NASA TM-86692

NASA Technical Memorandum 86692

Biomedical Research Division Significant Accomplishments for FY 1984

NASA

National Aeronautics and
Space Administration

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Biomedical Research Division Significant Accomplishments for FY 1984

Norman V. Martello, Johnson Engineering

Prepared for
Biomedical Research Division
Ames Research Center

February 1985

NASA
National Aeronautics and
Space Administration

Ames Research Center
Moffett Field, California 94035

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INTRODUCTION

The Biomedical Research Division (LR) at Ames Research Center, near San Francisco, California, continued to serve the scientific community as NASA's primary organization for basic research in space medcine and biology during fiscal year 1984. Our efforts in basic R&D covered a wide range of disciplines in the biological and behavioral sciences. Using both animal and human subjects, investigators examined the adaptation of various organisms and organ systems to the aerospace environment. To assure astronaut health and productivity in such environments required the study of physiological functions under the effects of acceleration, radiation and weightlessness. New insights into physiological changes during flight were provided by comparing data from actual flight in space to that from ground based simulations, such as bedrest with humans.

The English naturalist and theorist Charles Darwin noted that we could not experimentally remove the force of gravity on Earth, and he envisioned the importance of sensitivity to gravity as a factor in biological development, function and evolution. Spaceflight made research feasible in an environment virtually free from the influences of gravity. Thus, NASA's programs in the life sciences at LR benfited both the scientific and aerospace communities through: (1) research to ensure the health and performance of humans in space (Operational Medicine Program), (2) basic research to investigate major physiological challenges to humans in space, research which is also applicable to problems facing the health care community on Earth (Biomedical Research Program), and (3) research to understand the nature of life itself, particularly the role of gravity on the development and evolution of Earth's creatures (Gravitational Biology Program). These and other Life Sciences Programs were administered from NASA Headquarters in Washington, D.C. to the Ames Research Center, Johnson Space Center, the Jet Propulsion Laboratory, and Kennedy Space Center. Specifically in the Biomedical Research Division at Ames, the principal research objectives were:

- to improve human access to space by understanding the medical and psychological problems of spaceflight, and developing then implementing the solutions to them;

- to maintain the ability to conduct scientific and technical flight and ground-based projects in life sciences by integrating our engineering, scientific and technical talent with the appropriate facilities and equipment; and

- to improve our understanding of the role of gravity in biological processes.

Results from manned flight over the past year present new challenges for the Life Sciences in NASA. With the completion of the initial missions of the Space Transportation System (STS), or Space Shuttle, it is now recognized that astronauts must perform increasingly complex and demanding tasks in the weightless environment as well as skillfully pilot the Shuttle under the effects of reentry acceleration. Successful adaptation to the space environment ensures both the productive use of short-duration Shuttle flights, and the scientific and economic growth concomitant with the establishment of long-duration space stations.

During FY 1984 research at LR was conducted through a combination of intramural projects, using the specialized laboratories and aerospace test facilities at Ames, and extramural projects, contributing the talents of outside investigators from universities, medical schools, hospitals, and research institutes. Thirty-two in-house investigators performed 40% of all research activities, and coordinated the remaining 60%, which was conducted by outside institutions. The National Research Council's Post-Doctoral Fellowships, which are held generally for two-year periods, provided eight talented researchers in cardiovascular, muscular and neurophysiological research. Senior scientists of LR reported to NASA Headquarters on each unique research area through Research Technology Objectives and Plans (RTOPs), which are summarized in the following report.

Two Assistant Division Chiefs maintained close contact with the Program Managers at NASA Headquarters and with the Office of the Director of Life Sciences at Ames, as well as coordinated the efforts of the Biomedical Research Division. The Assistant Chiefs consulted with and received guidance from the Division Chief, Harold Sandler, M.D., to direct the overall research. On the basis of his internationally recognized contributions in cardiovascular research and the biomedical effects

of extended duration spaceflight, Dr. Sandler received the Space Agency's first Senior Executive Services Sabbatical and spent this time at nearby Stanford University School of Medicine, where he worked as a Visiting Professor.

The Division's staff includes a combination of Civil Service personnel, university collaborators, and contract personnel on-site. LR's complement of 36 civil servants includes 15 Ph.D.s, one D.V.M., two M.D.s, seven Masters and eight Bachelors level personnel engaged in biomedical and space biology research. On the staff are internationally recognized experts in the fields of biochemistry, endocrinology, cardiovascular physiology, environmental physiology, exercise physiology, neuroanatomy, and bone mineral metabolism. The Division staff members possess expertise in pharmacology, vestibular function, experimental patholgy, immunology, radiation biology, biorhythms, psychology, the biochemistry of proteins, carbohydrates and lipids, and gravitational biology.

Research and development on the ground also supported flight experiments in the Space Shuttle program, and on the latest in a series of joint US-USSR biological spaceflights: the unmanned biosatellite Cosmos 1514 launched by the Soviet Union in December, 1983. Echocardiography (ultrasound) studies were conducted on Shuttle crew members before and after flight, which will lead ultimately to obtaining cardiovascular data during flight.

To help the dissemination of scientific information and expertise, the research facility at Ames also provided a valuable training ground for 30 students, including 12 graduate students involved in thesis work directly applicable to the Division's current research projects. Such opportunities contributed to the training of skilled investigators to meet the continuing needs of advanced aerospace research at a time when the first generation of space biologists and psychologists are approaching retirement.

LR scientists also provided NASA Headquarters with scientific critique of new research proposals, and participated in a wide variety of scientific committees, working groups and advisory teams. Additional effort was initiated to integrate and present research findings in a useful fashion for review by NASA Headquarters, by review committees of the American Institute of Biological Sciences (AIBS), and by the biological, medical and aerospace communities in general. The descriptions that follow include results of research conducted by all Principal Investigators in the Division, as well as the research

conducted by universities and private industry, which was sponsored by NASA and monitored by personnel of the Biomedical Research Division at Ames. Further information on the programs of the Biomedical Research Division can be obtained by contacting any of the following individuals:

Harold Sander	Kenneth A. Souza	Malcolm M. Cohen
Division Chief	Asst. Div. Chief	Asst. Div. Chief
Mail-Stop 239-8	Mail-Stop 239-17	Mail-Stop 239-7

Ames Research Center, Moffett Field, California 94035
Telephone: (415) 694-5744

TABLE I. ORGANIZATION OF THE BIOMEDICAL RESEARCH DIVISION

Harold Sandler, Chief

Doris M. Furman, Secretary

Anne L. Goodwin, Technical Assistant

Kenneth A. Souza, Assistant Chief	Malcolm M. Cohen, Assistant Chief
Christine B. Anderson, Secretary	Rita L. Marks, Secretary
PROGRAM RESPONSIBILITIES	PROGRAM RESPONSIBILITIES
Cosmos & Spacelab Flight Experiments	Space Shuttle Flight Experiments
Gravitational Biology Biological adaptation	Operational Medicine Longitudinal studies Crew health maintenance Space adaptation syndrome
Biomedical Research one alterations Muscle atrophy Radiation effects & protection	Biomedical Research Cardiovascular deconditioning Neurophysiology Fluid and electrolyte changes Behavior and performance General biomedical research
Management Facilities Safety Property	Management NASA's Office of Aeronautics and Space Technology Department of Defense Programs

TABLE II. CIVIL SERVICE PERSONNEL IN THE BIOMEDICAL RESEARCH DIVISION

FUNCTION	BACKGROUND
Administrative	
D.M. Furman	clerical support to Division Chief
A.L. Goodwin	budget & logistics, medical technology, biochemistry, Division Technical Assistant
R.L. Marks	clerical support to Division administrators and personnel
C.B. Anderson	clerical support to Division adminstrators and personnel
Behavior & Performance Research	
M.M. Cohen	neurophysiology, aviation psychology, Assistant Division Chief
C.W. DeRoshia	chronobiology
E.M. Huff	human factors, aviation psychology
C.M. Winget	chronobiology, pharmacology, comparative physiology
Bone Alterations Research	
D.R. Young	bone and mineral physiology
Cardiovascular Deconditioning Research	
J.W. Hart	animal care
H. Sandler	cardiovascular physiology, medical doctor, Division Chief
Crew Health Maintenance Research	
D.J. Goldwater	human physiology, medical doctor
Gravitational Biology Research	
R.R. Adachi	analytical chemistry
B.C. Daligcon	physiology
H.J. Ginoza	genetics, physiology
E.M. Holton	bone and mineral physiology, pharmacology
J. Oyama	gravitational physiology
K.A. Souza	embryology, space biology, Assistant Division Chief
H.M. Mack	embryology, histology

Fluid and Electrolyte Research

J.V. Danellis	pharmacology, endocrinology
J.E. Greenleaf	environmental physiology
L.C. Keil	endocrinology

General Biomedical Research

C.B. Dolkas	physiology, insulin/glucose metabolism, biomedical engineering
A.D. Mandel	immunology, bacteriology
J.A. Williams	immunology

Muscle Atrophy Research

S. Ellis	biochemistry, muscle physiology
R.E. Grindeland	physiology, growth hormone research
P.R. Lundgren	biochemistry, analytical chemistry

Radiation Effects and Protection Research

R.L. Corbett	electron microscopy, zoology
L.M. Kraft	radiobiology, veterinary medicine
D.E. Philpott	cytology, electron microscopy, radiobiology
M.J. Stevenson	biochemistry, histology

Neurophysiology Research

R. Binnard	developmental biology, histology
J.O. Coleman	neurophysiology, animal care
M.L. Corcoran	experimental & behavioral psychology
P.S. Cowings	psychophysiology, psychology, biofeedback research
N.G. Daunton	neurophysiology, neuropsychology
W.R. Mehler	neuroanatomy

OPERATIONAL MEDICINE

OPERATIONAL MEDICINE PROGRAM

The Operational Medicine Program is responsible for assuring the health, well-being and performance of astronauts and other flight crew members while working in space. This crucial work, which is critical to mission success, is achieved through (1) clinical and preventive medicine programs and (2) operational research and development. The first activity requires the development and continuous update of astronaut medical selection and retention (annual) certification standards; pre- and postflight medical examinations of STS crews; early detection, prevention and/or treatment of crew illness; biomedical training of space crews in emergency medical procedures; and training of NASA/DOD (Department of Defense) medical personnel in principles and practice of space medicine. These activities are primarily accomplished through the establishment and maintenance of specialized biomedical laboratories and offices at Johnson Space Center (JSC) in Houston and Kennedy Space Center in Florida. The second activity addresses medical operational issues and problems which have been encountered in the conduct of previous manned missions. This program includes acquisition of trend data to elucidate the time course of long-term effects from repeated exposures to the space environment; the development of health maintenance protocols (such as exercise, anti-cardiovascular deconditioning measures, space motion sickness predictors and/or drugs, etc.), procedures, equipment and environmental monitoring for use during space missions; and simulations of STS flights that facilitate the testing and development of specific medical protocols on the ground prior to their use in space. These activities are conducted by JSC, Ames Research Center, and selected DOD and university research laboratories.

(From NASA Space Science and Applications Notice, October 25, 1982)

Arnauld Nicogossian
Director of NASA Life Sciences

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LONGITUDINAL STUDIES RTOP 199-10-22
D.J. Goldwater, manager

The basic medical research performed at Ames Research Center (ARC) under this RTOP provides medical data from astronauts and control populations over periods ranging from months to years. Longitudinal, retrospective studies compare these two groups revealing the magnitude of physiological changes that occur during spaceflight. This research, then, helps to define postflight recovery programs for the health and career longevity of astronauts. Criteria for the initial selection of personnel for the astronaut corps is also updated as required.

During the past decade the Human Research Facility at ARC (managed by Dee O'Hara of the Biosystems Division), and the Stanford University and Palo Alto VA Hospital clinical research centers, were used to study over 180 males and females, spanning the ages of 19 to 65 years, under simulations of Space Shuttle flight stress. Subjects underwent bedrest horizontally (0 deg) and head-down (-6 deg) to simulate many of the effects of weightlessness. Acceleration of +3 Gz (head to foot) on Ames' Human Centrifuge followed approximately a week of bedrest. (+1.2 Gz for 17 minutes is the typical acceleration force on humans during reentry of the Space Shuttle with the steepest reentry profile of +2.8 Gz). In past US and USSR manned flights, astronauts flew through a reentry profile different and less stressful physiologically from that of the Space Shuttle. Space travellers returned to Earth with their seats tilted back, withstanding up to +6 Gx (chest to back) for brief periods. Bedrest followed by +3 Gz acceleration allowed ARC's flight surgeons to identify predictive factors affecting orthostatic tolerance (susceptibility to greyout, blackout, or fainting). Some of the factors contributing to low orthostatic tolerance included aerobic exercise, younger age, taller height, feminine gender, low resting blood pressure and heart rate, and low levels of plasma renin activity and plasma norepinephrine.

Echocardiography plays an important role in identifying the effect of reduced size and volume of the heart resulting from bedrest or spaceflight. Echocardiography uses high frequency sound waves, or ultrasound, to visualize the heart and its great vessels. An echocardiogram data base of over 200 healthy men and women was established for comparison with astronauts. A valuable exchange of information and collaboration with flight surgeons and biomedical researchers at Johnson Space Center is also ongoing.

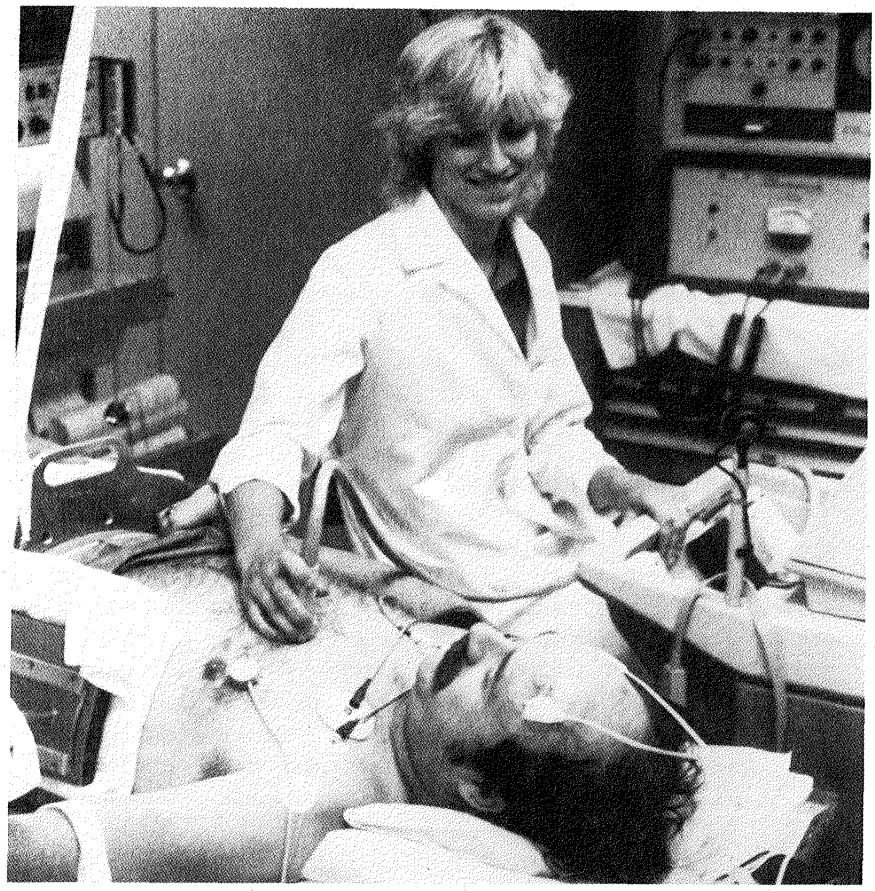

Fig. 1. Bedrest subject undergoes echocardiography during lower body negative pressure (LBNP), analogous to Shuttle crew postflight echocardiography. (Popp 199-10-22-10)

Evaluation of Echo-Ultrasonic Indices for Space Shuttle
199-10-22-10

R.L. Popp, Stanford University School of Medicine
D.J. Goldwater, Ames Technical Monitor

Weightlessness in spaceflight induces a lower cardiac workload on the heart and a smaller heart volume, which may cause weakening of the cardiac muscle and possible problems to some members of flight crews during reentry and return to terrestrial gravity levels. To monitor the magnitude of cardiac changes, as well as to assess potential countermeasures, echocardiograms were performed before and after flight on 17 Shuttle crewmen, covering STS-5 through STS-8. Echocardiography uses high frequency sound waves (ultrasound) to produce real-time images of the heart and permits an analysis of heart function. A portable ultrasonoscope was modified for the pre- and postflight measurements. Although heart rate increased immediately postflight, resting cardiac output was maintained. However, 7 to 14 days postflight it was found that ejection fraction (not heart rate) maintained cardiac output, as well as stroke volume and mean arterial pressure. Persistent postflight decreases in cardiac filling volumes after these five to eight-day Shuttle flights were similar to echo measures after the 84-day Skylab mission, and were also similar to results of 10-day bedrest studies at the Human Research Facility at Ames Research Center.

Comparative studies were also performed in the Human Research Facility at Ames on 10 athletic and 10 sedentary subjects during ten days of 6 deg head-down bedrest to simulate the effects of weightlessness (Fig. 1). Results of echocardiograms are currently being analyzed. Preliminary analysis indicates larger decreases in cardiac filling volumes in aerobically-trained subjects than in sedentary subjects, with change in end diastolic volume inversely proportional to plasma volume loss during weightlessness simulation.

Publications: (1)Sandler, H., D.J. Goldwater, M.W. Bungo, and R.L. Popp. Changes incardiovascular function: Weightlessness and ground-based studies. NATO-AGARD Aerospace Medical Panel Symposium on Results of Space Experiments in Physiology and Medicine. Istanbul, Turkey; 1984 September 24-28. (2) Sandler, H., D.J. Goldwater, R.L. Popp, L. Spaccavento, and D.C. Harrison. Beta blockade in the compensation for bedrest cardiovascular deconditioning physiological and pharmacological observations. Stanford University School of Medicine cardiology symposium. Carmel, CA; 1984 October 14-17.

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CREW HEALTH MAINTENANCE RTOP 199-10-32
D.J. Goldwater, manager

Over the past decade the Human Research Facility at Ames Research Center tested over 180 male and female subjects under head-down (-6 deg) and horizontal (0 deg) bedrest to simulate the deconditioning effects that occur during the weightlessness of spaceflight. Scientific experiments were devised to achieve medical techniques that enhance crew health and physiological performance preflight, inflight, during reentry, immediately postflight, and between flights. Cumulative effects from exposure to multiple simulations of spaceflight are evaluated, as well as minimal intervals necessary for safe recovery between flights. Lower body negative pressure (LBNP), a standard aerospace medical technique, was used to test subjects' orthostatic tolerance, their resistance to greyout or fainting. Different degrees of negative pressure (suction) can be applied to an enclosed area surrounding the individual from the waist down. Like the effect of gravity during spaceship reentry, LBNP shifts extracellular fluid back toward the legs and away from the head, particularly when LBNP is applied to prone or weightless individuals. Evaluations were made of methods to counteract deconditioning, such as exercise rehabilitation, repeated LBNP, drugs and use of the inflatable G-suit as added protection against orthostatic intolerance.

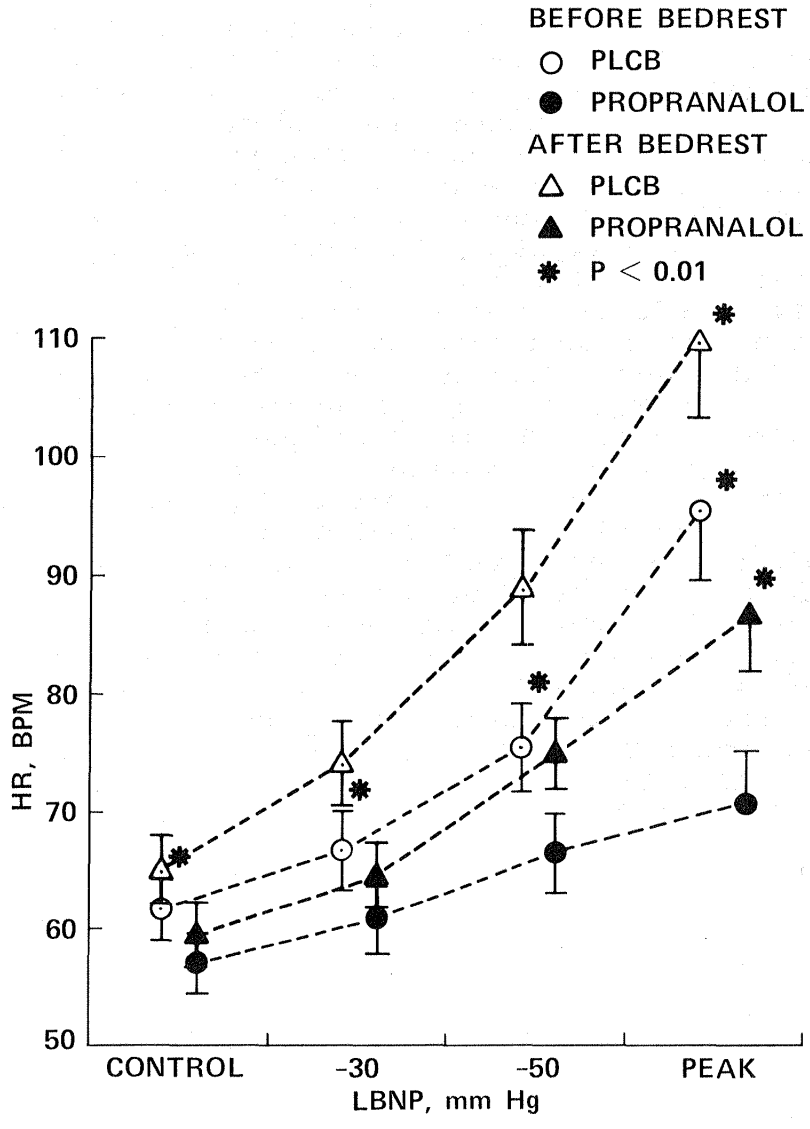

Fig. 2. Propranolol, a drug under consideration to treat spaceflight cardiovascular deconditioning, produced less of a heart rate (HR) decrease during peak LBNP levels compared to a placebo (PLCB) after bedrest simulation of weightlessness. (Harrison and Kates 199-10-32-09)

Pharmacologic Countermeasures for Cardiovascular Deconditioning during Shuttle Flight 199-10-32-09

D.C. Harrison and R.E. Kates, Stanford University School of Medicine
D.J. Goldwater, Ames Technical Monitor

An extensive study evaluated how well potential drug countermeasures (atropine, phenylephrine, and propranolol) could improve acceleration tolerance by constricting blood vessels, thus keeping blood pressure elevated during LBNP tests. In some cases, preliminary analysis revealed a differential drug effect depending on the subject's level of aerobic conditioning. All drugs were tested against placebo injection in single blind fashion. Phenylephrine significantly prolonged LBNP tolerance (+35%) after Shuttle flight simulation (-6 deg bedrest). Atropine tended to prolong lower body negative pressure (LBNP) tolerance to a greater degree after bedrest. After bedrest, the same dose of atropine produced a larger resting increase in heart rate over the placebo. This result suggested either lower vagal tone or greater resting beta-adrenergic sympathetic tone after weightlessness simulation. Because the response of the resting heart rate to propranolol (compared to placebo) was no different after bedrest, lower vagal tone at rest may be responsible for the increased effect of atropine.

During LBNP stress, sympathetic tone was greater after bedrest than pre-bedrest. Further, the same dose of propranolol produced less of a heart rate decrease during peak LBNP levels compared to the placebo (Fig. 2). Greater sympathetic tone may explain propranolol's less deleterious effect on LBNP tolerance after bedrest compared to pre-bedrest. This data suggested that phenylephrine and atropine may be useful during Shuttle reentry and post-fight periods; however a careful dose response study must be conducted to further evaluate propranolol. Phenylephrine appeared to be much more helpful for sedentary subjects in improving orthostatic tolerance than for athletic subjects.

