracture. There do exist a few studies of normal subjects immobilized by casts (5, 6, 7, 8). The Minnesota study (5,6) did not examine calcium excretion. The Cornell study (7,8) included complete metabolic balances for prolonged periods by competent and experienced investigators. It represents perhaps the most relevant information available but is a pitifully small sample (4 patients).

Fortunately, the results of this study compare qualitatively and quantitatively with an authoritative study (9) on fracture-patients, our next best source of material.

Even with this larger body of data, it is most difficult to relate a partial (at most) immobilization under gravity-conditions to the conditions of prolonged space flight.

SUMMARY OF RELEVANT DATA

Concurrent with the onset of immobilization there is a rise in fecal and urinary excretion of calcium which increases to a plateau in a few weeks. Maximum daily calcium excretion averaged 17 mEq/24 hrs. in normal subjects

(8), 26 mEq/24 hrs. in fracture-patients (9) as compared with normal values about 10 mEq/24 hrs. On total balance, the 4 normals averaged a loss of 14 gms of Ca in 6 - 7 weeks.

Serum calcium levels tended to rise (a mean increase of 0.4 mEq/l in normals (8) but occasional high values were seen (6.7 and 6.1 mEq/l (9) and 6 to 6.4 mEq/l (8)).

Urinary phosphate excretion is less consistent than calcium excretion. In general the pattern is one of an initial rise followed by a return toward normal levels after a few weeks (8,9). This is similar to nitrogen excretion. Average daily losses were 190 mgP with a maximum of about 370 mgP. Nitrogen losses ranged from 0.7 to 2.0 gms N/day averaged over 6 or 7 weeks with maximum losses ranging from 0.9 to 3.5 gms N/day.

Notable also were tendencies for urine volumes and citrate concentrations to remain relatively constant while urinary pH rose slightly. With hypercalcuria and phosphaturia, these conditions all favor calculus formation (10).

In fracture patients, an attempt was made to alter the urinary response to immobilization by manipulation of the diet (9). Increasing dietary calcium and phosphate simultaneously (milk supplement) increased urinary phosphate with no effect on urinary calcium. Increasing dietary calcium without concurrent phosphate additions, caused a small increase in urinary calcium and a fall in urinary phosphate. In general, the urinary calcium levels were relatively independent of dietary influence.

In both studies, upon remobilization, all parameters measured on all patients returned toward normal. Balances became positive for a number of weeks and recovery, as nearly as can be determined, was complete.

In recovery, the normal subjects noted mild dizziness for one to two days and unsteadiness of the legs for six to eight days. Stiffness and even soreness of the joints, particularly the knees, which began mildly during the last two to three weeks of immobilization, was evident for three to six weeks in recovery. One subject, who had had an injury to one knee years previously, had soreness of both knees for three to four months.

The primary assumption which must be made is that these studies on normal patients employed conditions comparable to the conditions of weightlessness in space flight. This assumption can be tested only to the extent that data are available from previous space flights. Briefly, the only data available to the author was Document NASA SP-6 summarizing urine and blood chemistries obtained from the

Glenn and Carpenter flights. These results are summarized in Table I.

TABLE I
CALCIUM METABOLISM IN ASTRONAUTS

	Pre-flight	In Flight	Post Flight	Normal
Pilot Carpenter				
Serum Ca mEq./l	4.8	---	4.1, 3.5	5.0
Urinary Ca* mEq./24 hr.	?	14.7	14	8-15
Pilot Glenn				
Serum Ca mEq./l	4.3	---	4.2, 4.5	5.0
Urinary Ca* mEq./24 hr.	---	12.9	15.7	8-15

* calculated to 24 hr. basis

? only one spot sample of 250 ml was reported. Given as 1 mEq/l this corresponds to a total daily excretion of only 1 to 1.5 mEq! If the unitage is mEq not mEq/l as is frequently found elsewhere in the document, the value is still very low, 4 - 6 mEq/day.