This laboratory also perfected a chromatographic assay for epinephrine and norepinephrine microdeterminations with a lower limit of sensitivity of 50 pg/ml. Investigators started assays on dozens of blood samples from this study that were taken during each level of LBNP so that the drug effects of orthostatic tolerance can be assessed. Vasoactive neuroendocrine responses of subjects with high LBNP tolerance (HT) and lower LBNP tolerance (LT) were compared by examining output of norepinephrine, antidiuretic hormone (ADH) and plasma renin activity (PRA). HT had greater increases

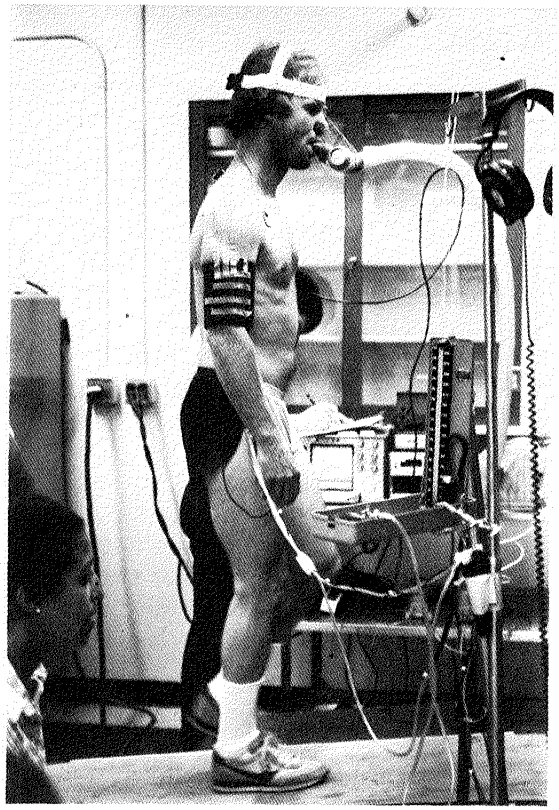

Fig. 3. Aerobically-conditioned subject undergoes treadmill exercise testing after bedrest simulation of Shuttle flight. (Goldwater 199-10-32-17)

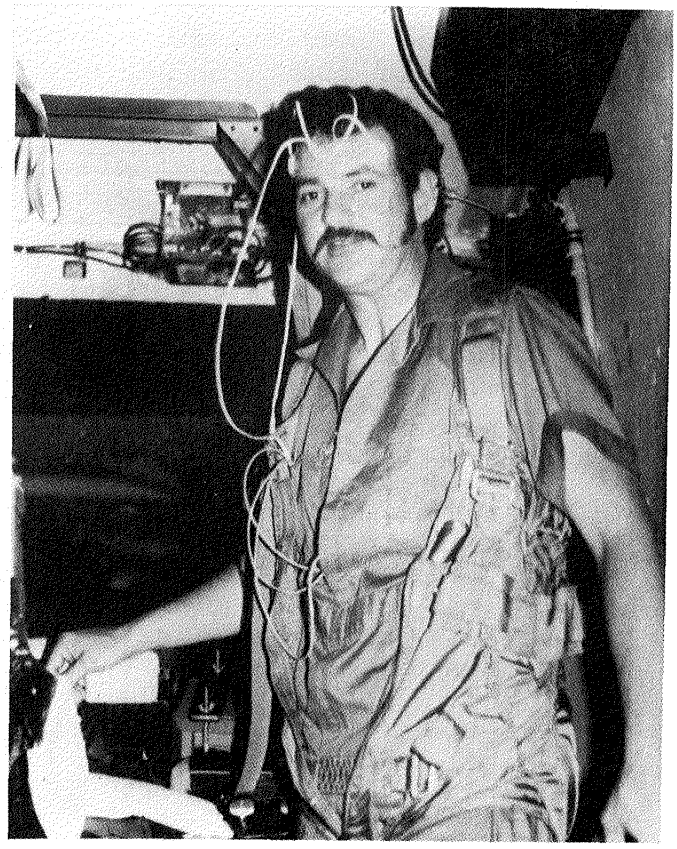

Fig. 4. Subject prepares to enter centrifuge for a +3 Gz acceleration test following sedentary recovery from simulated weightlessness. (Goldwater 199-10-32-17)

in PRA and ADH at peak LBNP stress than did LT. HT also had higher cardiac outputs and blood pressure during LBNP.

Athletic Conditioning and Repeated Weightlessness Exposures 199-10-32-17

D.J. Goldwater, Biomedical Research Division, Ames Research Center

Experiments suggest that intensive aerobic conditioning may predispose astronauts to orthostatic intolerance and possible fainting during Shuttle reentry. The last study in this series was completed with a group of aerobically-conditioned men in September 1984. Thirteen aerobically-trained men (Fig. 3) ages 35 to 50 years who ran more than 15 miles per week with maximum oxygen consumption (VO 2 max) at 47.4 + 16 ml/kg/min were compared to eight age-matched sedentary controls (VO 2 max at 35.2 + 1.5 ml/kg/min). Subjects went to greyout at +3 Gz before and after 6 days of 6 deg head-down bedrest (Fig. 4). Pre-bedrest acceleration tolerance for the athletically trained group was 372 seconds vs 537 seconds (NS) for the sedentary group. Post-bedrest G tolerance decreased significantly for the athletic group, falling 259 seconds to 113 seconds (68% change, p less than .01), while the sedentary group lost only 35% (165 seconds) to 372 seconds (NS).

Results indicate that athletic men have significantly lower +3 Gz acceleration tolerance after weightlessness simulation than our sedentary group. Athletic subjects also lost a significantly greater percent of their VO 2 max when tested after bedrest compared to sendentary subjects, and this loss was directly correlated with their greater loss of plasma volume. Athletes gained a higher percentage of body fat during the simulation. In addition, the proposed drug countermeasure, phenylephrine, was tested during lower-body negative pressure (LBNP) on both groups, and was more helpful in prolonging post-bedrest LBNP tolerance in sedentary men than in athletic subjects. The reasons for this qualitative difference will be investigated by examination of endocrine, echocardiography and impedance data from these studies.

Publications: Convertino, V., D. Goldwater and H. Sandler. 1984. "Oxygen uptake kinetics of constant load work: Upright vs. supine exercise." JOURNAL OF APPLIED PHYSIOLOGY 57(5): 1545-1550.

SPACE ADAPTATION SYNDROME RTOP 199-10-62
H.J. Finger, manager
P.S. Cowings, principal investigator

While individuals on the Skylab flights in the mid-1970's experienced different susceptibilities to the nausea of space motion sickness, they adapted to this effect of weightlessness within three to five days after launch. Because current Shuttle missions are generally of this duration, it is desirable to ameliorate space motion sickness during the susceptible period to maximize astronaut performance capability. Pioneer researchers in biofeedback over the past 20 years and a team of NASA scientists developed the technique of Autogenic Feedback Training (AFT), allowing subjects to successfully control their own motion sickness symptoms.

Functionally, as an individual thinks of any bodily movement, corresponding electrical activity can be measured in the nerves and muscles, even if the person does not move at all. Because the brain controls bodily functions, this basic physiological fact was used to develop a precise training regimen over the past decade at Ames Research Center. Using miniature electronic monitoring equipment, subjects easily learned to monitor and control some of their own vital signs and other physiological processes, such as heart rate, muscle tension, and motion sickness symptoms, using AFT. Following the training, individuals could use this ability without further need of bioelectric monitoring devices. Such self-suggestion techniques were used by the U.S. Air Force in a study to return to flight status 80% of pilots grounded for motion sickness. As a result, the USAF requested AFT for their astronauts in preparation for future Space Shuttle flights.

Using AFT in the laboratory: (1) subjects withstood Coriolis acceleration significantly longer and at higher velocities than control subjects; (2) subjects had equal success in controlling symptoms, regardless of their gender or their past susceptibility to motion sickness; and (3) subjects could be trained to control motion sickness under one type of stimulation (e.g., Coriolis acceleration), yet would be immune to motion sickness under other stimuli (e.g., visual stimulation or linear acceleration). No other motion sickness countermeasure, including drugs, has been shown to remedy several different stressful situations. Careful experimentation also yielded information on the types of schedules and electronic feedback displays that produce the greatest amount of learned self-control in a minimal amount of time. Some

subjects, who received only six hours of AFT, could control symptoms up to two years following training.

The scientific validation of AFT during spaceflight is scheduled to begin on Spacelab 3 with four astronauts: two trained and two untrained controls. The astronauts will monitor autonomic nervous activity to control their symptoms and to provide an objective measure of the success of AFT during spaceflight. With a good return on flight data, a minimum participation of 16 astronauts (eight trained, eight untrained) is required during flight tests to obtain a sufficient database for scientific statistical analysis.

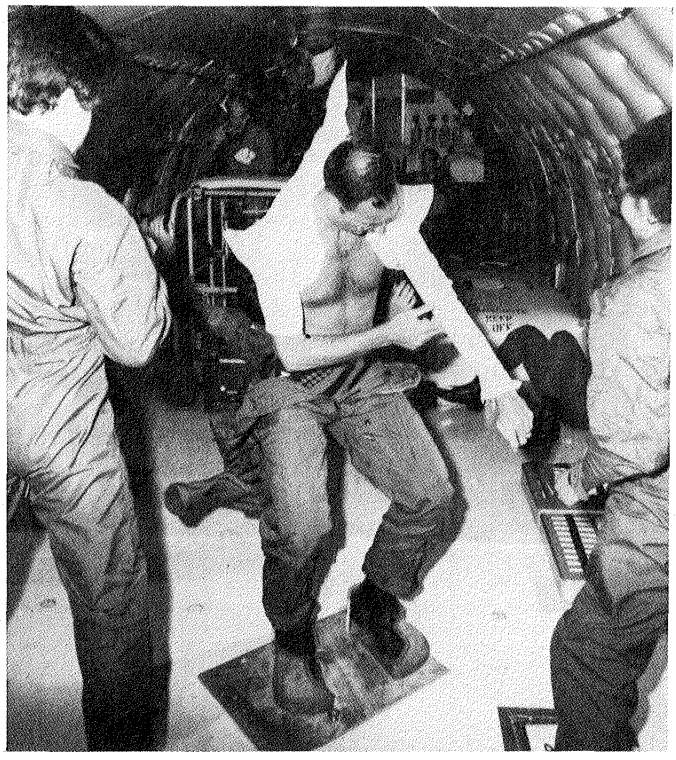

Fig. 5. Practice in the use of a biofeedback flight suit was conducted in the brief simulated weightlessness during parabolic arcs in training aircraft during preparations for Spacelab 3. (Cowings 199-10-62-01)

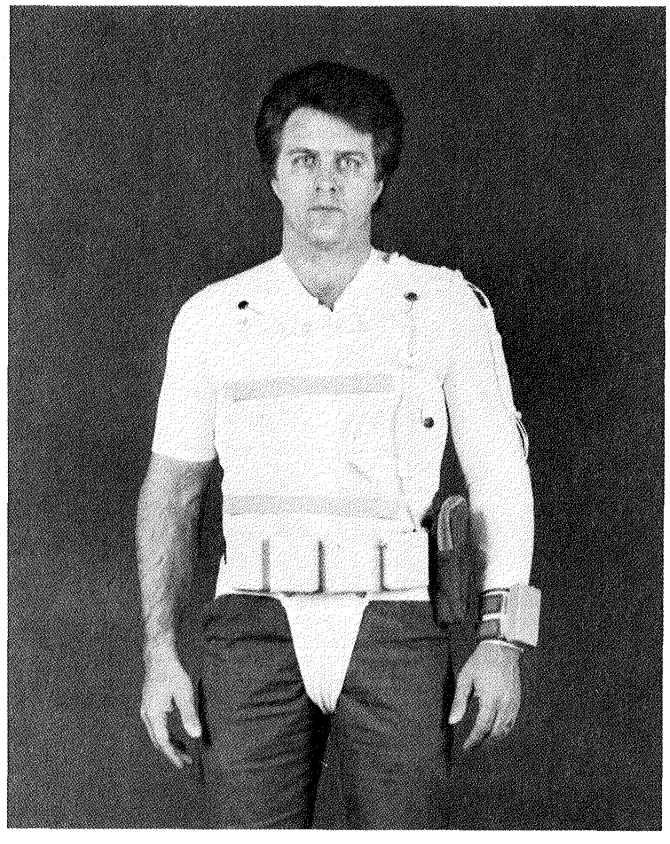

Fig. 6. Spacelab biofeedback flight suit, an ambulatory monitoring garment for motion sickness experiments. (Cowings 199-10-62-01)

Spacelab 3 Autogenic Feedback Training (AFT) Flight Experiment 199-10-62-01

Scientific Collaborators

P.S. Cowings, Biomedical Research Division, Ames Research Center

J. Kamiya and W.B. Toscano, Langley Porter Neuropsychiatric Institute, University of California Medical Center

N.E. Miller, Department of Psychology, Rockefeller University

J.C. Sharp, Deputy Director of Life Sciences, Ames Research Center

Engineering Design

H.J. Finger, Systems Engineering Division, Ames Research Center

L.E. Edsinger, Systems Engineering Division, Ames Research Center

This research task supported the preparation of the AFT test for the Spacelab 3 mission scheduled for launch on the Space Shuttle in 1985. Ground preparations covered the checkout of the Biofeedback Laboratory at Johnson Space Center (JSC) in Houston. Scientific investigators also conducted extensive preflight training at JSC, such as tests in the KC-135 aircraft (a military version of the Boeing 707) flying in a parabolic arc, wherein the aircraft's centrifugal force offsets the pull of gravity and causes a temporary simulation of weightlessness (Fig. 5).

Spacelab 3 will provide an environment for the first full-scale evaluation of AFT during spaceflight with two trained astronauts, and two untrained astronauts serving as controls. Each astronaut will wear an undergarment with biosensors for ambulatory monitoring of heart rate, respiration rate and volume, skin resistance as measured by perspiration, and blood volume pulse (Fig. 6). Physiological measures will be continuously recorded during each 12-hour work shift. (All equipment except for chest electrodes will be removed before sleep). The data will be recorded for subsequent analysis, and displayed in real time as biofeedback to the astronaut on a small wrist readout. Ultimatly, astronauts will not need the biofeedback equipment to monitor their physiological changes, but will have brought their symptoms of motion sickness under internal, voluntary control.

In addition the group trained in AFT will also rate, from mild to severe, nine motion sickness symtoms, such as pallor, stomach awareness and nausea. Therefore, physiological functions can be associated with

perceived symptoms. A tiny accelerometer worn on the head will measure bodily movement, which can also be correlated to motion sickness discomfort. Therefore, the AFT flight tests will provide a possible medical countermeasure, and generate a large data base for psychologists to study the human response to space adaptation.

Publications: Cowings, P.S. and F.V. Malmstrom. 1984. "What you thought you knew about motion sickness isn't necessarily so." FLYING SAFETY 40 (2): 12-17.

Psychophysiological Investigations of Space Adaptation Syndrome 199-10-62-03

P.S. Cowings, Biomedical Research Division, Ames Research Center

Psychophysiological methodology, an approach combining techniques from psychology and physiology, enabled scientists to establish associations between subjective symptoms of motion sickness and measured physiological activity; individual perception of malaise was linked to changes in heart rate, blood pressure, peripheral blood flow, skin temperature and electrical impedance, and electrical activity of the stomach. USAF astronauts, or Manned Spaceflight Engineers (MSEs), were studied using Ames Research Center's aircraft and Psychophysiological Laboratory for motion sickness testing. In association with the USAF School of Aviation Medicine, baseline physiological responses and subjective questionnaires were received from 17 MSEs. These preliminary tests resulted in scheduling as MSE as the first astronaut to participate in biofeedback testing in space.

Among 127 human subjects, those individuals disposed to motion sickness showed a higher resting heart rate and higher peripheral blood volume compared to less susceptible subjects. Physiological responses in individuals also remained constant over repeated tests on a rotating chair (Fig. 7) during Coriolis Sickness Susceptibility Index (CSSI) tests. On the chair, padded head rests were mounted on the left, right, front and back of the subjects allowing head movements at angles of 45 deg from the vertical. The CSSI tests started at a rotation of 6 rpm and increased by 2 rpm every 5 min. The maximum rotation rate was 30 rpm. Subjects made 45 deg head movements upon instruction at two-second intervals. During periods of no head movement, the blindfolded subjects were empirically evaluated on a standard index as to the severity of their sickness.

Electrical activity of the stomach, recorded as an

electrogastrogram (EGG), was highly correlated to motion sickness in a study of 20 subjects. Therefore, EGG may prove to be an effective, new biofeedback signal for learning to control motion sickness. This research task enabled the determination that biofeedback and voluntary control of supposedly autonomic (involuntary) responses can increase tolerance to motion sickness in the Earth environment.

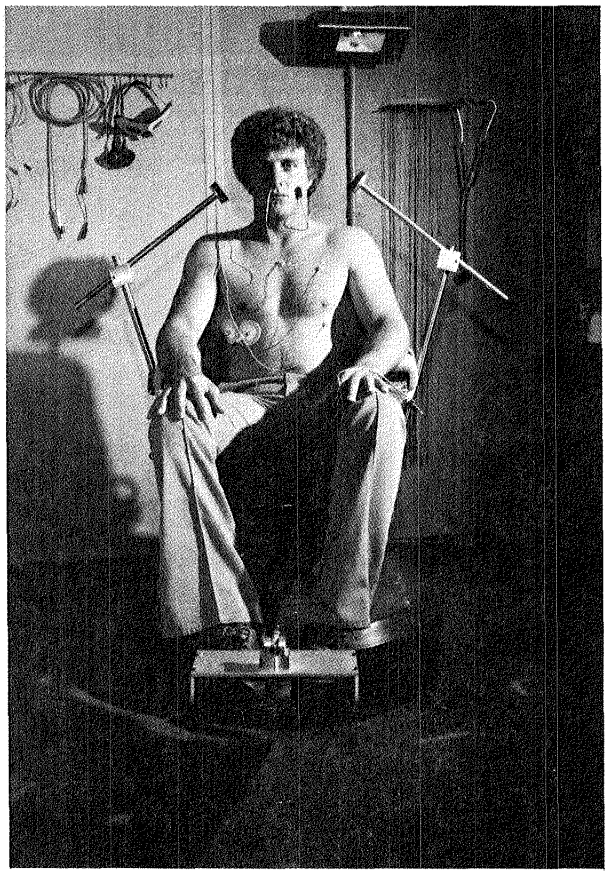

Fig. 7. Physiological responses are recorded during controlled scientific tests of motion sickness susceptibility using a special rotating chair. (Cowings 199-10-62-03)

BIOMEDICAL RESEARCH

BIOMEDICAL RESEARCH PROGRAM IN NASA

The Biomedical Research Program is designed to investigate the major physiological and psychological problems encountered by man in space and to develop solutions. The program strives for a better definition of each problem, an understanding of underlying mechanisms, and ultimately a means of prevention. The program deals with the specific physiological problems that have either been encountered in previous US and USSR manned spaceflight or are anticipated to occur as spaceflights become longer, traverse more distant trajectories or are otherwise different from previous missions. Currently, emphasis is placed on motion sickness and cardiovascular problems because of their potentially adverse impact on short duration Space Shuttle missions. Musculoskeletal research is undertaken because of the very important fundamental knowledge that must be acquired before countermeasures to the effects of repetitive or long-term flight can be devised. Increased concern for the radiation hazard has resulted in more attention being focused on the biological effects of high energy, high mass number particulate radiation and upon radiation protection. Major future thrusts must deal with the psychological challenges of spaceflight and in particular with the need to enhance human performance in all categories of inflight activity. Although the foregoing research is, by definition, ground based, it is important to note that through it are developed hypotheses that must ultimately be tested in space. The program is intimately related to the ongoing series of inflight experiments on the Shuttle and Spacelab.

(From NASA Space Science and Applications Notice, October 25, 1982)

Paul C. Rambaut
Program Manager

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CARDIOVASCULAR DECONDITIONING RTOP 199-20-12
H. Sandler, manager

Cardiovascular deconditioning has been a regular feature during and after all manned spaceflights to date. Findings consist of a loss of normal response to exercise and orthostatic provocative tests. Changes have become of clinical significance due to the occurance of presyncopal and syncopal responses immediately postflight. Significant changes have occurred both in the US and USSR programs after as little as six hours of flight, and have persisted despite the use of heavy exercise and fluid-loading countermeasures immediately prior to reentry. Loses in postflight exercise capacity have ranged from 10% to 50%, and heart size decreases 8% to 50% have been observed. Exact causes for these changes remain unclear and a topic for study using both human and animal subjects. Detailed physiological effects during reentry of the Space Shuttle remain unknown. Sustained head-to-foot (+Gz) acceleration experienced by astronauts sitting erect lasts 18 to 20 minutes, and is unique to the Shuttle.

Losses of intravascular volume, changes in control by the central and/or peripheral nervous system, and losses in ventricular muscle mass influence cardiovascular deconditioning, as deduced from both studies on Earth and results from flight. Following hypokinesia on Earth, rhesus monkeys (Macaca mulatta) lost heart muscle and registered reduced orthostatic tolerance (susceptibility to fainting). Involvement of the nervous system in control of cardiovascular functions appear to cause a 50% reduction in effectiveness of vasoactive drugs in the immobilized monkey. Astronauts and cosmonauts were not studied in this regard.

In addition to studies of horizontal immobilization on the rhesus monkey, immersion of animals and humans up to the neck in a bath of warm water also simulate some of the effects of weightlessness. Investigators use a tilt table following immersion to test for orthostatic tolerance as a sign of cardiovascular deconditioning.

Because actual results from flight are the final validation of hypotheses from ground experiments, miniature, implantable bioinstruments were developed and tested to record blood flow and pressure in a small rhesus monkey in preparation for flight on a five-day Cosmos mission. This engineering test flight, the first in the Cosmos series with a nonhuman primate, was the fourth unmanned flight of animals in a cooperative program with Soviet scientists.

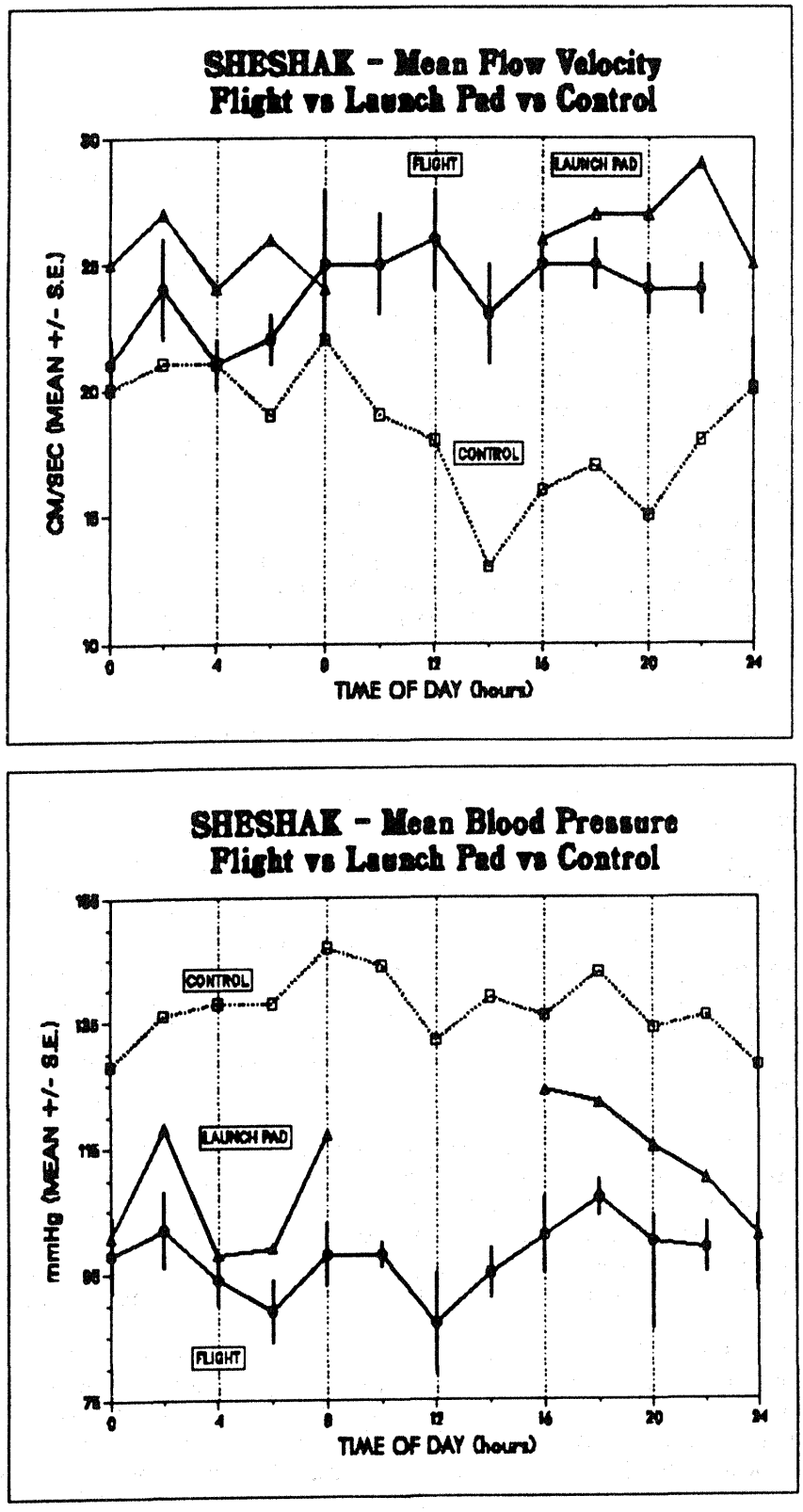

Fig. 8. Blood velocity (top) and pressure (bottom) were recorded in a small rhesus monkey during the joint US-USSR Cosmos 1514 flight in December 1983. (Sandler 199-20-12-03)

Cardiovascular Response to Simulated Spaceflight Stresses 199-20-12-03

H. Sandler, Biomedical Research Division, Ames Research Center
B. Benjamin and B. Halpryn, National Research Council Associates, Ames Research Center

Reactions to simulated weightlessness in animals on Earth were studied to understand the cardiovascular changes observed in humans during spaceflight. After one to four weeks of chronic restraint, blood pressure in rhesus monkeys (Macaca mulatta) responded less to the vasoconstrictive drugs norepinephrine and phenylephrine. These drug reactions were the first indications for involvement of central nervous system control in the deconditioning process because response to sodium nitroprusside, a drug directly acting on the blood vessel musculature, showed no evidence of change.

Cardiovascular measurements from one small rhesus monkey were recorded during Cosmos 1514, a joint US-USSR biosatellite flight test from December 14-19, 1983. Analysis of the data from an implanted cuff around the carotid artery confirmed an increase in blood velocity to the head during the duration of spaceflight, as well as slightly lower blood pressure and peripheral resistance in the vessels supplying blood to the head (Fig. 8). Preliminary science reports of these findings were prepared and presented to our co-investigators in the Soviet Union maintaining the cooperative status between the two countries in life sciences research.

Reduced left ventricular volume also results from spaceflight. To further research in this area the Cardiovascular Research Program also funded the research of S.A. Glantz at the University of California School of Medicine in San Francisco to describe the left ventricle's dynamic geometry with enhanced accuracy. Tantalum screws were implanted evenly around the ventricular cavity in canines to allow investigators to make exact measurements of dimension and shape. X-ray cineradiographs were taken of heart action for computational measures, and dissection allowed validation of computed volumes by comparison to actual left ventricular volumes.

Research into the physiological methods used by the body to increase or decrease heart muscle was initiated under NASA's Minority Grant Program through Howard University in Washington, D.C. The increase of heart muscle during hypertension was studied by comparing canines with renal artery constriction and ones with single kidney hypertension. Results suggest that an

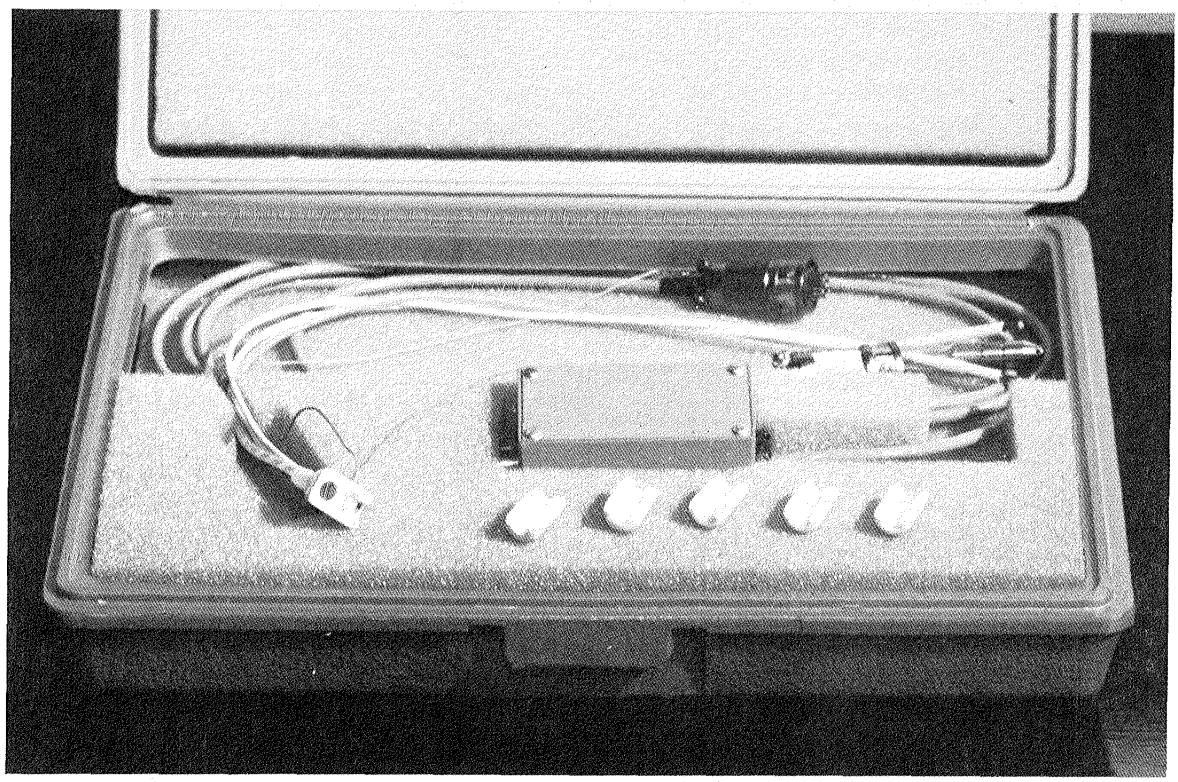

Fig. 9. Strain gauge transducer with Doppler flow crystals used on Cosmos 1514 to measure blood flow and pressure in a rhesus monkey. (Hines 199-20-12-07)

increase in myocardial contractility is necessary for the development of left ventricular hypertrophy.

To learn more about nervous system control of the circulation a Summer Research Conference on Central Neural Mechanisms in Cardiovascular Regulation, sponsored by the Federation of American Societies for Experimental Biology (FASEB) was also supported under this task.

Publications: (1) Convertino, V.A., D.J. Goldwater and H. Sandler. 1984. "Oxygen uptake kinetics of constant-load work: Upright vs. supine exercise." AVIATION, SPACE AND ENVIRONMENTAL MEDICINE 55: 501-506. (2) Ghista, D.N., G. Ray and H. Sandler. 1983. "Mechanocardiography: Theory, evaluation and significance of the regional distributions of myocardian constitutive properties and blood pressure in the left ventricular chamber." In Advances in Cardiovascular Physics, Vol. 5, Part 3: Diagnosis. Basel: S. Karger. pp. 59-83. (3) Hawthorne, E.W. and E.I. Franklin. Neurohumoral and mechanical factors in the modulation of left ventricular mass. (Progress report to NASA-Ames Research Center. Grant no. NAG 2-250). Washington, D.C.: Howard University; 1984 July 11. (4) Lewis, J.F., E.I. Franklin, C.L. Curry, and E.W. Hawthorne. The use of left ventricular mass determination in evaluating the effectiveness of antihypertensive therapy. Abstract presented to 38th annual fall conference of the Council for High Blood Pressure Research. Cleveland; 1984 October 10-12. (5) Walley, K.R., M. Grover, G.L. Raff, J.W. Benge, B. Hannaford, and S.A. Glantz. 1982. "Left ventricular dynamic geometry in the intact and open chest dog." CIRCULATION RESEARCH 50: 573-589. (6) Sandler, H., G.D. Meier and E.L. Alderman. 1984. "Ballistic motion of the heart." In Ventricular Wall Motion. Sigwart, U. and Heintzen, P.H., eds. New York: Verlag. pp. 1-13. Sandler, H., H.L. Stone, J.W. Hines, B. Benjamin, and B. Halpryn. Final science report for Cosmos 1514 primate cardiovascular experiment. NASA-Ames Research Center; 1984 August 27.

Biotelemetry Systems for Cardiovascular Flight Experiments 199-20-12-07

J.W. Hines, U.S. Air Force, Ames Research Center
H. Sandler, Ames Technical Monitor

Combined pressure and flow (CPF) cuffs (Fig. 9) were developed under this task and successfully flown on the joint US-USSR biosatellite, Cosmos 1514, during December 1983. The CPF cuff was designed for

implantation around the carotid artery in the neck of a small (3-4 kg) rhesus monkey (Macaca mulatta). Both the American and Soviet research groups implanted a total of 65 rhesus during development studies to refine transducer design, surgical procedures and data analysis techniques. In November 1983, US investigators assisted during a bioengineering simulation in the USSR, resulting in the decision by Soviet investigators to fly a rhesus nicknamed Bion in the Cosmos (a modified Vostok space ship) in December. Another animal, Abrek, served as a synchronous control on the ground. Data were collected for one day on the launch pad, for five minutes every two hours in orbit, and during one postflight test. The flight animal died 69 hours after landing due to a strangulated bowel, possibly a congenital defect, which was not attributable to the instrumentation. Data were transferred from Soviet to American recorders in February 1984.

Because tissue growth around the CPF cuff over the three-week period from pre- to postflight could cause discrepancies in gain and offset measurements from the pressure cell, the protocol included calibrations before and after the flight. Also, the pressure- sensing cells in the CPF cuff underwent a six-month performance test in vitro prior to implantation. Because of drift in baseline measures from the pressure cell, the actual intravascular pressure was measured invasively for calibration. This technique compared measures from needle puncture of the left femoral artery to pressure from the CPF cuff. Twenty days transpired from the time of this direct calibration technique to the end of the flight. Previously, data from the CPF cuff had not shown serious changes over this length of time. The first engineering test flight in space of the hardware was successfully completed and this task was terminated.

Publications: Sandler, H., H.L. Stone, J.W. Hines, B. Benjamin, and B. Halpryn. Final science report for Cosmos 1514 primate cardiovascular experiment. NASA-Ames Research Center; 1984 August 27.

Central and Peripheral Mechanisms Modulating Cardiovascular Deconditioning in Unanesthetized Primates 199-20-12-11

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H. Sandler, Ames Technical Monitor

A study in seven rhesus monkeys (Macaca mulatta) was performed to determine the effect of blood volume expansion on the cardiovascular response to carotid sinus hypotension. Specifically, the effect of carotid sinus hypotension on the ability of the autonomic

nervous system to alter total peripheral resistance (TPR) was examined. Bilateral carotid occlusion (BCO) was used to cause carotid sinus hypotension before and after a 25% blood volume expansion with dextran, a water soluble sugar. The BCO elicited significant increases in heart rate (HR, 28±5 bpm), mean arterial pressure (MAP, 54±9 mmHg) and TPR (0.08±0.003 mmHg/ml/min) coupled with a significant reduction in mean aortic flow (AOF, -246±57 ml/min). Volume expansion significantly attenuated the HR (14±6 bpm), MAP (30±5 mmHg) and TPR (0.04±0.008 mmHg/ml/min) response to carotid sinus hypotension. The change in AOF elicited by BCO was not significantly different between the control and volume expanded conditions. These data indicate that plasma volume expansion significantly attenuates the baroreceptor reflex control of the circulation with the greatest inhibition noted for the peripheral resistance component of the response.

Publications: Dickey, D.T., G.E. Billman, M.J. Keyl, H. Sandler, and H.L. Stone. Responses to bilateral carotid occlusion with volume loading in the Rhesus monkey. FASEB 43(4): 895, 1984.

Mechanisms of Circulatory Regulation with Volume Loading and Depletion in Conscious Animals
199-20-12-20

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H. Sandler, Ames Technical Monitor

Expansion, or loading, of plasma volume was hypothesized to occur in the upper body during the early period of weightlessness in space, and during headdown tilt and lower body positive pressure on Earth. Volume loading was stimulated in the unanesthetized baboon (Papio anubis), whose larger size permitted instrumentation with existing transducers. The diuresis and natriuresis accompanying volume expansion was associated with increased renal blood flow and decreased renal vascular resistance. These changes did not occur in conscious animals. Studies of conscious dogs also demonstrated that cardiopulmonary reflexes did stimulate afferents of the vagus nerve to the brain, helping to mediate water excretion. But cardiopulmonary reflexes neither mediated dilation of the renal vessels, nor enhanced sodium excretion in acute volume loading.

Publications: Zimpfer, M., W.T. Manders, A.C. Barger, and S.F. Vatner. 1983. "Pentobarbital alters compensatory neural and humoral mechanisms in response to hemorrhage." AMERICAN JOURNAL OF PHYSIOLOGY 243: H713-H721.

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NEUROPHYSIOLOGY RTOP 199-20-22
N.G. Daunton, manager

The limited room for movement, including head movement, by astronauts in the first generation space capsules may explain why space sickness was uncommon during the first decade of spaceflight. Since then nearly half of all space travelers experienced space motion sickness during the initial three to five days of weightlessness. During this period, half the duration of a typical Shuttle mission, many astronauts experienced malaise, nausea, or vomiting, although mission performance was maintained.

Investigators conducting basic research at LR study the neural connections and biochemistry of the vestibular system (the organs of the inner ear), which supplies the sense of balance and orientation for all higher animals, including amphibians, birds, fishes, and mammals. The end organs of the vestibular system sense changes in speed and direction during head movements. One part of the vestibular organs, the otolith organs, senses linear acceleration and gravity; the other part, the semicircular canals, senses angular acceleration, such as rotating the head. Unlike the otolith organs, the semicircular canals do not depend on gravity, although recent evidence suggests that the neural output of the canals is influenced by output from the otolith organs. In the weightlessness of space, the brain must adapt to changes in the function of the vestibular system by greater reliance on cues from other senses, such as the eyes and neck muscles.

Human subjects have participated in behavioral tests, involving linear acceleration, both before and after joint flight experiments by NASA and the European Space Agency (ESA) on Shuttle-Spacelab 1. Animals have been used in behavioral, neuroanatomical, and neurochemical experiments on Earth. Using fragile microelectrodes and chemical stains, neuroanatomical researchers traced previously unknown pathways between various vestibular end organs and the brain. Other LR researchers suggested that a neurochemical factor in the cerebrospinal fluid may trigger motion sickness because symptoms were prevented by blocking the flow of cerebrospinal fluid to a vomiting trigger zone in the brain.

The establishment of the Vestibular Research Facility (VRF) at Ames Research Center will provide investigators with specialized equipment and controlled experimental conditions to record eye movements and electrophysiological signals in a variety of species under many different conditions of visual and vestibular stimulation. NASA will provide engineering support and scientific coordination

through a VRF Science Director, and will provide access for qualified investigators from the scientific community to conduct vestibular experiments. Experience with the ground-based VRF will aid in the disign of critical spaceflight experiments to clarify the role of gravity in vestibular function.

The Anatomy and Physiology of the Vestibular System
199-20-22-03

W.R. Mehler, Biomedical Research Division, Ames Research Center

Studies of the connectivity of the emetic trigger zones in the brain continued using a new wheat germ agglutinin-horseradish peroxidase WGA-HRP method. Micro-injections of this enzyme into the parabrachial nuclei (pB) showed that cells in this region of the brainstem have reciprocal connections with the central nucleus of the amygdala and certain hypothalamic nuclei in the forebrain. (Vomiting has been elicited from electrical stimulation of the amygdala, but not from stimulation of the hypothalamus). These same experiments also showed that the pB region receives, and relays not only ascending nerve impulses from taste cells of the solitary nucleus in the lower brainstem, but also has connections originating from other types of visceral sensory relay cells in the solitary nucleus that help regulate other bodily systems (cardiovascular, gastrointestinal, etc.). The lateral pB nucleus, which projects chiefly to the amygdala, was found to be the selective target of nerve cell projections from the area postrema, the chemo-vomiting trigger zone. The distribution of vestibular nuclei projections to the thalamus was also determined, and a preliminary report was presented to the American Association of Anatomists.

Immunocytochemical methods were employed for the detection of glial fibrillary acidic protein (GFAP) in the area postrema of the cat For the first time evidence was found of a strong and abundant immunoreactivity to GFAP in both the ependymal cells and related neuroglial components of the area postrema of the cat, as opposed to its absence in the rest of the ventricular mural ependyma (the membrane lining of the cerebral ventricles). On the basis of these findings, the functions of the area postrema ependyma may be associated with the specialized (emetic) receptor role attributed to the ventricular surface and glial cells of the area postrema.

Publications: Mehler, W.R. 1983. "Observations on the connectivity of the parvicellular reticular formation with respect to a vomiting center." BRAIN, BEHAVIOR AND EVOLUTION 23:63-80.

Physiology of the Vestibular System in the Squirrel Monkey 199-20-22-04

J.M. Goldberg, Department of Pharmacological and Physiological Sciences, University of Chicago
N.G. Daunton, Ames Technical Monitor

Work continued on three lines of research. First, in the chinchilla (Chinchilla laniger), the peripheral innervation patterns of vestibular-nerve afferents were studied in relation to the sizes of their parent axons and to the locations of their terminations in the sensory epithelium. Nerve structure was revealed using extracellular injections of horseradish peroxidase (Fig. 10). Second, work continued on an intracellular study of secondary neurons in the vestibular nuclei of the anesthetized, paralyzed squirrel monkey (Saimiri sciureus). Intrasomatic recordings were used to characterize the vestibular-nerve inputs received by secondary neurons in and around the superior vestibular nucleus. Neurons were traced in the brain by electrical (antidromic) activation to the flocculus (FI), ascending in the medial longitudinal fasciculus, and either innervating the oculomotor nuclei or descending to the spinal cord. The three sets of neurons differ in the kinds of inputs that they receive (regular, irregular, or both) from the same, or from opposite sides of the body. Third, a combined behavioral and electrophysiological study was started to estimate the relative importance of the convection of heat in causing involuntary rapid eye movement (nystagmus) in the monkey. This last study was motivated by the findings of what was thought to be a caloric response during orbital flight in Spacelab 1, even though thermal convection cannot occur in weightlessness.

Publications: Goldberg, J.M., C.E. Smith, and C. Fernandez. 1984. "Relation between discharge regularity and responses to externally applied galvanic currents in vestibular nerve afferents of the squirrel monkey." JOURNAL OF NEUROPHYSIOLOGY 51(6): 1236-1256.

Functional Significance of Sensory Interactions in Self Motion Perception and Motion Sickness 199-20-22-05

N.G. Daunton, Biomedical Research Division, Ames Research Center

Both neurophysiological and behavioral studies suggest that motion sickness is greatest during conditions of sensory conflict, when postural control is maximally disrupted. Studies of single neurons in the vestibular nuclei (VN) showed that the gain of VN neurons

Fig. 10. Photomicrograph of a calyx-only afferent entering the utricular macula to innervate a few, most likely two, adjacent Type I hair cells in the anterior part of the striola. The afferent was marked by an extracellular injection of horseradish peroxidase into the vestibular nerve central to Scarpa's ganglion. 1600X. (Goldberg 199-20-22-04)

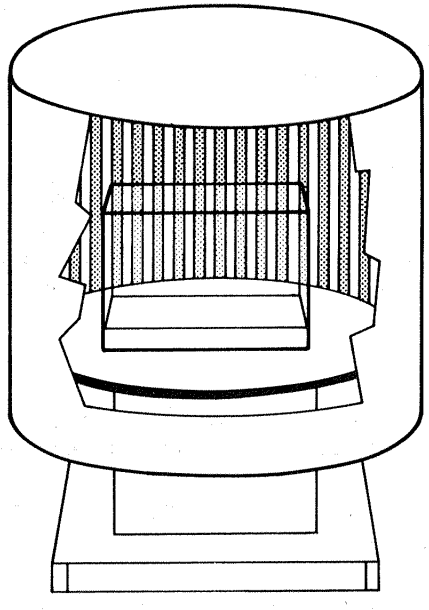

Fig. 11. Rate table with optokinetic surround used in studies with cats and squirrel monkeys to produce passive motion by rotating the turntable and cage, or visual motion by rotating the striped drum around the animal. (Daunton 199-20-22-05

is suppressed when their visual and vestibular inputs are in conflict, suggesting a neuro- physiological basis for disruption of postural control. Reports in the literature also show that this suppression of unit gain is reflected in the EMG response of leg muscles under similar conflicting visual-vestibular inputs.

In further studies of the role of vision in motion sickness, motion sickness was elicited in both cats and squirrel monkeys (Saimiri sciureus) by visual stimulation alone. Generally in squirrel monkeys, as in humans, those individuals that are highly susceptible to motion sickness induced by passive motion are also most likely to be susceptible to visual stimulation alone (Fig. 11).

In a continuation of comparative studies of the neural mechanisms underlying motion sickness, it was shown in the cat that emesis induced by motion does not require a functional area postrema, although emesis induced by the emetic drug Xylazine does require the area postrema. This result was surprising, because it is known that, in the dog, neither drug- nor motion-induced emesis can be induced without an intact area postrema (AP). In the cat, conditioned taste aversions (CTA) to motion, which possibly indicate nausea, were not eliminated by the removal of the area postrema, but CTA to the emetic drug Xylazine were eliminated by these AP lesions. Similar studies of CTA in the rat yielded similar results. However, in the rat, vagotomy (transection of the vagus nerve) was shown to eliminate CTA to motion. These studies were conducted in collaboration with K.R. Brizzee at the Delta Primate Research Center in Louisiana and R.A. Fox at San Jose State University in California.

Publications: Fox, R.A., A. Lauber, N. Daunton, M. Phillips, and L. Diaz. 1984. "Off-vertical rotation produces conditioned taste aversion and suppressed drinking in mice." AVIATION, SPACE AND ENVIRONMENTAL MEDICINE 55: 632-635.

Habituation to Novel Visual Vestibular Environments with Particular Reference to Spaceflight 199-20-22-09

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N.G. Daunton, Ames Technical Monitor

Ocular torsion is the counterrolling of the eyes in

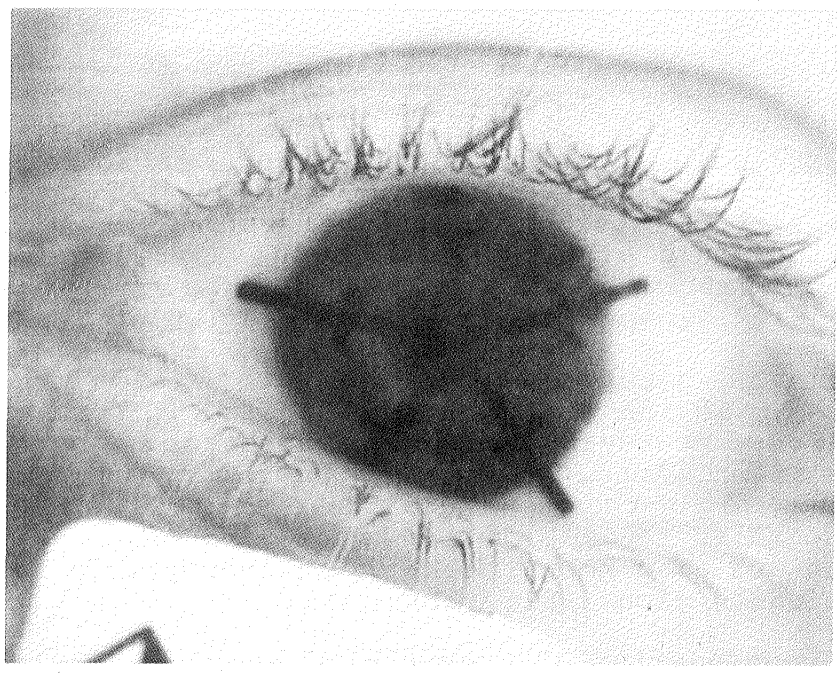

Fig. 12. Ocular torsion, or rotation of the eye in response to motion stimuli, was recorded using a video camera and specially-marked contact lens. During experiments on Earth and on Spacelab 1, subjects stared into a rotating dome, which produced a wide-field display that rotated around their sagittal axis. (Young 199-20-22-09

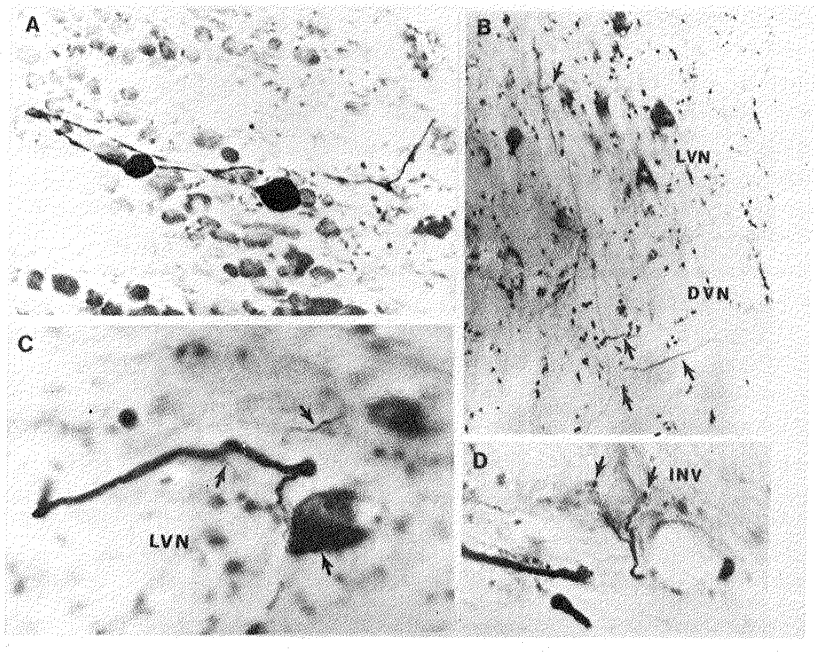

Fig. 13. Intracellular labeling of primary vestibular otolith afferents using the enzyme horseradish peroxidase revealed: (A) two labeled ganglion cells indicating cell body size variations and differences in axonal diameters (i.e., central processes to the left are thicker); (B) descending branch of a single otolith afferent with secondary branches projecting into the lateral vestibular nucleus (LVN) and the descending vestibular nucleus (DVN); (C) termination of otolith afferent fibers onto a second-order neuron in LVN arborization of parent axon at arrows; and (D) synaptic bouton terminals of otolith afferent within the interstitial nucleus of the vestibular nerve. (Perachio, p. 45, 199-20-22-15)

response to bodily tilt or perceived tilt. Progress towards the automatic processing of ocular torsion data proceeded along two avenues: automated computer analysis of video data, and measurement of torsion using magnetic search coils embedded between soft contact lenses. An ocular torsion analysis program was written which calculates torsion angles from digitized video images (Fig. 12). The system, although slow, is operational. Horizontal and vertical eye movements were successfully measured with soft lenses, which adhere firmly to the eye for periods in excess of 90 minutes by spraying with distilled water. Further measurement of ocular torsion is under investigation. Present work is centered on reducing the noise levels in the magnetic coils to permit meaningful measurements.