Unfortunately, these data are not very helpful. Apart from some general confusion in the unitage (mEq vs. mEq/l) employed in the report in expressing results, there are individual values which are of doubtful validity; for example: Glenn's preflight and Carpenter's post-flight serum levels of 4.3 and 3.5 mEq./l respectively (normal values are taken to be 5.0 ± 0.3). There exist no pre-flight base-line data on which to compare the limited in-flight and post-flight results.*

With respect to the effects of weightlessness on electrolyte metabolism, then, and calcium metabolism in particular, no definitive conclusions can be drawn from orbital flights thus far. It is possible that the effects of weightlessness would not, in any event, result in urinary changes in flights of short duration. Definitive signs of calcuria in the Cornell study (7,8) took a day or two to develop.

Under the circumstances, we have only common sense on which to base a judgement. In this spirit, it seems reasonable that orbital flight conditions will simulate partial immobilization and will be less severe than those endured by bulbar poliomyelitis patients confined to respirators. We should expect, therefore, persistent but mild: bone resorption, hypercalcemia and hypercalcuria.

* Results of the Third United States Manned Orbital Space Flight, NASA SP-12, Dec. 1962, became available after this report was first written. These new data do not, however, provide a definitive basis for evaluating changes; if any, in calcium metabolism.

Clinical experience with persistent hypercalcemias and hypercalcurias shows an increased incidence of renal calculi (10). In addition to the formation of renal stones, with their frequent sequelae of pelvic and ureteral obstruction and pyelonephritis, severe hypercalcuria may result in diffuse deposition of calcium in the renal parenchyma. In the kidney, as in other organs, calcium frequently precipitates in dead or dying tissues. In diseases characterized by hypercalcuria, calcification has a tendency to occur predominantly in the collecting ducts and in the medulla. Bell (11) found in a case of hyperparathyroidism that all the calcium was in the medulla in the shape and direction of collecting tubules. In experimental studies of vitamin D poisoning, the earliest and most numerous lesions are in the collecting tubules, where cells are injured with and without histologically demonstrable precipitates of calcium. With more severe intoxication, calcium deposition extends generally throughout the kidney to involve the thin loops and convoluted tubules, as well as, in advanced instances, the glomeruli and renal vasculature (12). In the later stages of nephrocalcinosis, and notably in chronic hyperparathyroidism, the deposits of calcium are predominantly interstitial (13).

The nature of the lesions associated with hypercalcemia has been clarified by studies using the techniques of micro-dissection and electron microscopy. Degenerative and necrotic changes appear in microdissected nephrons in focal areas of the ascending loop of Henle, the distal convolution, and throughout the entire collecting system, where they are more severe and more numerous (14). Basement membranes in regions of epithelial necrosis are frequently calcified. Casts of calcified epithelial debris obstruct some tubules and cause dilatation of the nephron proximal to the obstruction. Proximal convoluted tubules are relatively uninvolved. The absence of obvious structural changes in the glomeruli suggest that the marked fall in glomerular filtration rate which accompanies hypercalcemia of great magnitude is contributed to by obstruction in the collecting system or changes in renal blood flow. One to six weeks following parathyroid injection, after the serum calcium has been allowed to return to normal, fatty changes are noted in the same locations, together with proliferative collections of regenerating epithelial cells. Calcification, initially intracellular or intratubular, later appears in an interstitial position as regenerating epithelium grows into or around the calcified intraluminal casts in the medullary collecting ducts.

The problem of importance in the present context is to evaluate the quantitative relationship between hypercalcemia and hypercalcuria on the one hand and renal damage and calculi on the other. Particularly, it would be helpful to know if a threshold concentration (in serum or urine) exists below which the kidney is free from possible harm.

It is, however, possible to consider the worst possible case, that of long-term respirator patients suffering from polio. Here, loss of nervous function and flaccidity of muscles would be expected to accentuate or aggrevate calcium mobilization and therefore increase the occurrence of renal damage and calculi. Under such circumstances serum Ca values as high as 8.6 mEq/1 have been reported. Typical experience is summarized in Table II.