Results from Spacelab 1 experiments appeared to support the hypothesis that the balance organs of the inner ear do not provide head pitch or roll angle in weightlessness, requiring a readaptation in the body's sense of balance in space. There may be an increased reliance on vision for orientation.

Publications: Young, L.R., C.M. Oman, D.G.D. Watt, K.E. Money, and B.K. Lichtenberg. 1984. "Spatial orientation in weightlessness and readaptation to Earth's gravity." SCIENCE 225(4658): 205-208.

Histochemical Characterization of the CNS Emetic Apparatus 199-20-22-11

K.R. Brizzee, Delta Regional Primate Research Center,
Tulane University, Covington, LA
W.R. Mehler, Ames Technical Monitor

In studies evaluating the effectiveness of anti-motion sickness drugs in the squirrel monkey (Saimiri sciureus) the antiemetic drug astemizole, administered daily for two weeks, was ineffective in preventing motion-induced emesis. However, the antiemetic drug l-sulpiride was effective in preventing motion sickness in the squirrel monkey. This information has been provided to the NASA's Life Sciences Flight Experiments Program in response to their request for information on antiemetics for use with the Spacelab 3 squirrel monkeys.

The role of the otolith organs in motion sickness induced by rotation is being investigated in collaboration with M. Igarashi of the Baylor College of Medicine in Houston. Thus far, utriculosacculectomies

(ablation of the otolith organs, the utricle and saccule, with the semicircular canals left intact) in three squirrel monkeys prevented rotation-induced emesis. These preliminary results suggest that the otolith organs may play a major role in the etiology of motion sickness resulting from rotation.

Significant increases in radioactive 2-deoxyglucose uptake were observed in autoradiographs from tissue of animals exposed to motion, but not from tissue of control animals. The increased activity was noted in all vestibular nuclei, nucleus prepositus, and in the nodulus, uvula and lingula of the cerebellum.

Vestbulocollic Reflexes of Otolith Origin
199-20-22-14

V.J. Wilson, Rockefeller University, New York
N.G. Daunton, Ames Technical Monitor

Earlier work showed that neurons in the lateral vestibular nucleus of the cat respond to a preferred direction of tilt (polarization vector). Recent experiments showed that the direction of this vector is independent of tilting frequency. An algorithm was developed to model the neural networks that may produce the response of vestibular nucleus neurons. One typical response may be produced by parallel excitatory and (high-pass-filtered) inhibitory limbs. The inhibitory limb could be in the cerebellum.

Spinal interneurons were found to have particular response vectors during neck rotation and whole body tilt. Some of these cells, which code neck and whole body position, are proprio-spinal neurons. Such neurons are one point of intersection of neck and vestibular inputs, and seem to be important components of tonic neck and vestibulospinal reflex pathways.

Control of vomiting was studied by examining the neural control of abdominal muscles, which are important in producing this behavior. Many respiratory neurons project to the lumbar cord, and some branch in the area of the motor nuclei. Their connections with abdominal muscle motoneurons, however, are mainly indirect.

Publications: (1) Ezure, K. and V.J. Wilson. 1984. "Interaction of tonic neck and vestibular reflexes in the forelimb of the decerebrate cat." EXPERIMENTAL BRAIN RESEARCH 54: 289-292. (2) Wilson, V.J., K. Ezure and S.J.B. Timerick. 1984. "Tonic neck reflex of the decerebrate cat: Response of spinal interneurons to natural stimulation of neck and vestibular receptors." JOURNAL OF NEUROPHYSIOLOGY 51(3): 567-577.

Central Otolith Mechanisms in the Squirrel Monkey
199-20-22-15

A.A. Perachio, Department of Otolaryngology, University of Texas Medical Branch, Galveston
N.G. Daunton, Ames Technical Monitor

The neuroanatomical projections and terminations of the vestibular primary afferents innervating the saccular maccula were stained with injections of horseradish peroxidase (HRP), and axons of these primary afferents were traced into (1) the interstitial nucleus of the vestibular nerve, (2) the central portion of the lateral vestibular nucleus, (3) the descending and medial vestibular nuclei (particularly the caudal portion), (4) the accessory or lateral cuneate nucleus, (5) cell group Y, and (6) into the cortex of the nodulus of the cerebellum. No terminals were observed in the floccular cerebellar cortex (Fig. 13). Labeling individual primary afferents with HRP also allowed an analysis of the relationship between cell body size and the types of information which the cell transmits. Regularly firing afferents were significantly smaller than those that discharged irregularly. In studies of vestibular compensation (adaptation after unilateral loss of vestibular function), the spontaneous activity of neurons in the medial vestibular nucleus reverted to an uncompensated level of activity when the spinal cord was transected. These findings may be relevant to the understanding of vestibular compensation and adaptation to altered gravity environments.

Physiology of Cat Vestibular System Efferent Neurons
199-20-22-20

D.L. Tomko, Department of Physiology, University of Pittsburgh Medical School
N.G. Daunton, Ames Technical Monitor

The investigator continued to develop and refine procedures for producing yaw (left-right rotational) sinusoidal head movements from awake cats, who could freely move their heads. Using water as a reward, each cat tracked a servo-driven, sinusoidally-oscillating drinking tube. A rotary potentiometer attached to the head monitored movement. Hardware was also implemented to record eye movements of cats using silver/silver chloride electrodes, and computer software was developed to analyze the data.

An addition was made to the vestibulo-ocular reflex (VOR) experiment to include a vertical (VVOR) axis. When an animal is pitched while lying on his side (i.e., not changing the position of the head with respect to

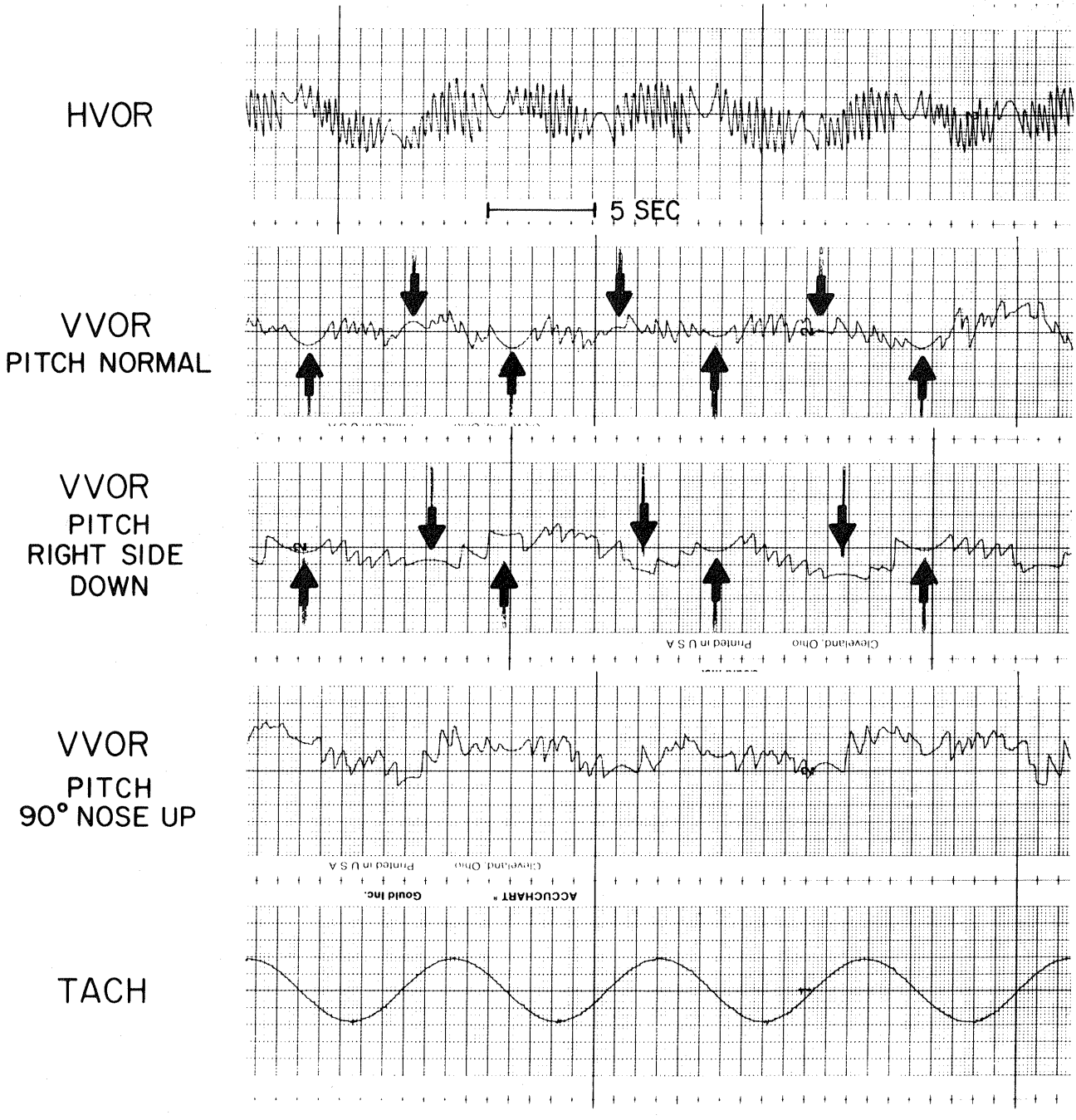

Fig. 14. The vertical vestibulo-ocular reflex (VVOR) of the cat is illustrated under two conditions: VVOR pitch normal (VVOR-N) and VVOR pitch right-side down (VVOR-RSD). The VVOR-N plot shows eye position changes in response to 0.5 Hz turntable oscillations, which pitched the cat in his normal position. The VVOR-RSD plot shows eye position changes in response to pitch delivered while the animal lay on his right side. Note that in the VVOR-N plot, the dark arrows which mark the eye position turn-around are evenly spaced, whereas in the VVOR-RSD graph they are unevenly spaced (asymmetric). The only difference between the two conditions is that when the cat is lying on his side, pitching does not change the position of his head with respect to gravity. The vertical VOR system may need gravity input to function normally. (Tomko 199-20-22-20)

gravity), the VVOR is asymmetric, and has a lower gain than the horizontal VOR; in marked contrast, when the animal is pitched normally (i.e., with the head changing position with respect to gravity), the VVOR is symmetric and has a higher gain, indicating that gravity plays an important role along with the vertical canals in controlling the VVOR (Fig. 14).

The addition of a postdoctoral fellow, F.R. Robinson, in the laboratory staff enabled an expansion of this work to include recordings of the inferior olivary nucleus, a major source of inputs to the cerebellar nodulus and uvula. Cells in this structure responded to yaw rotational accelerations in cats. Although the uvula and nodulus have been shown by others to be related to motion sickness susceptibility in animals, the neurophysiological properties of their cells and their inputs have not yet been characterized.

Publications: (1) Peterka, R.J. and D.L. Tomko. 1984. "Differences between cats in response properties of horizontal canal primary afferents." EXPERIMENTAL BRAIN RESEARCH 56: 162-166. (2) Schor, R.H., A.D. Miller and D.L. Tomko. 1984. "Responses to head tilt in cat central vestibular neurons. I. Direction of maximum sensitivity." JOURNAL OF NEUROPHYSIOLOGY 51(1): 136-146.

Vestibular System and Neural Correlates of Motion Sickness
199-20-22-21

A.D. Miller, Rockefeller University, New York
N.G. Daunton, Ames Technical Monitor

Investigations continued of the brainstem control of the muscles (abdominals and diaphragm) that produce vomiting, which is the most reliable symptom of motion sickness in animals. A long term goal is to study the input to the brainstem areas that produce vomiting during motion sickness. Brainstem respiratory neurons that project to the lumbar portion of the spinal cord are likely to affect the activity of abdominal muscles, while other major respiratory muscles are supplied from higher portions of the spinal cord. The contribution of various brainstem respiratory neurons to the lumbar projection was tested in cats using antidromic electrical activation from the lumbar cord. Possible monosynaptic connections between descending neurons and abdominal motoneurons were then tested by cross-correlation between the firing of these neurons and abdominal nerve activity. Although expiratory neurons in the caudal ventral respiratory group have a large projection to the lumbar cord, few monosynaptic connections exist between these neurons and abdominal motoneurons. (Fig. 15).

Publications: Miller, A.D. and V.J. Wilson. 1983. "Vestibular-induced vomiting after vestibulocerebellar lesions." BRAIN, BEHAVIOR AND EVOLUTION 23: 26-31.

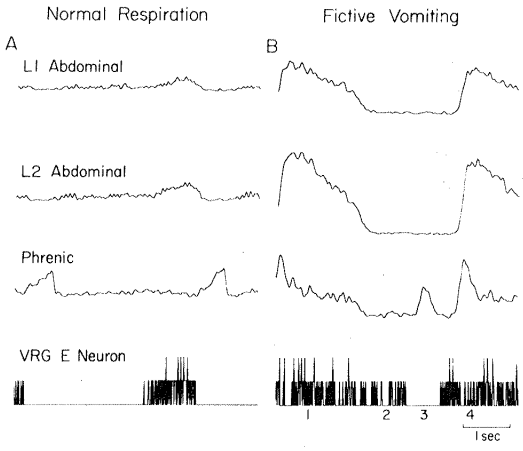

Fig. 15. Activity of brainstem respiratory spinal neuron during respiration (A) and fictive vomiting (B) in a cat. An expiratory neuron recorded from the ventral respiratory group fires in phase with abdominal nerve activity during respiration. These neurons are known to be inhibited during inspiratory phrenic nerve activity. During fictive vomiting (elicited by the emetic agent xylazine), the neuron fires in phase with co-active abdominal and phrenic nerves. Thus, this neuron exhibits the appropriate behavior to control abdominal muscle activity during both respiration and vomiting. (Miller, p. 47, 199-20-22-21)

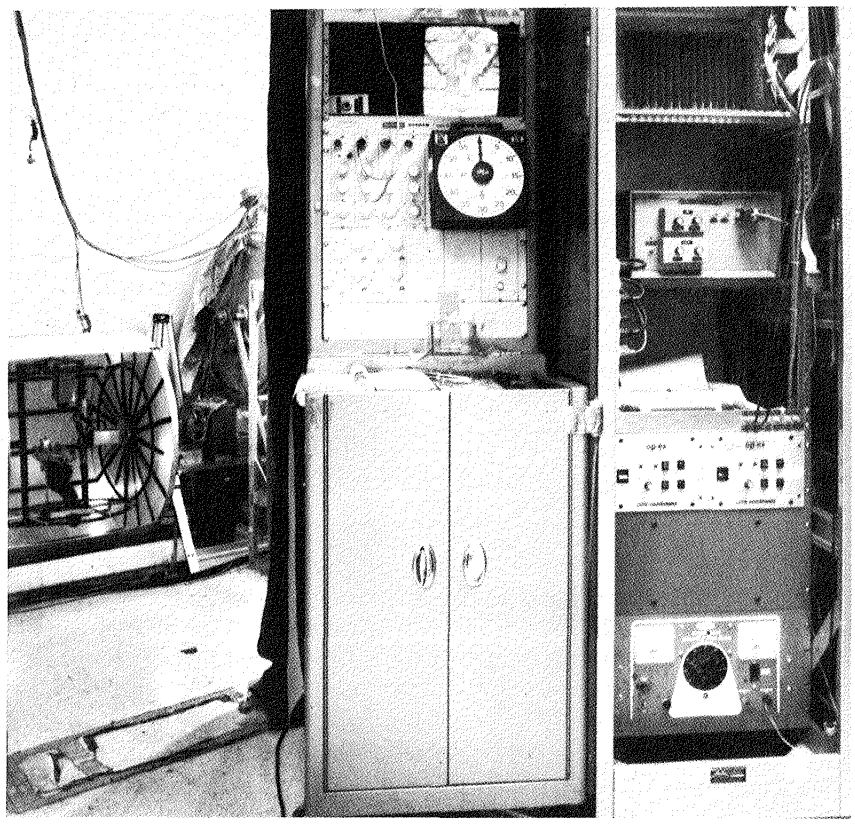

Fig. 16. From left, the pitch conflict device for the squirrel monkey (turntable plus optokinetic drum), monitor and polygraph recorder, and microprocessor to operate the device. (Igarashi, p. 50, 199-20-22-26)

Investigations of Vestibular Response Dynamics Using the Vestibular Research Facility 199-20-22-22

M.J. Correia, Departments of Otolaryngology and Physiology and Biophysics, University of Texas Medical Branch, Galveston
N.G. Daunton, Ames Technical Monitor

Two experiments were conducted at the Vestibular Research Facility (VRF) at Ames Research Center. Experiments were conducted to test: (1) the hardware and software elements of the VRF with a gerbil in vivo, and (2) the null hypothesis that tilt-sensitive canal afferents do not respond in a systematic way to increasing levels of G-force produced by centrifugation. Extracellular single neuron recordings can be made from a rodent on-board the VRF centrifuge during different levels of centrifugation, and the recordings can be analyzed and reduced on-line in quasi real-time. However, a larger number of neurons must be sampled to draw conclusions regarding the null nypothesis. This work provided the VRF research team (resident and visiting staff) with experience in obtaining, recording, and analyzing extracellular single unit potentials from vestibular primary afferents in the decerebrate cronically-instrumented, gerbil.

Role of Biochemical Factors in Motion Sickness 199-20-22-23

G.H. Crampton, Department of Psychology, Wright State University, Dayton, OH
N.G. Daunton, Ames Technical Monitor

Xylazine (Rompun), a veterinary anesthetic, provokes emesis in cats if administered in sub-anesthetic amounts. An animal's emetic sensitivity to xylazine was correlated with its motion sickness susceptibility. Yohimbine, an antagonist of several effects of xylazine, was evaluated for antagonistic properties against xylazine-induced emesis, and against motion sickness. It was found that pre-treatment with 0.125 mg/kg of yohimbine was moderately effective in blocking xylazine emesis, but only marginally effective in blocking motion sickness, and only in the animals least susceptible to motion sickness. A laboratory apparatus for provoking motion sickness in cats was designed, fabricated and evaluated. This device, modelled after a carnival Ferris Wheel, provides a benign, controlled and effective wave motion that produces a high rate of motion sickness in cats. A new surgical approach for implantation of chronic cannulae in the fourth ventricle of cats was refined. Using this approach cerebrospinal fluid (CSF) can be withdrawn before, during and after motion-induced emesis.

Semicircular Canal and Otolith Interaction Processes
199-20-22-26

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N.G. Daunton, Ames Technical Monitor

In studies of visual-vestibular conflicts in the yaw vs. the pitch plane in the squirrel monkey (Saimiri sciureus), the rate of emesis proved much greater when conflicts occured in pitch (48% of 25 animals vomited) as compared with yaw (9% of 11 animals vomited). In addition, half of the animals, which vomited in response to pitch conflict stimulation, vomited after exposure to the stimulus, rather than during stimulation. These findings indicate that, at least on the first exposure, visual-vestibular conflict in the pitch plane is more stressful than that in the yaw plane. This result agrees with the astronauts' reports that head movements in pitch are more stressful in space than those in yaw.

Adaptation to visual-vestibular conflict in the pitch plane was studied by exposing animals to five conditions of visual-vestibular conflict in pitch (Fig. 16) over 10 consecutive days. Even though the five conditions were different from the initial pitch conflict condition, when the animals were retested for motion sickness under the initial pitch condition, the emetic incidence was reduced to 0% (as compared with 75% on the initial test). When the same animals were tested again after 10 days with no exposure to pitch conflicts to assess retention of the adaptation, 50% of the animals vomited, showing that the adaptation was not retained. These results suggest that susceptibility to sickness induced by pitch conflicts can be reduced by training and that visual-vestibular conflicts in pitch can be used to study the process of adaptation. (This task was transferred to Ames from Johnson Space Center).

Publications: (1) Igarashi, M. 1984. "Vestibular compensation: An overview." ACTA OTOLARYNGOLOGICA Suppl. 406: 78-82. (2) Igarashi, M., H. Isago and T. O-Uchi. 1984. "Comparative morphometry of mammalian otolith organs." ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY Suppl. 122, 93(4 pt. 2): 49-51. (3) Ishikawa, K. and M. Igarashi. 1984. "Effect of diazepam on vestibular compensation in squirrel monkeys." ARCHIVES OF OTO-RHINO-LARYNGOLOGY 240: 49-54.

Spontaneous Vestibular Primary Afferent Discharge 199-20-22-27

M.J. Correia, Departments of Otolaryngology and Physiology and Biophysics, University of Texas, Galveston
N.G. Daunton, Ames Technical Monitor

In studies of the morphological basis of the gravity sensitivity of semicircular canal axons in the 8th Nerve, there is no evidence for collateralization (branching) of single axons to both the utricle and semicircular canals. Thus, it appears unlikely that there are receptor-to-receptor fibers which underlie the effects of gravity on semicircular canal units in the pigeon (Columba livia). (Intra-labyrinthine divergence of axons to the utricle and semicircular canals has been postulated as a possible mechanism for space motion sickness.)

In the anterior semicircular canal of the pigeon 64% of the cup-shaped nerve endings (calyxes) in the neuroepithelium surrounded more than one Type I hair cell (Fig. 17) and the ratio of Type I to Type II hair cells was 65:35 in a sample of 54 hair cells studied by light and transmission electron microscopy. The density of Type I hair cells was found to be greatest, not in the center, but on the peripheral slopes of the crista ampullaris, the area on the inner surface of each semicircular canal duct which contains innervated hair cells responsive to movement of the endolymph. Thus, the synaptic processes in the neuroepithelium of the bird appear to be similar to those of mammals. (This task was tranferred to Ames from Johnson Space Center).

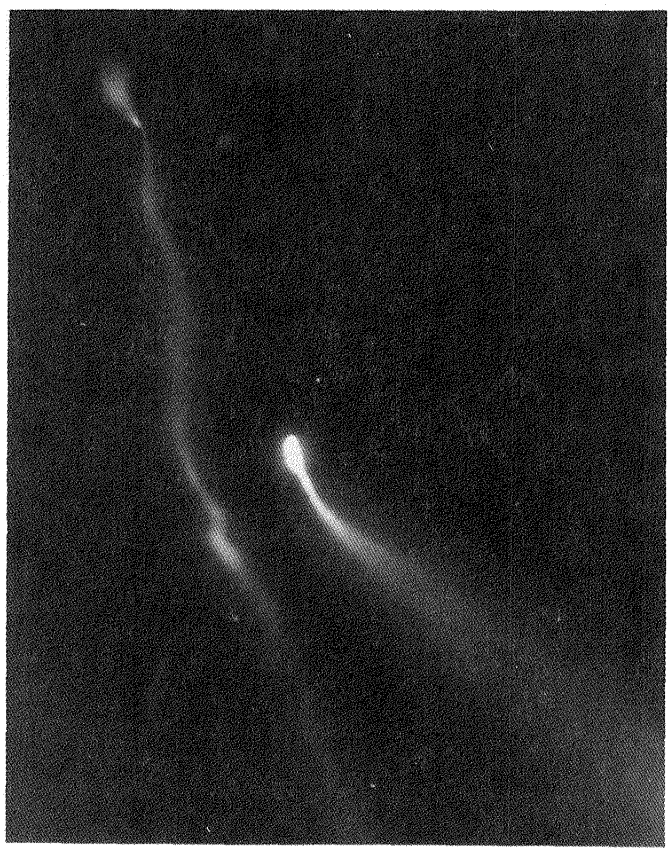
Publications: Correia, M.J., A.R. Eden, K.N. Westlund, and J.D. Coulter. 1983. "A study of some of the ascending and descending vestibular pathways in the pigeon (Columba livia) using anterograde transneuronal autoradiography." BRAIN RESEARCH 278: 53-61.

Identification and Pharmacology of Neurotransmitters in the Vestibular Nuclei 199-20-22-30

J.P. Gallagher, Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston
N.G. Daunton, Ames Technical Monitor

Brain slices of the rostral medulla of the rat were taken to identify neurotransmitters in the vestibular nuclei. Neither acetylcholine, histamine nor adenosine evoked electrical potentials, and thus cannot serve as the excitatory transmitters in the vestibular nuclei. An excitatory amino acid, most likely glutamate or aspartate, is the probable transmitter. If the normal synaptic transmission can be affected by drugs, those drugs may prove useful in the management of the space adaptation syndrome.

Fig. 17. A flourescent photomicrograph showing a multiple calyx hair cell (left) stained by intra-axonal injection of Lucifer yellow. This calyx, containing multiple hair cells, is located within the horizontal semicircular canal crista. A single calyx Type I hair cell (below) stained by intra-axonal injection was also located within the utricular macula. (Correia, p.51 199-20-22-27)



Brain-Gut Interactions in Motion Sickness Anatomical and Physiological Studies 199-20-22-33

R.H.I. Blanks and G.R. Mason, Departments of Anatomy and Surgery, University of California, Irvine
N.G. Daunton, Ames Technical Monitor

In an anatomical study, investigators used horseradish peroxidase to trace and stain neurons that are related to gastro-intestinal (GI) activity during motion sickness. Pre-ganglionic sympathetic neurons, which project via the greater splanchnic nerve to the GI tract, occupy a much larger area in the spinal cord than formerly thought.

Another anatomical study, using radioactive leucine and autoradiography, began to examine the outfolw of the cerebellar fastigial nucleus to identify those trans-cerebellar pathways related to the sympathetic outflow to the gut. Significant fastigial projections to the brainstem nuclei known to be related directly to the parasympathetic system (e.g., dorsal motor nucleus of the vagus, the nucleus tractus solitarius) and indirectly to the sympathetic system (e.g., catecholaminergic A-5 group) were observed. These latter projections provide the anatomical basis for the noted fastigial effects on heart rate, salivation, GI tract, and circulating levels of catecholamines observed with electrical stimulation of the fastigius.

Physiological data related to the changes in intestinal motility during (sickness-inducing) visual-vestibular and visceral afferent stimulation are being collected from chronically-instrumented cats. Sickness-inducing stimulation causes a reduction in amplitude of the basal electrical rhythm (BER) of the intestine, which is similar to the amplitude reduction seen with chemically-induced vomiting in the cat. In addition, there are changes in the frequency of the BER in the mid-ileum segments with the greatest frequency increase during visual-vestibular stimulation. This increased frequency of the BER occurs prior to initiation of the retrograde peristaltic activity in the intestines. If intestinal reflexes play a role in motion sickness, it may be possible to devise an adequate treatment using pharmacologic agents that act on different parts of the gut.

Fig. 18. The Vestibular Research Facility centrifuge is shown. The main centrifuge drive sits atop the cone-shaped structure bolted to the floor. There are two arms on the main drive, each ending in a bracket-shaped yoke. The nearer yoke in the photograph has been completed; it contains two a dditional rotational axes. The specimen under study is contained within the barrel shaped container on the right. (Daunton 199-20-22-35)

Vestibular Research Facility (VRF) Science Program
199-20-22-35

N.G. Daunton, Biomedical Research Division, Ames Research Center

A major step in the development of the VRF scientific program was the selection of a Director for the Facility. Dr. David Tomko was named director and has been brought to Ames on an Intergovernmental Personnel Agreement between NASA and the University of Pittsburgh. He played a major role in the testing of the VRF centrifuge and specimen test container (Fig. 18), in the equipping of the VRF laboratory, and in providing information about the VRF to the scientific community. Plans have been made for use of the VRF centrifuge by the Science Director in studies of the effects of hypergravity on the vertical vestibulo-ocular reflex.

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BONE ALTERATIONS RTOP 199-20-32
D.R. Young, manager

Despite an adequate diet and daily physical exercise, astronauts lost body calcium and bone mass during the Skylab flights of two to three months duration in the early 1970's. Russian cosmonauts lost 3.2% to 7.0% of bone mineral content during flights of six months duration. Typically, weightlessness primarily affected the weight-bearing bones. The pattern of recovery after flight remained poorly defined and weakening of the skeleton continued to be a possible hazard. The consequences of space osteoporosis for passengers and crew members in future, long duration missions and from successive exposures to spaceflight were not determined.

Animals showed similar changes during flight in Soviet Cosmos biosatellites. Dogs lost mineral content in their legs. Three weeks of weightlessness in the young, growing rat arrested growth of the osteoblasts (bone-forming cells) in the leg bones, while bone resorption by osteoclasts continued normally. (Osteoblasts form a contiguous layer, covering the bone matrix; osteoclasts have long projections across the surface of the bone to resorb any exposed matrix). In addition rhesus monkeys immobilized in a semi-reclined position showed a loss of compact bone.

The metabolic data derived from Skylab experiments suggest the possibility that intestinal malabsorption of calcium may be one mechanism contributing to bone mineral loss. The homeostatic mechanisms of the response would include alterations in serum level of two potent bone resorbing factors (1,25-dihydroxyvitamin D and parathyroid hormone), which induce bone loss. Ground-based models of adult-acquired osteoporosis suggest that reversible osteoporsis is associated with increased activation of remodeling, resorption, and bone turnover. Thus, adult-acquired osteoporsis may be prevented by suppressing the number of active remodeling sites.

The need is clear for a responsive experimental model of reversible adult-acquired osteoporosis to elaborate and define alterations of intestinal absorption, and the relationship with bone-remodeling regulatroy factors and calcium homeostasis. Interdisciplinary investigations have been undertaken to develop a nonhuman primate model with bone remodeling functions similar to those observed in humans.

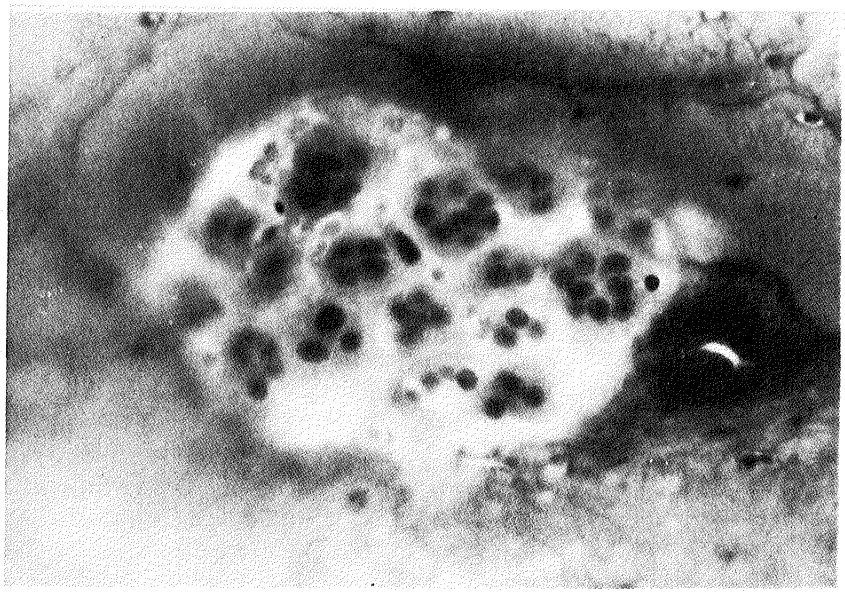

Fig. 19. Cavity in the tibial cortical bone formed by massive recruitment of multi-nucleated osteoclasts after ten weeks of immobilization in the rhesus monkey. (Young 199-20-32-01)

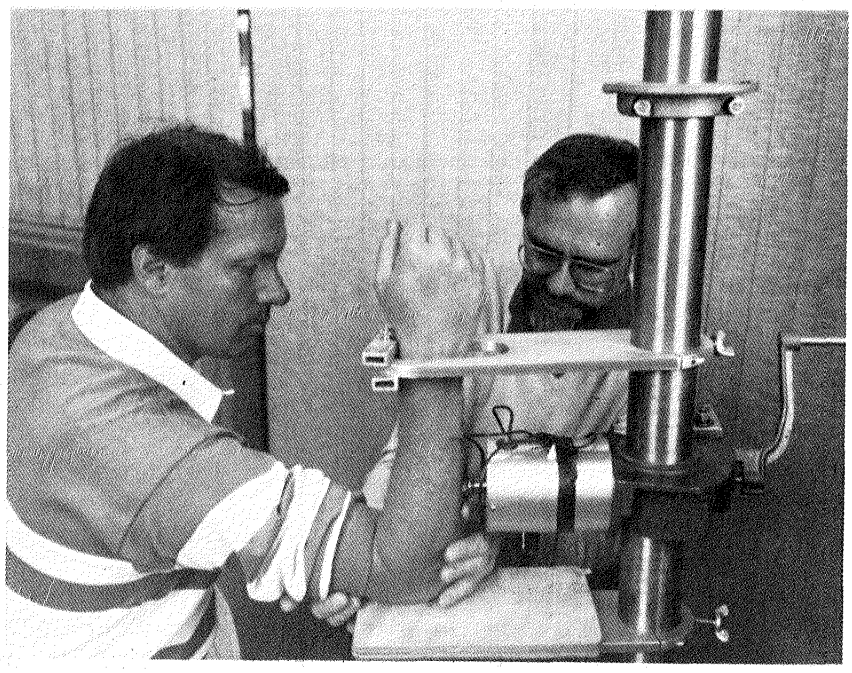

Fig. 20. To evaluate skeletal condition in athletic subjects, ulnar bending stiffness was measured in rugby players. An electromagnetic shaker and impedance head is positioned at the bone's midshaft. Gross bending stiffness is determined from the response to forced vibration. (Steele 199-20-32-02)

Bone Metabolism and Biomechanics 199-20-32-01

D.R. Young, Biomedical Research Division, Ames Research Center

To evaluate the nature of the skeletal changes and bone loss reported in human spaceflight and to develop remedial countermeasures, ground-based studies were conducted with immobilized primates (Macaca nemestrina). Immobilization was used to simulate the stress history of bones and their relative unloading during weightless spaceflight.

Osteoporosis associated with immobilization occurs as a result of a rapid and massive loss of bone. The loss is due to unrestrained activity of osteoclastic cells (Fig. 19) without the controls and regulations characteristic of adaptive systems under normal conditions. The chaotic pattern of bone resorption without a proper balance of bone formation persisted throughout the longest immobilization studies of seven months. Adaptive reconstruction of cortical bone occured during re-ambulation. Bone reconstruction rejuvenated the matrix and crystal structure, restoring mechanical properties, especially bending stiffness. However, the replacement of trabecular bone was incomplete. Therefore, repeated exposures to hypodynamic-hypogravic environments (spaceflight or unloading of weight-bearing structures in the body) would probably lead to thinning of the cortex and reduction of bone volume.

The massive breakdown of bone structure (collagen and hydroxyapatite crystals) by osteoclasts indicates that attempts at pharmacologic intervention simply by stabilizing the bone crystal structure through dietary supplements of fluoride or diphosphonate may not be successful. Further focus on the requirements for skeletal loading to preserve a healthy skeleton are required.

Publications: Young, D.R. Reversible osteoporosis in a primate model. Third International Symposium on Osteoporosis. Copenhagen, Denmark; 1984 June 3-8; pp. 475-479.

Bone Elasticity 199-20-32-02

C.R. Steele, Department of Applied Mechanics, Stanford University
D.R. Young, Ames Technical Monitor

The Steele Oxbridge Bone Stiffness Analyzer

was developed for the rapid, reproducible and non-invasive mechanical measurement of stiffness and mass in the long bones. Impedance probes permit the diagnosis, monitoring and response for treatment of skeletal abnormalities which result from injury or disease, aging, disuse (e.g. long-term bedrest) and weightless spaceflight. Dependability was increased by taking measurements from volunteers, evaluating results and upgrading the data reduction algorithms. In addition the hardware was modified to increase the vibration of bone at higher frequencies, thus increasing the resolution of the measurements. Although extensive clinical trials were approved, the development of an adequate data base requires evaluation of healthy skeletons. Tests on rugby players (Fig. 20) were conducted to develop nominal data for bone stiffness in healthy subjects. To broaden the experimental data base, such athletic subjects with a high degree of physical development will be evaluated.

An older system for measurement of bone stiffness has been restored to good operating condition with full documentation of the hardware and software, and backup microprocessors. This system will be used at Ames Research Center for serial studies of osteoporosis and risk factors in immobilized monkeys (Macaca nemestrina).

Publications: Steele, C.R. and S. Bockman. Non-invasive determination of bone stiffness with mechanical measurement. Abstract presented to Workshop on Advances in NASA-Relevant Minimally Invasive Instrumentation. Pacific Grove, CA; 1984 April 25-27; p. 8.

Mechanisms of Action of Glucocorticosteroids and Flouride on the Growing Skeleton 199-20-32-18

W.S.S. Jee and D.M. Woodbury, Department of Pharmacology, University of Utah School of Medicine
D.R. Young, Ames Technical Monitor

Several hormones act as agents of bone remodeling in the individual Haversian systems (Fig. 21), a dense array of microscopic, cylindrical structural units of compact bone composed of concentric layers of bone around a central canal. Some hormones depress activation of Haversian units, and other hormones increase Haversian activation. Research to date showed that the actions of fluoride and glucocorticoids do not adequately relate to the induction and time-course of space osteoporosis reported in manned spacecraft. On the other hand, administration of prostaglandin PGE2, a fatty acid that affects the action of certain hormones, increased the hard tissue mass at the wide ends of the shaft in long bones.

Strain-generated osteogenic stimuli may be a more important factor than the hormones themselves for the maintenance of normal skeletal mass. Because mechanical stress applied to osteoblasts results in the production of prostaglandins, a major reorientation of this research effort will test the hypothesis that PGE2 is synthesized by bone cells in response to loading and strain. PGE2 may be the local factor which inhibits bone resorption and stimulates new osteoblasts. Using animals in hypodynamic simulations will permit researchers to monitor for any depressed synthesis of PGE2 during the loss of skeletal loading.

Publications: (1) Jee, W.S.S. and J.M. Smith. 1984. "Image analysis of calcified tissues," In Methods of Calcified Tissue Preparation. G.R. Dickson, ed. Amsterdam: Elsevier. pp. 673-696. (2) Ueno, K., D.B. Kimmel, T. Haba, and W.S.S. Jee. 1984. "Increased metaphyseal hard tissue mass in growing long bone following prostaglandin E adminstration," In Endocrine Control of Bone and Calcium Metabolism. Cohn, D.V., T. Fujita, J.T. Potts, and R.V. Talmage, eds. Amsterdam: Elsevier. pp. 151-154.

Biomedical Changes in Bone in a Model of Weightlessness
199-20-32-20

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D.R. Young, Ames Technical Monitor

Fibrils of collagen act as a flexible protein matrix for the deposition of hard mineral salts in bone. Investigators examined non-mineralized collagen from the bones of vitamin-D deficient rats and chicks, and of chickens with osteoblastoma (a benign, vascular tumor in bone). The non-mineralized collagen in these mineral-deficient osteoids contained more than 90% pyridinoline crosslinks, confirming an earlier similar study.

Pyridinoline formation and strengthening in collagen is a maturation process and is a relatively long-time phenomenon compared to the mineralization process. Researchers found that the molecular structure of older collagen (synthesized earlier in the body and containing more pyridinoline) was more tightly knit than the newer collagen formed during recovery after bone loss. The bi-functional crosslinking in new collagen had fewer crosslinks and greater angular distances between links than did the tri-functional crosslinking (pyridinoline) in more mature collagen. The tighter crosslinks of pyridinoline could possibly inhibit the early stages of mineralization: the formation of crystalline hydroxyapatite in the fibrils. Conversely, the build-up of mineral in bone may prevent the collagen molocules from attaching and forming pyridinoline.

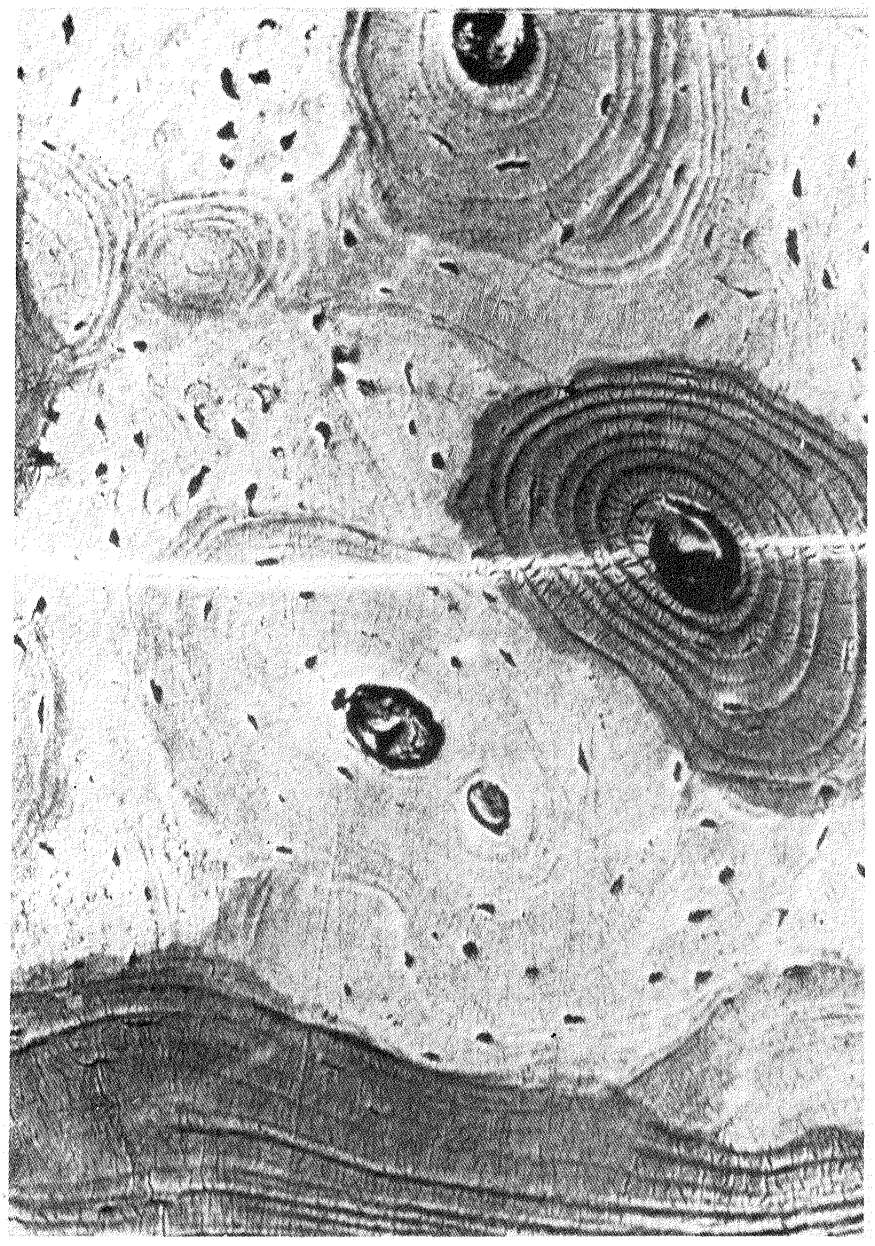

Fig. 21. Adaptive reconstruction of Haversian units in cortical bone during recovery from osteoporosis associated with immobilization. Back-scattered electron images from the scanning electron microscope show recently-formed, darker, partially-mineralized osteons and endosteal surfaces. Track of the analyzing beam can be seen. Newly-formed bone contains 18% less calcium than adjacent older bone. (Bunch 199-20-32-19)

Electron Probe Analysis of Trabecular and Cortical Bone 199-20-32-19

T.E. Bunch, Extraterrestrial Research Division, Ames Research Center
D.R. Young, Ames Technical Monitor

After immobilization of a nonhuman primate (Macaca nemestrina) and a period of normal recovery, cortical bone was evaluated by microradiography, and the results correlated with electron probe analysis. Young osteons contained approximately 18% less mineral than older osteons (Fig. 21). During bone resorption there was a non-specific mineral loss of 2% to 5% from all osteons. Less mineral was seen at the Haversian canals than in the area radiating outward through the osteon to the cement line. During recovery from osteoporosis, newly-formed osteons had a higher than normal ratio of calcium to phosphorus and lesser amounts of fluorine. The studies provided evidence that new bone formed during recovery contains mostly precursors of hydroxyapatite crystals.

Publications: Niklowitz, W.J., T.E. Bunch and D.R. Young. 1983. "The effects of immobilization on cortical bone in monkeys (M. nemestrina)." PHYSIOLOGIST 26(6): S115-S116.

Identification of an Unknown Humoral Agent Responsible for Bone Mobilization 199-20-32-21

H.F. DeLuca and H.K. Schnoes, College of Agricultural and Life Sciences, University of Wisconsin, Madison
D.R. Young, Ames Technical Monitor

Experiments continued to determine the hormones responsible for mobilization of calcium from bone during lactation. Bromocyptine stopped both lactation and bone loss. Controlling administration of the hormone prolactin, secreted from the anterior pituitary, for experimental purposes could not be accomplished in pregnant rats due to many deaths and lactation failure following hypophysectomy (removal of the pituitary gland). However, it was discovered that prolactin secretion was highest in the mother at birth, while mineral loss from bone is highest midway during lactation. Therefore, it was unlikely that prolactin mobilized calcium from bone during lactation. Removal of the parathyroid gland from lactating rats did not reduce their bone loss even when they were fed a high calcium diet. (On a normal diet the animals died of tetany and could not be used to study the question).

Apparently, the parathyroids were not involved in the mobilization of calcium from bone resulting from lactation. Also, removal of the adrenals did not affect bone loss. By the elimination of prolactin, the adrenals, the parathyroids and vitamin-D, an apparently unknown hormone caused the bone loss of lactation.

On a low calcium diet, rats were injected intraperitoneally daily with blood plasma taken from cows during their peak period of lactation. The blood calcium levels of the rats rose 1.5 to 2.0 mg/100 ml. Calcium levels remained at a normal level of 5.5 mg when rats were injected with plasma from non-lactating cows. The results suggested the existence of an unknown factor in lactating cows that mobilizes calcium.

Samples of plasma were analyzed from monkeys (Macaca nemestrina) immobilized at Ames Research Center. Surprisingly, 1,25-dihydroxyvitamin-D levels were unexpectedly high (150 pg/ml). Plasma from non-immobilized control monkeys will be checked for comparison. Levels of the active forms of vitamin-D, which normally mobilizes calcium from old bone, will also be measured in plasma taken from astronauts on the upcoming Shuttle-Spacelab 2 mission.

Dietary Modification of Bone Loss 199-20-32-26

S.B. Arnaud, Department of Pediatrics, University of California at San Francisco.
D.R. Young, Ames Technical Monitor

The only therapy that successfully prevented a large negative calcium balance in immoblilized human subjects is supplementation of the diet with calcium and phosphorus (Schneider 1984). To establish the mechanism of these positive results, a study was initiated of the response in the bone and the parathyroid/1,25-dihydroxyvitamin-D axis during immobilization of the rhesus monkey (Macaca nemestrina) fed high and low levels of dietary calcium, and a stable level of phosphorus. Species-specific assays of parathyroid hormone and microassays of vitamin-D metabolites were developed under this first phase of the study. Three derivatives of vitamin-D were assayed: 25- hydroxyvitamin-D; 24, 25-dihydroxy-vitamin-D; and 1,25-dihydroxyvitamin-D.

Results revealed a unique characteristic of the metabolism of vitamin-D in the monkey. Values for the circulating derivatives of vitamin-D in the blood of healthy animals were six times greater than values in normal human subjects. The parathyroid hormone assay revealed that the values of the intact 1-84 molecule in the monkey were similar to values in humans, and showed the expected physiologic changes during induced hypo- and hyper-calcemia. This parathyroid hormone data and the absence of metabolic abnormalities characteristic of vitamin-D intoxication in these animals suggests that hypervitaminosis-D is characteristic of the normal vitamin-D metabolism in Old World Monkeys.