TABLE II
INCIDENCE OF RENAL CALCULI IN RESPIRATOR-PATIENTS (15)

Study	No. Patients	Calculi Incidence %
A	98	34
B	47	40
C	66	33
D	675	15
E (Untreated)	34	27
E (Treated)	55	6

Even with these rather desperate conditions, attention to preventative measures (avoidance of renal infection, maintenance of urine acidity, insuring adequate urine volume, etc.)

reduced the incidence of renal calculi to 6% (Study E (treated)). Also, many of these patients are subjected to frequent catheterization, a procedure involving trauma and possible infection. The procedure itself could be expected to increase somewhat the incidence of calculi formation.

Finally, hypercalcemia per se is known to have marked effects on renal function (10). It produces a polyuria resembling that of potassium deficiency. Inability to concentrate the urine can be so severe that there is no response to intravenous vaso-pressin. This point is especially relevant since there was a marked polyuria evident in the Glenn flight and Carpenter put out a dilute urine in the face of hemoconcentration from excessive sweating. It is, of course, perfectly possible that this tendency toward polyuria is referrable to any one or a combination of many factors other than hypercalcemia. With the information available, this is an open question of considerable importance. The significance is that, if caused by hypercalcemia, the polyuria indicates a degree of hypercalcemia much greater than expected or assumed in this report.

EVALUATION

It is reasonable to expect that astronauts, with restricted activity and free of gravity, will incur persistent hypercalcemia and hypercalcuria. The degree of hypercalcemia cannot be estimated with present information.

If possible, a regular exercise program should be provided, one which would permit working muscles and bones (including the spine) against a resisting force (springs).

With this provision, disturbances of calcium metabolism should be minimal. In any event, the calcium loss *per se* can be neglected. If astronauts were to lose in two weeks as much as normal immobilized patients lose in 6-7 weeks, the total excess calcium lost represents no more than 1% of the skeletal content and will be reversibly recoverable post-flight.

There is a possibility that some renal damage may be incurred particularly if the hypercalcemia is severe. To minimize this possibility the following provisions should be made: an exercise program, adequate fluid intake, acid-ash diet, moderate to low calcium intake, and moderate to high phosphate intake. In addition, salt pills should be available in the event of persistent polyuria and/or excessive sweating.

With these provisions, the likelihood of serious problems <u>from disturbances in calcium metabolism</u> are small in comparison with other potential hazards of space flight of two weeks' duration.

RECOMMENDATION

Previous orbital flights have not provided much information which can be used to evaluate the hazards to be expected from alterations in calcium metabolism during prolonged periods of weightlessness. While it is the impression that no serious problems should be encountered in flights of two weeks duration, it would be most helpful if plans were made now to obtain information on this point in projected flights.

It seems perfectly possible that ambulatory balance studies could be performed on the astronauts before and after flight without in any way interfering with the conduct or timing of the shots. These data (for other electrolytes as well as calcium) would be most helpful in providing baselines and recovery patterns against which to evaluate data derived in flight. Perhaps the wisest course would be to charge a small panel of electrolyte-clinician experts to propose a study plan to maximize the information to be derived from future flights.

Experimentally, it would be very helpful to know the quantitative relation between levels of hypercalcemia and renal injury. Such studies would be difficult to design to produce unambiguous answers. Perhaps immobilization of dogs would provide an approach. It would also be highly desirable to obtain accurate serum calcium values on animals and astronauts during periods of prolonged weightlessness.

For flights longer than two weeks, particularly space capsule flights of indefinite length, grave questions of the continued normalcy of bone architecture and bone development arise. Flotation experiments with man and animals should be undertaken. Plans should be activated for experiments with, say, weanling mice which could be orbited for extended periods and either recovered for study or x-ray data telemetered to Earth. For all we presently know of mice and men, when raised in space, they may assume a globular shape.

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