Publications: Arnaud, S.B., D.R. Young, C. Cann, T.A. Reinhardt, and R. Hendrikson. Is Hypervitaminosis D normal in the rhesus monkey? Abstract presented to Sixth Workshop on Vitamin D. Merano, Italy; 15-22 March 1985.

MUSCLE ATROPHY RTOP 199-20-42
S. Ellis, manager

Significant atrophy of skeletal muscle develops in both men and rats during spaceflight. In the late 1970s rats showed a 30% loss of mass in the soleus muscle of the hindlimb following flight on joint US-USSR unmanned satellites. These flight data confirmed findings from the early 1970s of a 25% reduction in leg volume and strength of astronauts during 28 and 56-day missions of Skylab. Exercise on the last, 84-day Skylab flight cut the loss to 8%. Although exercise on a treadmill reduced the severity of the problem, muscle atrophy was not prevented entirely. Therefore, muscle atrophy remained a risk, particularly during longer missions required by astronauts for the construction and operation of a space station or a voyage to another planet.

Besides elucidating the mechanism of muscle atrophy, countermeasures may be achieved through specific types of exercise, applying electrical stimulation, and loading or stretching of muscles that are sensitive to gravity. These gravity-sensitive muscles include two basic types of fibers: the slow twitch and the fast twitch. Slow twitch fibers, which predominate in a muscle like the soleus, adapted through evolution for long, slow contraction to maintain posture. On the other hand, a muscle having a predominance of fast twitch fibers, like the gastrocnemius, developed with fewer fibers to contract for a shorter duration, thereby providing quick, accurate movements. In weightlessness, slow twitch fibers tend to convert to fast twitch, which fatigue sooner.

Investigators consider various hypotheses to explain the opposing functions which operate in concert to regulate muscle mass: the rate of contractile protein biosynthesis, and regulatory degradation. Muscle mass increases in the presence of peptides, such as insulin growth factors (IGF), pancreatic insulin, and probably many other endogenous growth factors as yet unidentified. Steroids also affect protein turnover, mainly by regulating rates of protein synthesis. In addition, immobilized muscle shows a decrease in number of glucocorticoid receptors. Recent studies have suggested that protein synthesis and degradation may be regulated by prostaglandins, and these processes appear to be modified by inhibitors of prostaglandin synthesis. Another hypothesisis is based on neural control of atrophy as indicated by severing the nerve from the muscle, which may prevent a biochemical, neurotrophic factor from regulating the rate of growth and breakdown via the neuromuscular junction.

Although disuse of muscle may cause a deficit of growth factors or a change in receptors in muscle, biochemical inhibitors were also detected in fractions of serum and muscle fibroblasts. Proteases contained in cellular lysosomes appeared to act as a link in the atrophy process. Tripeptidyl aminopeptidase was successfully isolated from lysosomes and many of its properties were determined. Another degradative protease, which is activated by the calcium content of the muscle, is located in the muscle cell's cytosol. An indication of the importance of proteolysis comes from the inhibition of muscle breakdown, both in vitro and in vivo, by a nontoxic microbial peptide, leupeptin, which acts as a protease inhibitor.

Investigators can test these various hypotheses in part by employing tissue cultures of myoblasts. Other experiments are performed in vivo with rats physically immobilized in casts, or suspended by the hindlimbs to remove the load on their muscles. Still other techniques include denervating specific muscles, severing the tendon between the muscle and the bone (tenotomy), and manipulating hormone levels through injections of glucocorticoids or inhibitors of prostaglandin synthesis. Because these methods can only simulate the effects of weightlessness on Earth, definitive tests must be performed in space, such as the one scheduled on the upcoming flight of Spacelab Life Sciences 2.

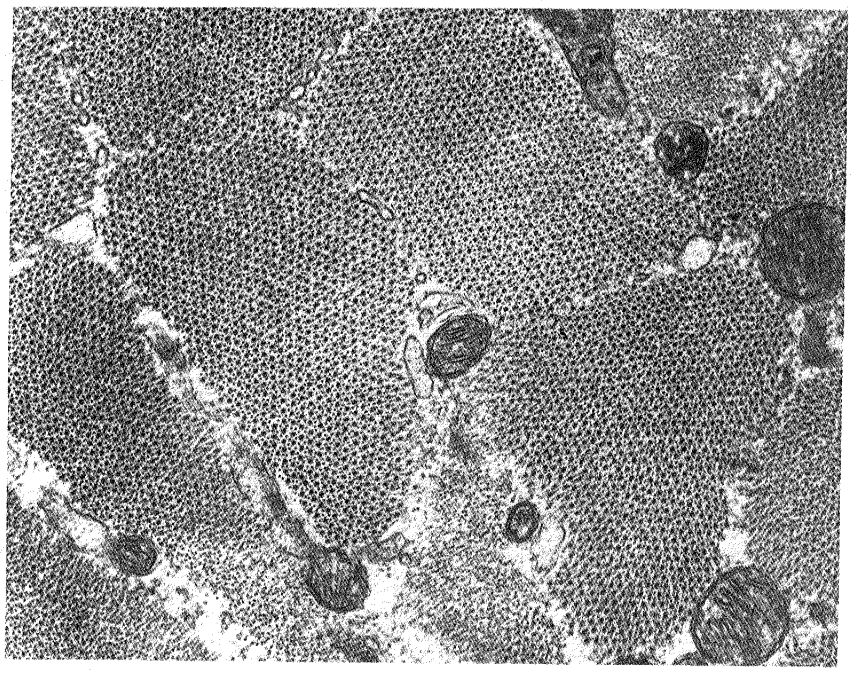

Fig. 22. Normal soleus muscle. (Ellis 199-20-42-01)

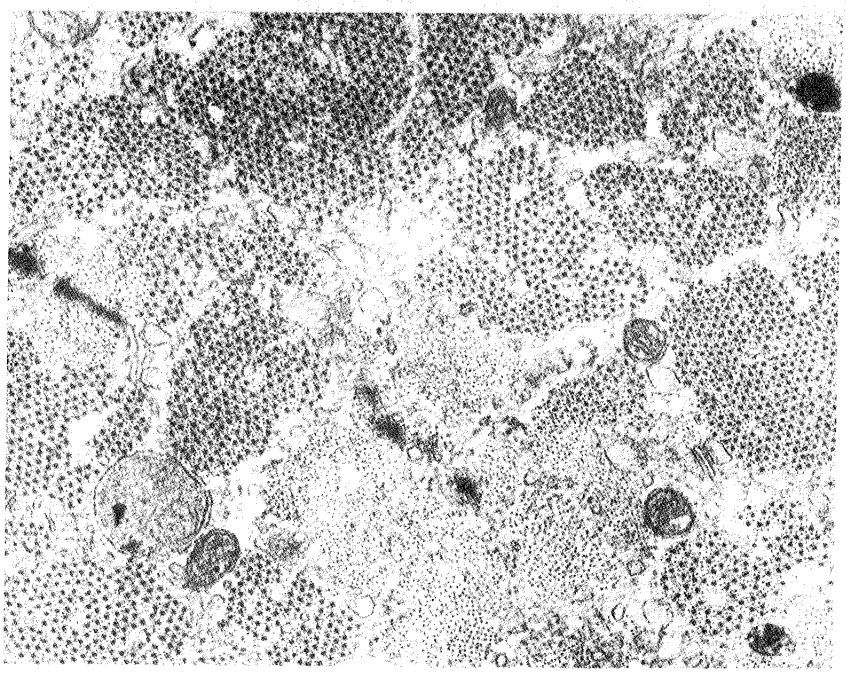

Fig. 23. Atrophying soleus muscle. (Ellis 199-20-42-01)

Proteolysis in Muscle Atrophy 199-20-42-01

S. Ellis, Biomedical Research Division, Ames Research Center
D.A. Riley and J.L.W. Bain, Department of Anatomy, Medical College of Wisconsin, Milwaukee
J.G. Barnett, National Research Council Associate, Ames Research Center

Investigators are seeking the basic proteolytic enzymes, pathways, and regulatory mechanisms that breakdown skeletal muscle. Current emphasis is on the role of specific lysosomal and nonlysosomal muscle proteases in muscle atrophy. Electron microscopic examination of the myofibrils of soleus muscle taken from rats after 10 to 12 days of disuse by suspension reveal a striking deletion of contractile myofilaments because of proteolytic degradation. Cross-sectional views of control and atrophying soleus muscles are shown in Figs. 22 and 23 respectively. The majority of fibers in atrophying muscles show uniform 'moth-eaten' fibrils, which are filled with sarcoplasmic reticulum. Examination of soleus muscles from rats exposed to seven days of suspension shows that the myofilament loss is predominantly focal and at the peripheral portions of the myofibrils. Mildly atrophic myofibers that exhibit focal extraction alternate with more atrophic fibers that show larger areas of myofibril disruption, i.e., individual fibrils seem to be atrophying at their own individual rates. The number of extremely atrophic myofibers is greatest at the myotendinous junction. Control soleus myofibrils show minimal amounts of focal myofibril disruption. These studies are being performed concurrently with biochemical measurements of cytosolic and lysosonal proteases. Ultimately, immunochemical analyses will be undertaken to show which specific proteases contribute to disruption of the myofibrils.

Publications: (1) Ellis, S. and P.A. Nagainis. 1984. "Activity of calcium activated protease in skeletal muscles and its changes in atrophy and stretch." PHYSIOLOGIST 27(6, Suppl.): S73-S74. (2) Riley, D.A., S. Ellis and J.L.W. Bain. 1984. "Ultrastructural cytochemical localization of carbonic anhydrase activity in rat peripheral sensory and motor nerves, dorsal root ganglia and dorsal column nuclei." NEUROSCIENCE 13(1): 189-206.

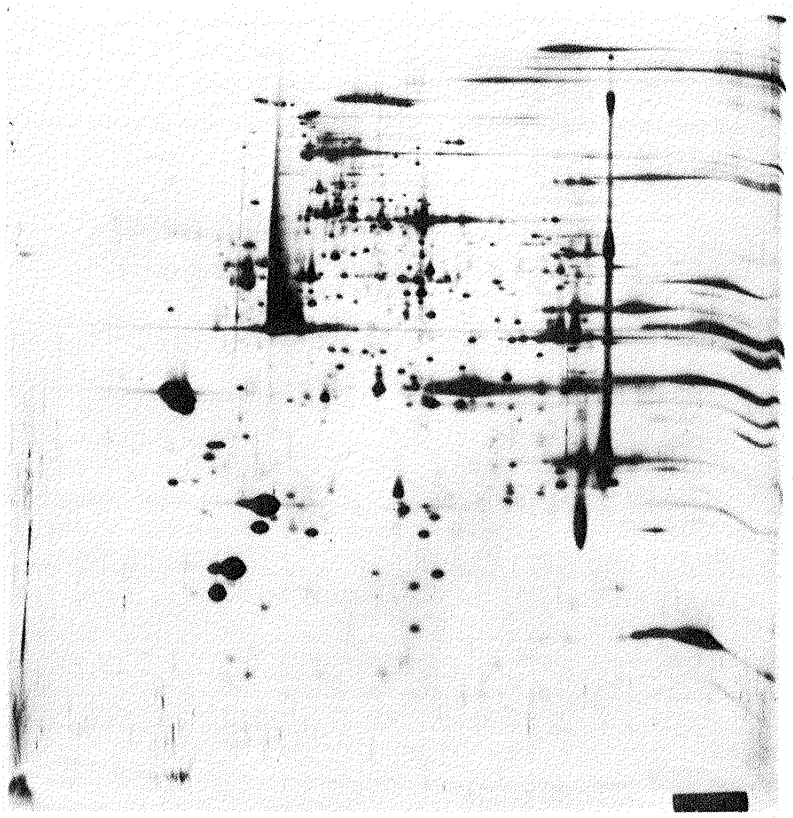

Fig. 24. An example of two-dimensional protein analysis of the atrophying soleus muscle from a rat undergoing 10-day hypodynamia/hypokinesia. An average of 246 protein spots per muscle are revealed by this technique. (Ellis 199-20-42-02)

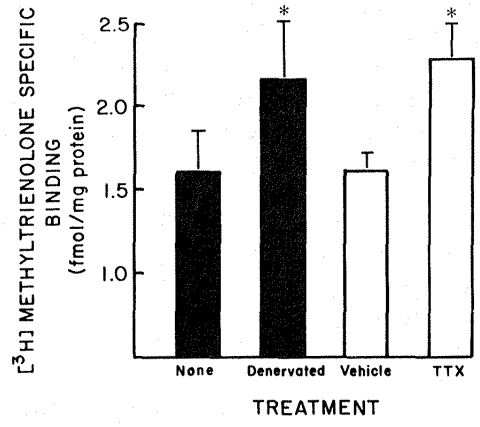

Fig. 25. Transient increases in cytosolic androgen receptor binding in the extensor digitorum longus and the tibialis anterior muscles of the rat during denervation and disuse (TTX). To delay absorption an oil was used as the injection medium (Vehicle). The processes indicate a redistribution of the cell's steroid receptors from the nucleus to the cytoplasm. (Max 199-20-42-06)

Growth Factors and Muscle Atrophy 199-20-42-02

S. Ellis, Biomedical Research Division, Ames Research Center
G.L. Choate, National Research Council Associate, Ames Research Center

Proteins from whole homogenates of rat soleus and extensor digitorum longus (EDL) muscle from control limbs and limbs held in suspension for 10 days to induce muscle atrophy were separated by two-dimensional electrophoresis (Fig. 24): isoelectric focusing in the first dimension and sodium dodecyl-sulfate polyacrylamide gel electrophoresis in the second dimension. The proteins were detected by silver staining and the resulting patterns were analyzed with computerized image processing. Four sets of marker proteins were identified: (1) proteins predominant in control soleus samples, (2) proteins predominant in EDL samples, (3) proteins showing a measurable increase or decrease in atrophied soleus, and (4) proteins showing an increase or decrease in atrophied EDL. Twenty-five protein changes were found in the atrophied soleus muscle and only nine in the atrophied EDL. Atrophied soleus muscle expressed proteins normally found in EDL, and atrophied EDL muscle expressed proteins normally seen in soleus: 28% of the proteins in the atrophied soleus and 56% in the atrophied EDL were markers of the opposite muscle type in control samples. Each of the muscle types also showed quantitative increases or decreases in proteins associated with the respective control muscles and a set of proteins found only in atrophied muscle of either type.

The Role of Bioassayable Growth Hormone in Protein Balance 199-20-42-03

R. E. Grindeland, Biomedical Research Division, Ames Research Center

Synthetic growth hormone releasing factor stimulated depletion of pituitary growth hormone (GH) and accelerated bone growth in rats. Hypophysectomized rats were implanted with rat pituitary cells; Amicon hollow fibers were filled with a mixture of pituitary cells (starts). Type 1, or Type 2 growth hormone-secreting cells (somatotrophs). Only Type 2 cells, the source of bioassayable growth hormone, significantly stimulated increases in body weight, thymus weight, tibial epiphyseal thickness, and muscle (gastrocnemius and soleus).

Somatotrophin cells were purified by electrophoresis on Earth and in microgravity on Shuttle flight STS-8. Evidence was obtained, by biological and immunological assays, that Type 1 and Type 2 somatotrophs could be separated by this procedure on Earth. Due to bacterial and fungal contamination of spaceflight samples it is uncertain whether Type 1 and 2 somatotrophs separated during spaceflight; clearly GH-secreting cells did separate from other pituitary cell types. Microgravity electrophoresis established that (1) cell density is not the determining factor in electrophoretic separation on Earth, and (2) different pituitary cells have different electrical charges.

Gonadal Steroids and Muscle Atrophy 199-20-42-06

S.R. Max, Department of Neurology, University of Maryland
S. Ellis, Ames Technical Monitor

Androgens stimulate muscle mass and function. The primary step in androgen action is interaction of the hormone with a receptor. Thus the number of such receptors may be an important determinant of the sensitivity of muscle to androgens. In the past year studies continued on regulation of anrogen receptors. We have focused on hindlimb skeletal muscle, and on the effects of disuse and denervation on muscle androgen receptors.

Denervation of rat hindlimb muscles caused a transient 50% increase in the number of androgen receptors in cytosol (the liquid medium of the cell's cytoplasm) (Fig. 25). This increase was not blocked by cycloheximide, suggesting that receptor synthesis was not involved. Also, the effect of denervation was mimicked by subperineurial injection of tetrodotoxin, showing that disuse is the causative agent. In contrast to the increase in cytosolic receptors, total (homogenate) receptor binding was not enhanced by denervation. An increase in cytosolic receptor with no increase in total (homogenate) receptor is consistent with a redistribution of receptors from nucleus to cytosol. The hypothesis is that the increase in cytosolic receptors results from decreased affinity of the receptor for the nucleus, and that this change reflects diminished sensitivity of muscle to androgens. This postulated decrease in sensitivity to anabolic hormones might be important in the progression of disuse atrophy, because it could permit catabolic infuences to predominate.

Effects were studied of androgens and estrogens on compensatory muscle hypertrophy resulting from functional overload of rat plantaris muscle caused by synergist removal. This mode of overuse of muscle had no effect on muscle androgen receptors. Further, in both male and female rats, no effect was found of sex steroids on the progression of muscle hypertrophy in this model. Results suggest a lack of beneficial effect of sex hormone status on the process of hypertrophy and on blochemical changes in overloaded muscle. Such findings are not consistent with the idea of synergistic effects of sex steriods and muscle usage.

Publications: (1) Bernard, P.A., N.E. Rance, P.S. Fishman, and S.R. Max. 1984. "Increased cytosolic androgen receptor binding in rat striated muscle following denervation and disuse." JOURNAL OF NEUROCHEMISTRY 43: 1479-1483. (2) Max, S.R. and R.F. Mayer. 1984. "Physiological and biochemical aspects of denervation and reinnervation of muscle." In Peripheral Neuropathy, 2nd ed. Dyck, P.J., et al., eds. W.B. Saunders; pp. 400-419. (3) Max, S.R. and N.E. Rance. 1984. "No effect of sex steroids on functionally overloaded rat plantaris muscles." JOURNAL OF APPLIED PHYSIOLOGY 56: 1589-1593. (4) Rance, N.E. and S.R. Max. 1984. "Modulation of the cytosolic androgen receptor in striated muscle by sex steriods." ENDOCRINOLOGY 155: 862-866.

Mechanism and Control of Disuse Atrophy in Skeletal Muscle 199-20-42-10

J.D. Etlinger, Department of Anatomy and Cell Biology, State University of New York Downstate Medical Center, Brooklyn
S. Ellis, Ames Technical Monitor

The release of calcium stores in the many sarcoplasmic reticulum in muscle play an intergral role in the normal contraction of muscle fiber. Calcium can also regulate protein turnover and may be involved in mediating muscle growth and atrophy linked to activity, stretch and endocrine function. Both intact animals and organ-cultured rat muscles were used to study selective agents directed against calcium, beta adrenergic receptors, prostaglandins, and proteases.

A study was completed which characterized the effects on protein turnover of calcium ionophores at sub-contraction threshold levels in chick myofibers. Altering calcium distribution resulted in selective effects on individual myofibrillar proteins: there was increased lysosomal degradation of myosin light chains and tropomyosin, whereas the other contractile proteins

showed decreased or unchanged breakdown during proteolysis. These differential effects on the myofibrillar proteins are consistent with a disassembly step preceding lysosomal proteolysis. With increased mobilization of calcium, causing tension in rat soleus muscle, lysosomal proteolysis is inhibited. (Lysosomal proteolysis is inhibited by methylamine, ammonium chloride, chloroquine, and monensin). Several additional inhibitors of calmodulin (calcium-modulating proteins) were also found to inhibit lysosomal proteolysis in order of potency reflecting their ability to inhibit calmodulin.

In contrast, non-lysosomal leupeptin-sensitive proteolysis is stimulated by increased calcium and tension in rat soleus muscle. Further study of muscle fiber length regulating proteolysis has demonstrated that the non-lysosomal, calcium-dependent, leupeptin-sensitive pathway is blocked by moderate stretch. In addition, this same pathway appears to be regulated by the beta-agonist isoproteranol and by thyroxin. These studies continue to support the hypothesis that calcium plays a pivital role in mediating effects of endocrine factors and activity on muscle protein turnover.

Publications: Janeczko, R.A. and J.D. Etlinger. 1984. "Inhibition of intracellular proteolysis in muscle cultures by multiplication-stimulating activity." JOURNAL OF BIOLOGICAL CHEMISTRY 259: 6292-6297.

Biochemical Adaptations of Antigravity Muscle Fibers to Disuse Atrophy 199-20-42-12

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S. Ellis, Ames Technical Monitor

The goal of this research task is to delineate the mechanism which initiates a decrease in muscle protein synthesis in immobilized limbs. Recent strategy has been to learn whether or not a decrease in the content of alpha-actin mRNA initiates the immobilization-induced decrease in actin synthesis rate in skeletal muscle fibers. Experiments did not support this possibility. Future strategy will be to determine if some initiation factor effects protein modification and might cause actin synthesis rate to decrease in the first few hours of limb immobilization.

Publications: (1) Butler, D.T. and F.W. Booth. 1984. "Muscle atrophy by limb immobilization is not caused by insulin resistance." HORMONE AND METABOLIC RESEARCH 16: 172-174. (2) Nicholson, W.F., P.A. Watson and F.W. Booth. 1984. "Glucose uptake and glycogen synthesis in muscles from immobilized limbs." JOURNAL OF APPLIED PHYSIOLOGY 56: 431-435. (3) Nicholson, W.F., P.A. Watson and F.W. Booth. 1984. "Levels of blood-bourne factors and cytosol glucocorticoid receptors during the initiation of muscle atrophy in rodent hindlimbs." PFLUGERS ARCHIV EUROPEAN JOURNAL OF PHYSIOLOGY 401: 321-323. (4) Watson, P.A., J.P. Stein and F.W. Booth. 1984. "Changes in actin synthesis and alpha-actin mRNA content in rat muscle during immobilization." AMERICAN JOURNAL OF PHYSIOLOGY 247: C39-C44.

Alterations in Skeletal Muscle with Disuse Atrophy 199-20-42-13

R.E. Fitts, Department of Biology, Marquette University, Milwaukee, WI
S. Ellis, Ames Technical Monitor

Electrophoresis (one-dimensional) in the presence of detergent after solubilization of single muscle fibers, or parts of a fiber, results in a protein banding pattern (after silver staining) that is characteristic of the specific fiber-type: a slow type I fiber from the soleus muscle, a fast type IIa fiber from the red region of the lateral gastrocnemius muscle, or a fast type IIb fiber from the superficial region of the vastus lateralis muscle (Fig. 26). Type I fibers can be identified by their characteristic myosin light chains, while type IIa and IIb fibers can be separaed by the appearance of a 30,000 molecular weight band in the IIa, but not the IIb, fiber. Because this band appears in gels from type I as well as type IIa fibers, it is most likely a mitochondrial protein or the soluble protein carbonic anhydrase. This technique will be employed to charaterize the protein composition of fibers isolated from atrophing muscle.

Immobilization/Re-immobilization and the Regulation of Muscle Mass 199-20-42-14

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S. Ellis, Ames Technical Monitor

The model of limb immobilization developed in this task mimics the effect of weightlessness on skeletal muscle. There is severe atrophy of tonic, oxidative fibers (40% in six days) and low-level atrophy of phasic glycolytic fibers (13-15%).

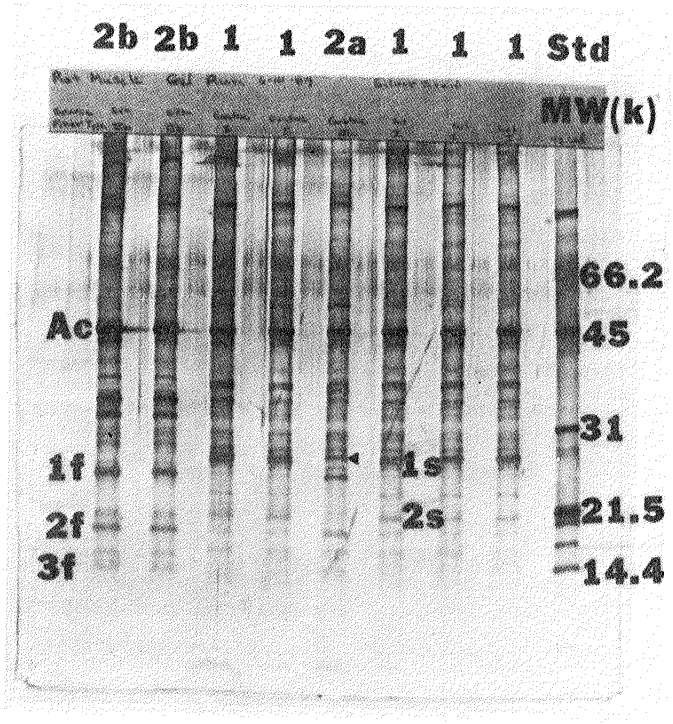

Fig. 26. SDS-polyacrylamide gel of rat single muscle fibers identified at the top of each gel as type 2a, 2b, or 1. The fast type 2 and slow type 1 fibers are identified by their characteristic myosin light chain patterns, while 2a and 2b fibers are distinguished by the appearance of a 30,000 molecular weight (MW) protein in the 2a fiber (arrow in the center of the figure), but not in the 2b fibers. Ac represents the contractile protein actin. (Fitts, p. 75, 199-20-42-13)

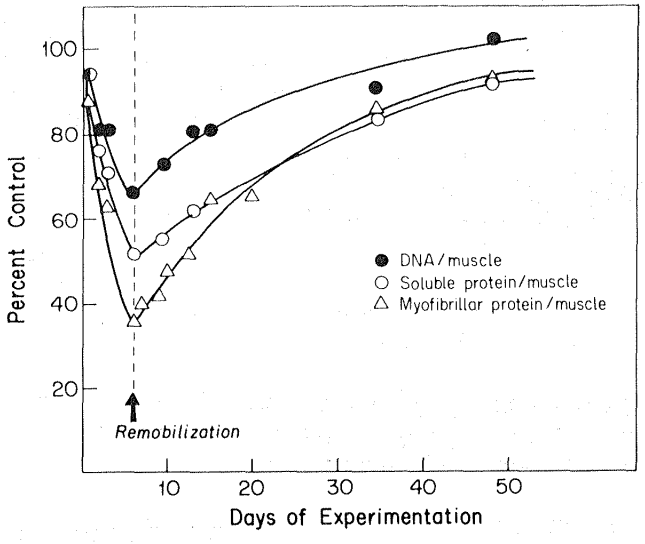

Fig. 27. The effect of immobilization followed by remobilization on the tonic soleus muscle of the rat. (Almon 199-20-42-14)

The tonic muscles showed a significant loss of protein in all compartments. This loss ranges from 64% of the myofibrillar protein to 52% of the soluble protein after six days. A major unexpected finding was a significant loss of DNA (Fig. 27). Specifically, a 34% loss of DNA in the tonic muscle followed six days of immobilization in 50g 26-day-old rats. At present it is unknown if this loss is due to fewer nuclei per fibers or fewer fibers. If these data do indicate fewer fibers then the result would suggest a loss of motor units in the spinal cord. The procedure causes a massive stress reaction in the animals. This is reflected by some wasting in the entire body musculature, a significant down regulation in the number of glucocorticoid-receptor sites in all muscles, and a significant shift in apparent receptor binding affinity.

With respect to the cytosolic glucocorticoid-receptor sites. The concentration drops precipitously beginning within hours after immobilization. By six days of immobilization, the cytosolic concentration of glucocorticoid receptor sites is extraordinarily low. Given our extensive previous data this was an entirely unpredictable result. This result may indicate that the receptor sites have been driven into the decreasing number of nuclei by the combination of virtually absolute immobilization and very high corticosterone levels due to stress. If this is true, then our protein turnover studies should indicate very high turnover rates. Conversely, the result may indicate that the muscle has virtually gone dormant. Such a situation has been observed with burn trauma. If these results are true, then turnover experiments should yield very low synthesis and high degradation. It should be pointed out that these muscles are not damaged by the procedure. They are not inflammed and edemitous. Data show that wet and dry weight change proportionately. Finally, the results demonstrate that it takes an extraordinarily long time for muscle to recover from the atrophy caused by the short six-day immobilization period. In particular, it takes more than 40 days for most characteristics to even approach normal.

The Combined Influence of Stretch and Mobility on Muscle Atrophy Caused by Immobilization 199-20-42-15

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S. Ellis, Ames Techincal Monitor

During the past year of this study two models were employed to investigate disuse atrophy in muscle: hindlimb cast fixation and suspension, to define the precise changes which occur in rodent hindlimb muscles in response to hypokinesia and hypodynamia. In particular, this task used the recently developed and highly sensitive techniques for measuring in vivo rates of protein synthesis to describe how the atrophy is brought about in different types of muscle. Using such biochemical techniques in combination with histochemical procedures, the usefulness of passive stretch in combination with electrical stimulation as a means of retarding muscle atrophy was also investigated.

Rats were subjected to hypokinesia and hypodynamia (H + H) by suspending them in a harness. After only 5 days of H + H, appreciable muscular atrophy was apparent, preferentially expressed in certain muscles, i.e. soleus (41%), plantaris (32%) gastrocnemius (31%) tibialis anterior (19%), and extensor digitorum longus (16%). Rates of protein synthesis were measured and degradation in these five hindlimb muscles in vivo using the most accurate and reliable method currently available. This method involves the injection of large doses of H^3 phenylalanine, which "swamps" the amino acid pools in the animal's tissues. Protein synthesis decreased rapidly in the soleus and gastrocnemius muscles. However, in subsequent experiments in which these muscles were stretched in one leg of a suspended rat by casting in fully dorsi-flexed position, atrophy was prevented and protein synthesis did not decrease. It is known that stretching of a muscle leads to the addition of sarcomeres at the ends of the muscle. Histochemistry carried out on these muscles showed that stretching also prevented decreases in fiber diameter during atrophy.

FLUID AND ELECTROLYTE CHANGES RTOP 199-20-62
L.C. Keil, manager

Fluids are redistributed in the body during weighlessness. More blood shifts to the head and thorax during spaceflight, instead of pooling in the lower limbs as under the effects of normal gravity. Facial puffiness and nasal congestion accompany fluid shifts. Investigators were first able to study these effects on astronauts during the lengthy missions of Skylab in the early 1970's

Apparently this headward shift of fluids alters the level of hormones in the blood from the cortex of the adrenal gland, changing the homeostatic control that balances salts and water in the body. Because fluid-retaining hormones decrease, blood volume decreases. During bedrest studies to simulate the effects of weightlessness, the circulating level of these hormones decreases for 24 hours and then adapts to a new, stable level. The resulting reduction of fluid volume provides a lower than normal blood flow to the head under the +Gz forces similar to those experienced during reentry of the Space Shuttle. Hormonal changes also trigger an excretion of sodium (Na) and, to a lesser extent, potassium (K), along with water. Salt losses continue for the duration of bedrest studies, as the body eliminates more salt than it takes in. These fluid and hormonal shifts may also affect metabolism as it relates to motion sickness, muscle atrophy and bone loss.

This RTOP investigates changes of the hormones in urine and plasma that regulate the excretion and reabsorption of salt and water from the kidney. These hormones include:

- glucocorticoids such as cortisol, which maintains blood volume and pressure in the body (produced in the adrenal cortex);
- mineralocorticoids such as aldosterone, which controls sodium levels in the body (produced in the adrenal cortex);
- arginine vasopressin, the anti-diuretic hormone (ADH), which maintains fluid volume in the body (produced in the pituitary);
- a natriuretic hormone, a recently discovered protein (hormone),which causes sodium excretion in the urine.

Basic research at Ames focuses on a variety of studies with animals, as well as studies with humans, who are subjected to bedrest in a gentle, head-down (-6 deg) position to simulate the hemodynamic effects of weightlessness.

Hormone Mechanisms Regulating Fluid and Electrolyte Metabolism in Weightlessness and Bedrest 199-20-62-01

J. Vernikos-Danellis, Biomedical Research Division,
Ames Research Center

Head-down (6 deg) bedrest was used in a series of studies as a model of the effects of weightlessness that astronauts experience during spaceflight. Reaction to head-down bedrest and spaceflight are similar in that blood and other fluids shift from the extremeties to the chest and head, and a similar loss of fluid volume and sodium occurs during the first few days. This antiorthostatic bedrest causes an immediate decrease in the levels of hormones that regulate water and electrolyte balance in response to the central shift in volume, as predicted by Gauer and Henry in 1956. The decreases in hormonal levels are followed by a diuresis and natriuresis, and a decrease in plasma and blood volume. During the six days of head-down bedrest, the normal balance between plasma renin activity (PRA) and aldosterone is altered such that PRA is elevated and aldosterone is decreased. The adrenals respond with appropriate changes in aldosterone secretion both to the stimulus of ACTH and to inhibition by a volume-induced decrease in PRA. Renal responsiveness to aldosterone is unchanged during head-down bedrest, and urinary sodium loss is increased slightly because of the tonically low aldosterone levels during the head-down condition.

Susceptibility to fainting was studied in male and female subjects by standing immediately after bedrest. Those subjects who fainted had the highest resting plasma volumes (PV), the smallest decreases in plasma volume on standing, and the largest resting blood pressures (BP) at the start of the studies. The preservation of an expanded PV becomes a very critical mechanism for the maintenance of BP in these individuals even under normal ambulatory conditions.

With continuing bedrest, plasma volume may tend to be restored, while cardiovascular instability becomes more prominent, which suggests that other mechanisms perhaps compensatory to the decreased volume, are primarily responsible for the orthostatic intolerance after bedrest. Of these the autonomic nervous system seems critical.

Plasma norepinephrine responses are lower and less sustained in those individuals who show the greatest orthostatic intolerance after bedrest. It is also possible that the orthostatic hypotension which develops after short-duration bedrest when plasma volume is still reduced, may be brought about by different mecnanisms than those which are evident after longer exposures. If this is the case, then preventive measures effective in one situation may not necessarily be effective in the other.

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Central Nervous System Mechanisms Affecting Salt/Water Balance 199-20-62-02

L.C. Keil, Biomedical Research Division, Ames Research Center

The research in this task is aimed at identifying the brain's role in the regulation of electrolyte and water excretion under conditions of headward fluid shifts. This task is complicated by the fact that brain regulation of fluid and electrolyte metabolism, under normal conditions, is not completely understood. Therefore much of the research is directed toward understanding the basic mechanisms that control fluid and electrolyte metabolism.

A number of significant findings have resulted from research during the past year. For example, the administration of vasopressin into the cerebroventricles lowers cerebrospinal fluid (CSF) pressure. This evidence indicates that vasopressin may be necessary in the reduction in CSF pressure that results from headward fluid shifts during head-down bed rest, water immersion or spaceflight. Other findings were concerned with angiotensin release of vasopressin; plasma volume and osmolality as a stimulus for vasopressin secretion; areas of the brain that regulate drinking and fluid intake; and the effect of certain drugs on vasopressin secretion.

Because changes in body salt balance and blood pressure occur as the body adapts to space, the salt-saving hormone, aldosterone, may affect the subcommissural organ (SCO) of the brain and cause changes in the adrenal gland. Conscious rats were given aldosterone into the SCO area. Aldosterone in the SCO reduced the cross-sectional area of the adrenal medulla (core of the gland), where adrenalin is made and secreted into the blood (Fig. 28).

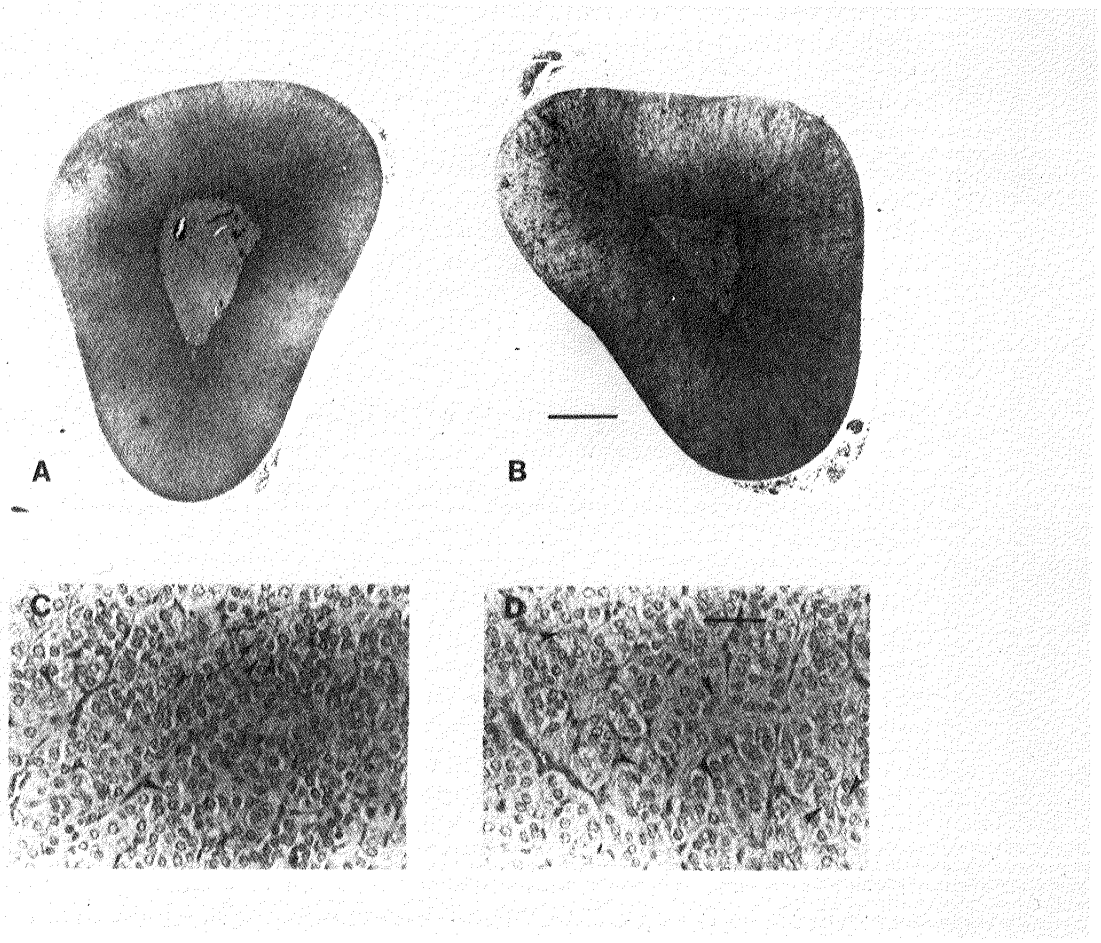

Fig. 28. Aldosterone administered to the subcommissural organ of the brain reduced the size of the adrenal medulla (B) compared to the adrenals in control rats (A), although in both cases, core cell density was not changed (C and D). (Keil 199-20-62-02)

This new discovery could be relevant in understanding how the rearrangement of hormone systems in space affect the body's ability to function under stress. Adrenalin is, of course, an important hormone released by stress.

Publications: (1) Ben, L.K., J. Maselli, L.C. Keil, and I.A. Reid. 1984. "Role of the renin-angiotensin system in the control of vasopressin and ACTH secretion during the development of renal hypertension in dogs." HYPERTENSION 6: 35-41. (2) Kravik, S.E., L.C. Keil, J.E. Silver, N. Wong, W.A. Spaul, and J.E. Greenleaf. 1984. "Immersion diuresis without expected suppression of vasopressin." JOURNAL OF APPLIED PHYSIOLOGY 57(1): 123-128. (3) Raff, H., J. Shinsako, L.C. Keil, and M.F. Dallman. 1984. "Feedback inhibition of adrenocorticotropin and vasopressin responses to hypoxia by physiological increases in endogenous plasma corticosteriods in dogs." ENDOCRINOLOGY 114: 1245-1249. (4) Reid, I.A., J.N. Ahn, T. Trinh, R. Shackelford, M. Weintraub, and L.C. Keil. 1984. "Mechanism of suppression of vasopressin and adrenocorticotropic hormone secretion by clonidine in anesthetized dogs." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 229(1): 1-8. (5) Thrasher, T.N., C.E. Wade, L.C. Keil, and D.J. Ramsay. 1984. "Sodium balance and aldosterone during dehydration and rehydration in the dog." AMERICAN JOURNAL OF PHYSIOLOGY 247: R76-R83.

Fluid and Electrolyte Shifts during Immersion: Metabolism, Work Performance and Acceleration Tolerance
199-20-62-06

J.E. Greenleaf, Biomedical Research Division, Ames Research Center

Dr. Michael Harrison has been conducting studies to determine the effects of hydration status on orthostatic responses to head-up tilt, and has shown that the dehydrated test subject is a valuable physiological model for elucidating the causes of orthostatic intolerance. The levels of systolic and pulse pressures and plasma renin activity appear to allow discrimination between orthostatically tolerant and intolerant subjects. This finding could have application for astronaut selection. A second research area involves use of a neck-suction technique to study the effect of alterations in central blood volume (CBV) in the heart and lungs on carotid and baroreceptor function. Increasing CBV by head-down tilt causes a greater slowing of the heart in response to neck suction, than when supine or head-up.

These results suggest that part of the cardiovascular response to the headward shift of blood in weightlessness may involve a "resetting" of baroreceptor sensitivity, which in turn could contribute to the overall phenomenon of weightlessness deconditioning. Dr. Helmut Hinghofer-Szalkay is testing a newly developed mechanical oscillator technique (MOT) using a high precision fluid mass density analyzer. The MOT can detect rapid and small hematocrit and plasma protein changes in blood and can be used to measure changes in plasma volume continuously. Fluid-protein shifts occur with many different experimental conditions such as changes in posture, exercise, thermal stress, blood loss, volume loading, and in acceleration stress. These conditions are of interest for space-related applied physiology. Dr. Ghislaine Geelen and Dr. Stein Kravik from France and Norway, respectively, have returned to Ames to continue their collaboration in a 6-month exercise training study. The purpose is to determine whether induced physical conditioning reduces tilt-table tolerance similar to that observed in some endurance-trained athletes. If the training lowers tolerance, the physical training programs of astronauts (especially pilots) should probably be monitored closely or modified to deemphasize leg exercise. If there is no significant change in orthostatic tolerance after training, then the reduced tolerance observed in endurance-trained athletes could be attributed to some inherited traits. This finding suggests that care is needed in the selection of astronaut pilots from an endurance-trained population; they would likely have a lower orthostatic tolerance which may compromise flight performance during the increased G-levels encountered during reentry.

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BIOLOGICAL EFFECTS OF PARTICLE RADIATION
RTOP 199-20-72
D.E. Philpott, manager

Ionizing radiation in space, including electrons, protons, neutrons. x-rays, and galactic cosmic rays, represents a potential danger to the health of astronauts and their performance during flight operations. The long-term effects from low doses of heavy, high-energy (HZE) particles, such as carbon, iron and argon, have never been studied extensively. Experimental studies of radiation effects by the scientific community in the past primarily focused on the problem of the short-term effects of a large, single exposure to radiation. With Shuttle astronauts in orbit at more frequent intervals, and with future operations at higher orbits for long periods of time, the risk of long-term effects from radiation is significant. Radiation levels also increase in high inclination orbits, such as the polar orbits planned for Space Shuttles launched from the Western Test Range at Vandenberg AFB. A solar flare in 1972 would have exposed an astronaut in polar orbit to 200 rads. NASA's limits for radiation exposure to the eyes are currently 0.3 rad. The average exposure on the Shuttle in low earth orbit is 5 to 6 millirems per day, with 27 millirems recorded during the complete STS-5 mission.

Research under this RTOP includes determining both short- and long-term effects of HZE particles on cells and organs, including the possible risk of cancer. The threshold exposure for radiation is studied, above which deleterious biological effects are expressed, especially affecting the aging and mortality of neural and retinal tissue. The effects of multiple exposures of biological tissue to radiation is also investigated.

HZE Particle Radiation and Life Span: Histopathological Studies 199-20-72-08

L.M. Kraft, Biomedical Research Division, Ames Research Center
W.L. Savage, Department of Biological Sciences, San Jose State University, San Jose, CA

Studies have continued on the reduction in life span due to lethal tumors in mice exposed to HZE (heavy, high energy) particle radiation in the BEVELAC at the University of California, Berkeley. Data are being accumulated from mice irradiated with silicon, argon, iron, neon, and carbon particles and with gamma rays from cobalt-60. A total of about 3400 mice have been examined since the initiation of this study, approximately 700 since the beginning of 1984.

Work has begun in cooperation with Dr. Ann Cox, Colorado State University, in the use of morphometric techniques to study late effects of radiation on certain brain structures in rabbits and mice. For example, computer assisted measurements of stained microscopic sections of the olfactory bulbs of such animals have been used to assess the volume of the glomeruli of the olfactory bulb. Data from rabbits irradiated with relatively high doses of gamma rays, neon and argon particles indicate a reduction in the mean volume of these glomeruli. Since the glomeruli consist of dendritic endings of various olfactory nerve cells synapsing with the axons of sensory cells from the olfactory nasal mucosa, it is thought that the reduced volume of the glomeruli in the irradiated animals represents a reduced nerve cell population and/or a reduction in the number of prolongations from damaged nerve cells. It is expected that this model system in the olfactory bulb will be utilized in the cerebral cortex and other structures of the brain to ascertain late radiation damage in diverse regions of the central nervous system.

Publications: (1) D'Amelio, F., L.M. Kraft, E. D'Antoni-D'Amelio, E.V. Benton, and J. Miquel. 1984. "Ultrastructural findings in the brain of fruit flies (Drosophila melanogaster) and mice exposed to high-engery particle radiation." SCANNING ELECTRON MICROSCOPY/1984/II Chicago: SEM Inc. pp. 801-812. (2) Cox, A.B. and L.M. Kraft. 1984. "Quantitation of heavy-ion damage to the mammalian brain: Some preliminary findings."

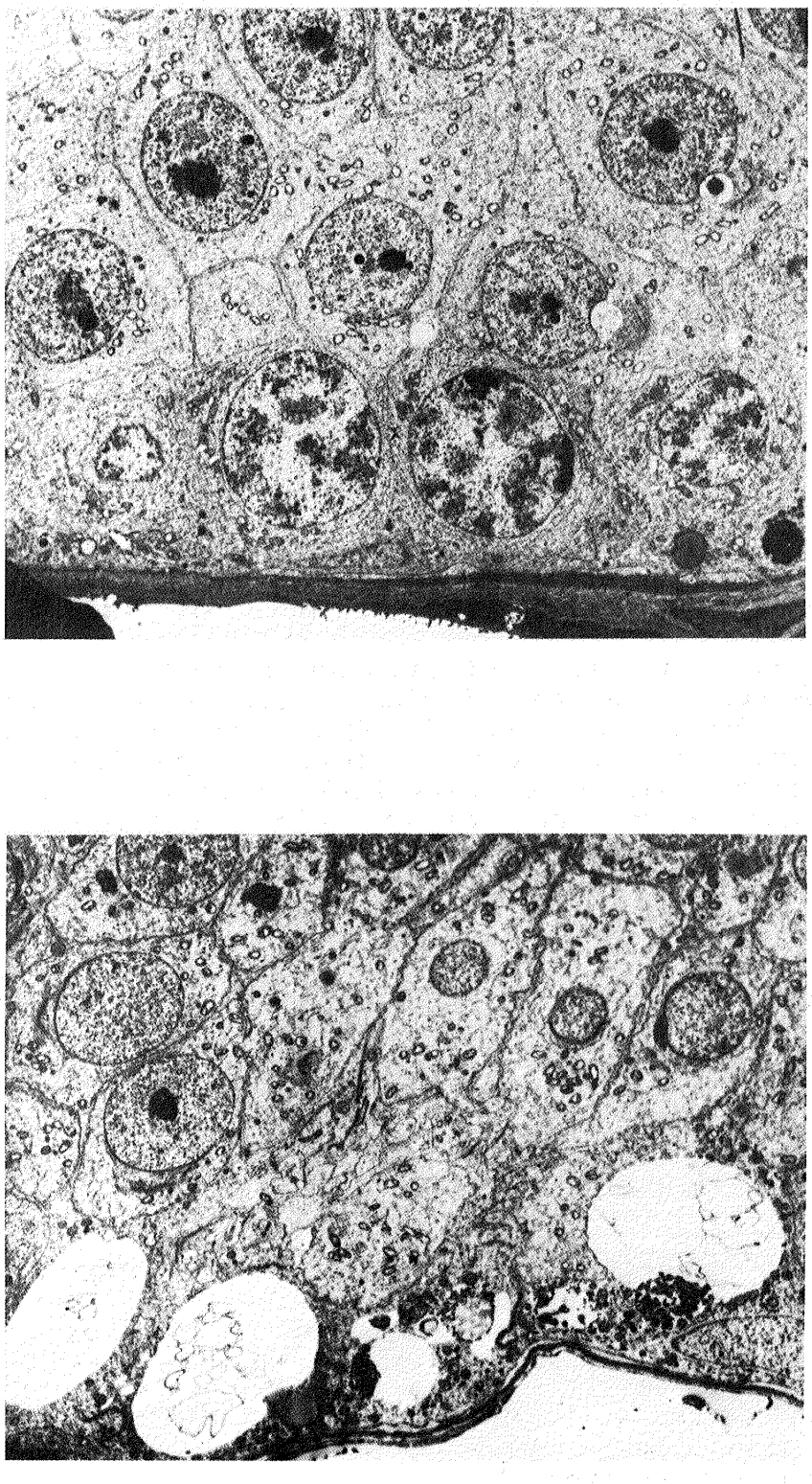

Fig. 29. Testes of control mouse (top) compared to mouse testes after irradiation with 80 rads of helium. (Philpott 199-20-72-11)

Effects of Particle Radiation on the Aging of Retina and Brain 199-20-72-11

D.E. Philpott and J. Miquel, Biomedical Research Division, Ames Research Center

Results from irradiation of the testes in mice (Fig. 29) included doses of HZE particles as low as 0.5 rad. Results clearly showed the effects of cell death six months after irradiation. Therefore, the time element is not critical for cell counting measurements after irradiation, and testes could be used as a biological dosimeter during space missions. In addition, mice showed a performance decrement up to one year after irradiation with 50 rads of HZE argon particles. A performance decrement was noted at a dose as low as 0.5 rad, and further testing may show performance decrements at even lower doses. Accompanying the performance decreases, the synapses in the brain's hippocampus decreased in length with an increase in radiation dose. This area of the brain is considered to be a site of behavior modification. In summary, results indicated an increase in aging from high energy particle radiation at doses as low as 0.5 rad.

Two Space Shuttle flight experiment proposals were also submitted. One study will determine the changes in interocular pressure, and the extent that it can rise during spaceflight to present a danger of glaucoma. Another proposed study would examine aging effects of spaceflight in mice by evaluating free radical formation, heart ultrastructure and energetics, behavior and nutrition.

Publications: Philpott, D.E., W. Sapp, C. Williams, J. Stevenson, S. Black, and R. Corbett. 1984. "Response of a single spermatogonial cell type in mouse testes to HZE radiation." PROCEEDINGS OF THE ELECTRON MICROSCOPE SOCIETY OF AMERICA 42: 194-195.

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Human Circadian Rhythms: Performance and Physiological Deconditioning in Simulated Space Environment

199-20-82-01

C.W. Winget, Biomedical Research Division, Ames Research Center

Human subjects were studied in two groups of three members for 105 days to evaluate the effects of isolation and confinement on adaptability to a simulated long-term space mission. After relatively high levels of anxiety, increased cortisol levels, and increased heart rate during the initial exposure to isolation and confinement, the subjects adapted well to the simulated space mission environment. Social interaction between the members of a small, isolated group can affect physiological processes in a positive manner by reinforcing synchronization of rest-activity rhythms, or in a negative manner by contributing to rhythm desynchronization associated with a stress response (e.g., relatively higher levels of cortisol, heart rate and test performance errors). Sleep disturbances significantly increased in experimental subjects, but not in control subjects. Ranking of activity by the subjects themselves showed that one experimental group of less compatible members preferred activities that were indicative of personal enrichment, or they preferred group activities which did not require extensive social interaction. The group with more compatible members preferred activities which required interaction over activities of personal enrichment. The less compatible group showed greater desynchronosis. These results demonstrate the importance of identifying psychological and physiological factors which influence the adaptability of small groups to simulated long-term space station missions.

In another study multiple physiological measurements and a self-assessment of arousal were recorded in eight men on the first, third and fifth days of bedrest. Additional measurements of memory and dexterity task performance were made on the third day. Although none of the individual physiological variables predicted subsequent performance decrements, the individual patterns of correlations between variables increased on the performance day, indicating an increase in behavioral activation elicited by the performance tasks. This study indicates that measurement of a selected combination of physiological variables could be useful in predicting subsequent performance in future missions.

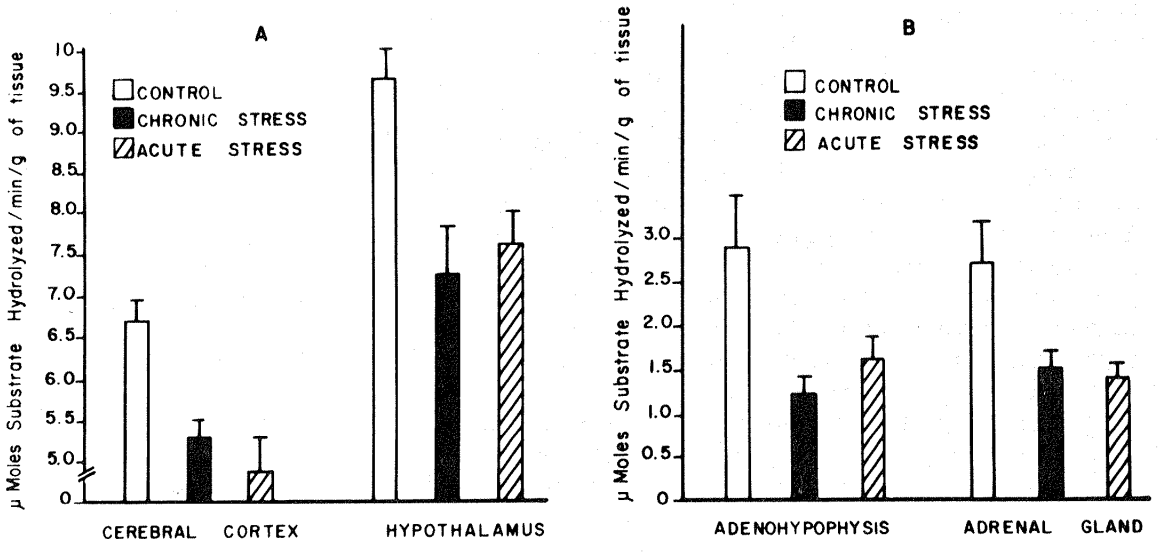

Fig. 30. Effect of acute immobilization stress or chronic cold stress on the cholinesterase activity of the brain-pituitary-adrenal axis in the rat.

This investigator also monitored related research that was funded under NASA's Minority Grant Program at the College of Pharmacy at Florida A & M University. A number of treatments have been tested or suggested to alleviate the deleterious symptoms associated with rhythm desynchronization or to hasten the readaptation process. These treatments include exercise, pre-adaptation by altering sleep/wake cycles, relaxation techniques, electrosleep therapy, acupuncture, altered meal timing and constituents, and drug administration. Researchers evaluated the effects of drugs on the cholinergic enzyme system of various rat brain regions to study their reported use in facilitating readaptation following phase shifts. Theophylline, caffeine, imipramine, and ethanol are representative chronobiotic drugs tested in these studies. The hypothalamus, hippocampus, midbrain and cerebral cortex of rats were dissected, and their choline acetyltransferase (ChAT) and acetyl-cholinesterase (AChE) were determined by spectrophotometric assays. The results obtained clearly indicate that all four drugs, which are known to affect the circadian rhythms and which have been used one way or another to facilitate readaptation to phase shifts, affect the cholinergic enzyme system of various brain regions. These findings suggest that the cholinergic system may play an important role in phase shift adaptation.

In other studies Florida A & M researchers found that exposure to stress had a definite effect on the cholinergic enzymes of the brain. In one study, stress resulted in a decrease in the activity of cholinesterase enzyme activity in the cerebral cortex (hypothalamus) of the brain, as well as in the pituitary and the adrenal glands of rats (Fig. 30). This effect was not present if animals were adrenalectomized. The exposure to stress resulted in an increase in the activity of brain choline acetyltransferase in the different brain regions studied. The results obtained are of great interest because the cholinergic system is involved in behavior and performance, and increasing the cholinergic activity might lead to different types of stress-related disorders. In another experiment, exposure to stress led to dramatic changes in the levels of the cholinergic enzymes of the gastrointestinal tracts. These effects were related to the availability of adrenal cortex hormones. One of the tissues that was very sensitive to stress exposure was the ileum. In another study, stress-induced analgesia, was mediated through the elevation of blood glucose levels. Hyperglycemia, associated with analgesia, can be reversed by insulin administration.

Publications: (1) Gabriel, N.N. and K.F.A. Soliman. 1983. "Effect of stress on the acetylcholinesterase activity of the hypothalamus-pituitary-adrenal axis in the rat." HORMONE RESEARCH 17: 43-48. (2) Soliman, K.F.A., J.N. Pinkston and J.O. Owasoyo. 1984. "The role of the adrenal gland in ethanol triglyceride mobilization." PHARMACOLOGY 29: 94-98. (3) Walker, C.A., M.R.I. Soliman and K.F.A. Soliman. 1983. "Chronopharmacology and chronotoxicology of CNS drugs: Interrelationships with neuromodulators." JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY 2(6): 359-370. (4) Winget, C.M., C.W. DeRoshia, C.L. Markley, and D.C. Holley. 1984. "A review of human physiological and performance changes associated with desynchronosis of biological rhythms." AVIATION, SPACE AND ENVIRONMENTAL MEDICINE 55: 1085-1096.

GENERAL BIOMEDICAL RESEARCH RTOP 199-20-92
A.D. Mandel, manager

The main objective of this program is to provide research in areas not specifically covered by other RTOP's. Studies currently focus on detection of infectious disease effects of weightlessness on the immune system, and nutritional metabolism.

Prolonged bedrest decreases effectiveness of the body to metabolize glucose. (Following bedrest, subjects' plasma levels of insulin was 200% above normal and glucose was 10% above normal). Apparently the body's secretion of insulin is not capable of returning plasma glucose to normal levels under these conditions, and muscle cells are especially insulin resistant. Excess glucose would then be stored in the body as triglycerides, which in high concentrations can clog blood vessels and lead to cardiovascular maladies such as atherosclerosis. Although the exact process causing the insulin resistance is unknown, a low calorie diet prevents excess glucose and triglycerides accumulating in the blood.

Confinement in the Space Shuttle favors the exchange of microorganisms among crew members. The most common types exchanged are simple respiratory and gastrointestinal organisms although latent infections from viruses can persist in the body for long periods without obvious symptoms. If a virus does develop further, it tends to be severe. Preventative measures developed include assays that allow rapid detecion of infectious disease in astronauts prior to launch. To indicate the presence of infection, such assays measure numbers of lymphocytes, the body's defense cells, or lymphocytes' secretion of interferon, the body's initial chemical defense to prevent viruses from replicating.

Immunologists also use mitogenic compunds to stimulate the immune response of lymphocytes, which then grow into larger blast cells, mature, and undergo cell division, as if in response to a naturally-occuring antigen. Generally, mitogens elicit a reduced response in lymphocytyes from the blood of cosmonauts or astronauts after flight; on the other hand lymphocytes from rats flown in space for twenty days show a strong blastogenic response against several mitogens.

Weightlessness may interfere with the activity of lymphocytes and other cells by disrupting cellular transport and concentration of biochemical metabolites, disrupting distribution of cellular organelles, or disrupting some forms of cellular differentiation itself, such as the blastogenic activation of leucocytes. In weightlessness a lymphocyte may become spherical, causing lower DNA synthesis in the cell than in healthy, active, normally-flattened lymphocytes. Lymphocyte response is monitored in experiments on Earth with techniques simulating weightlessness in animals, and in flight experiments, for example, treating lymphocyte cultures with mitogens as in the Shuttle-Spacelab 1 experiment of Swiss researcher Agusto Cogoli.

Since the late 1960's nutritional research sponsored by Ames Research Center ellucidated the effects of different foods on brain biochemistry. Since then, biochemical evidence revealed that different nutrients will change the amount of various neurotransmitters in the brain, thereby affecting performance. Nutrients were found to alter the synthesis of neurotransmitters, such as serotonin, dopamine, and norepinephrine. The amounts of these transmitters, is limited by the amounts of certain amino acids provided by the proteins in food.

Serotonin assists in inducing relaxed sleep, the desire for a balance of types of food, increased motor activity, stimulating smooth muscle contraction, and decreasing sensitivity to pain, although serotonin is not as strong as opiates. Serotonin is also a potent vasoconstrictor. Animals sleep less when given a substance that blocks serotonin synthesis. After one carbohydrate meal both older and younger human adults did worse on performance tests.

Serotonin is made directly from the dietary protein tryptophan. A meal rich in carbohydrates usually precedes serotonin release from the brain. This increase in serotonin acts as a signal to choose more protein and less carbohydrate at the next meal.

Catecholamines, another biochemical group of neurotransmitters, appear to be evolutionarily very old. High protein meals provide the amino acid tyrosine, the dietary precursor of the catecholamines dopamine and norepinephrine. Both are synthesized in the neuron along a single pathway: from tyrosine to dihydroxy-phenalalanine, or DOPA, to dopamine to norepinephrine. Dopamine helps to regulate the mental activities of memory and emotion, and to coordinate fine muscular movement, such as picking up small objects.

Norepinephrine aids alertness, the coordination of body movement and balance, and control of the hypothalamus, which in turn regulates hunger, thirst, body temperature, and blood pressure. Copper and vitamin C also appear to be used in the formation of norepinephrine from dopamine. Future research should continue to correlate plasma amino acids with changes in physiological performance.

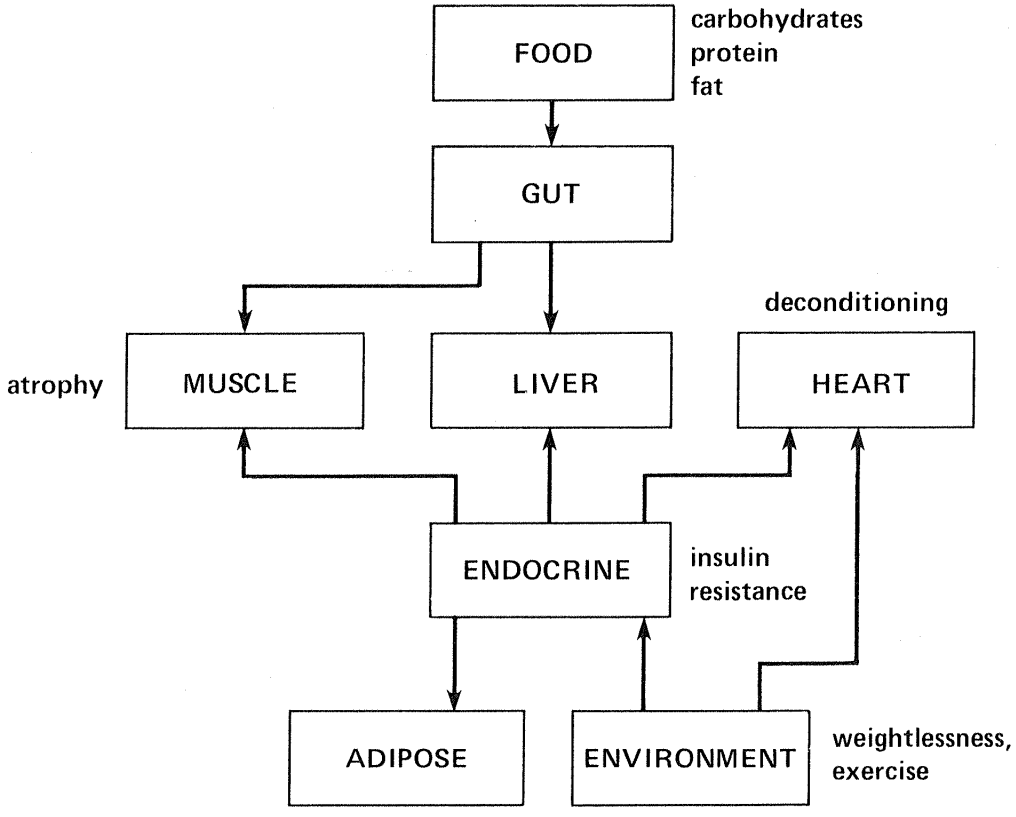

Fig. 31. A simplified version of a computer simulation is depicted to show different bodily functions and relevant conditions affecting normal glucose tolerance in humans. To stimulate the effect of weightlessness, experiments are performed using suspended rat hindlimbs for the study of atrophied soleus muscles. Quantitative data from these experiments, e.g., reduced glucose uptake, are fed into the computer model to study systematically the development of specific abnormalities. (Dolkas 199-20-92-02)

Mechanisms of Insulin Insensitivity in Muscle
199-20-92-02

C.B. Dolkas, Biomedical Research Division, Ames Research Center

Studies in human subjects have shown that both insulin resistance and muscle weakness occur with extended inactivity during prolonged bedrest. Although insulin resistance has not, as yet, been demonstrated in spaceflight, muscle atrophy and weakness has been demonstrated. A similar atrophy of the soleus muscle has been noted in the hindleg of laboratory rats placed in suspension hypokinesia, as a model for weightlessness. Recent studies have shown a near normal weight gain in rats placed in a tail/hindlimbs suspension, while the soleus muscle atrophies to one half of control muscle size after two weeks of suspension. A protocol was developed for exercise training sedentary year-old rats and evaluating its effect on reducing insulin resistance. Enhanced insulin sensitivity seven days after the end of exercise training is retained if body weight gain is reduced. Sensitivity to insulin-induced glucose disposal is also enhanced in control rats by reducing caloric intake. This results in partial depletion of glycogen stores in the liver and skeletal muscle, and glucose uptake is enhanced.

A large computer model was developed (Fig. 31) which can simulate a normal oral glucose tolerance test (OGTT) in an average man by simulating the principal, pertinent biochemical pathways of the body. If a faithful computer model of an OGTT can be developed, this non-animal model could be the basis for assessing, quantitatively, the various factors and tissue sites that contribute to the apparent insulin resistance. For example, the changes in glucose uptake in the liver and muscle tissues found in these studies on insulin-resistant rats could likewise be put into the model to evaluate the effect of a particular parameter on the total functioning of insulin resistance. The level of insulin in the body is an important factor regulating protein balance in skeletal muscle. Considering food intake in addition to the levels of insulin, studies have shown that insulin not only promotes protein synthesis (by promoting the net uptake of amino acids by muscle, and then into protein), but also inhibits protein degradation.

Publications: Narimiya, M., S. Azhar, C.B. Dolkas, C.E. Mondon, C. Sims, D.W. Wright, and G.M. Reaven. 1984. "Insulin resistance in older rats." AMERICAN JOURNAL OF PHYSIOLOGY 246: E397-E404.

Immune Response in Simulated Weightlessness
199-20-92-07

A.D. Mandel, Biomedical Research Division, Ames Research Center

Investigators studied the effect of suspension (simulated weightlessness) on resistance to infectious disease in mice. For periods of one and two weeks, mice were suspended in an antiorthostatic (head-down) position, which closely simulates the effects of weightlessness. Mice in control groups were suspended in an orthostatic position (head-up), were not suspended, or were allowed to recover for a week after head-down suspension with other mice in colony cages. Members of each group were infected with Salmonella typhimurium LT2. Preliminary results suggest dramatic changes in spleen weight in antiorthostatically suspended mice compared to controls, and possibly other changes in immunological parameters. The very early preliminary data suggested that the mice suspended in the model were dying faster than the controls; however, these studies were extended and the data at the present time indicate no significant differance in survival time among the groups. Preliminary data also suggest that low-dose treatment of mice with gamma-interferon may alter the sensitivity of the mice to Salmonella. Studies were started to determine if antiorthostatic suspension can affect the susceptibility of normally-resistant mice to the diabetogenic strain of encephalomyelitis virus.

J.A. Williams collaborated with researchers at Memorial Sloan-Kettering Cancer Center in New York City on a promising new technique for the magnetic removal from bone marrow of a specific cell, the T-4 lymphocyte. The presence of this cell is known to reduce the effectiveness of therapy for bone cancer. Monoclonal antibodies, which were made by complexing magnetic microspheres with antibodies that bind to T-lymphocytes, proved more effective in removing the T-4 cells than previously reported techniques. Research at Ames originally developed monoclonal antibodies that bind to viruses for a rapid assay to detect the earliest stages of infection in astronauts up to the day of a space launch.

Publications: (1) Rose, A., J.M. Steffen, X.J. Mussachia, A.D. Mandel, and G. Sonnenfeld. 1984. "Effect of antiorthostatic suspension on interferon alpha/beta production by the mouse." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 177: 253-256. (2) Steffen, J.M., R. Robb, M.J. Dombrowski, X.J. Musacchia, A.D. Mandel, and G. Sonnenfeld. 1984. "A suspension model for hypokinetic/ hypodynamic and antiorthosatic responses in the mouse." AVIATION,

SPACE AND ENVIRONMENTAL MEDICINE 55: 612-616. (3) Williams, J.A. 1984. "Effect of medium concentration on antibody production." JOURNAL OF TISSUE CULTURE METHODS 8(3): 115-118.

Nutritional Control of Neurotransmitters 199-20-92-10

R.J. Wurtman, Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge
C.M. Winget, Ames Technical Monitor

Research under this task showed that the amounts of tyrosine that must be suppiled to slices of rat brain caudate nucleus to sustain dopamine release in vitro depend on the frequency at which the slices are depolarized, and the number of depolarizations. Environmental stresses depleted rat brain norepinephrine levels, and modified subsequent motor activity and coping behavior; both of these effects were prevented by supplemental dietary tyrosine. The ability of an anorexic drug to suppress eating depends on the composition of the test diet: serotonin-releasing drugs suppress consumption of high-carbohydrate foods, but not of protein-rich foods. A serotonin-releasing drug, fenfluramine, selectively diminished snack carbohydrate consumption among carbohydrate-craving obese people, without affecting protein intake. The brain phospholipids (i.e., lecithin) formed by methylation, have different fatty acid compositions, and probably different functional and behavioral roles, from those phospholipids formed by incorporating pre-existing choline.

Human studies confirmed that single, isocaloric, protein vs. carbohydrate meals have opposite effects on the ratio of human plasma tryptophan to the other large neutral amino acids, and therefore are likely to differentially affect brain tryptophan and serotonin. A large behavioral study was completed which examined the behavioral effects of protein vs. carbohydrate meals on human performance and mood (40 subjects were tested). Preliminary data analyses indicate that, as predicted, carbohydrate meals can increase drowsiness and impair performance. In another study low and moderate doses of caffeine significantly improved human performance (vigilance and choice reaction time) without causing any decrement in accuracy or alteration in subjective mood. Development continued on an ambulatory activity monitoring system. With these monitors, patterns of spontaneous motor activity exhibited by humans can be reliably recorded, and circadian and ultradian rhythms can be quantified with Fourier analysis.

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GRAVITATIONAL BIOLOGY

THE GRAVITATIONAL BIOLOGY PROGRAM

The objective of gravitational biology is twofold: to provide an adequate base of fundamental biological information for future space missions, and to use the unique properties of the space environment to enlarge our concepts of terrestrial biology. It is the necessary prelude and foundation for the biological use and habitability of space. The answers we seek to questions vital to space habitation include: can plants and animals survive more than one generation in space; what minimum G load is required for normal development; and can some other stimuli like light or vibration be used as a substitute for gravity in space. The pervasiveness and antiquity of gravity's effect has shaped terrestrial life since its very origin. This makes gravity a unique and ideal tool that only NASA has the capability to fully manipulate and utilize. Ground-based research has not only led to flight experiments selected for Spacelab missions and also flown in the Shuttle orbiter and on Cosmos satellites, but has produced valuable results on the ground. For example, studies of the physiology of the inner ear have contributed significantly to understanding Meniere's disease, an affliction characterized by vertigo, nausea and progressive deafness that affects many people on Earth. Other gravitational studies are directed toward understanding the pathology of osteoporosis, an insidious crippler that accompanies aging especially in women; the physiology of lignification, the very structural fiber of plants; and the role of gravity in calcium mediated physiological mechanisms and calcium metabolism in both plants and animals. Gravitational biology research, therefore, forms a fundamental scientific foundation applicable to solving biological problems both in space and on Earth.

(From NASA Space Science and Applications Notice, October 25, 1982)

Thora Halstead
Program Manager

BIOLOGICAL ADAPTATION RTOP 199-40-32
E.M. Holton, manager

Understanding how organisms adapt to changes in gravity aids biologists in understanding the evolution of structures and functions among different species of plants, invertebrates and vertebrates. Biological processes studied under the aegis of the Biological Adaptation RTOP include structure, movement, thermoregulation and the transport and regulation of fluids and minerals during changes in gravity. Manipulation of gravity below 1 G for more than a few seconds at a time can only be accomplished during spaceflight.

Investigators study various organisms and their structural elements, such as cellulose and lignin in plants, and bone, cartilage and chitin in animals. In fact, calcium-modulating proteins (e.g., calmodulin) may have been a critical event in the evolution of eukaryotes. The development of calcium as a regulator of cellular function and as a structural material may have allowed multicellular organisms to grow and multiply under Earth's gravity. If gravity played a role in the evolution of the calmodulin system, what would happen to this system after multiple generations living without the stimulation of gravity in a weightless environment?

Bone specimens from laboratory rats flown for periods just under 20 days on three unmanned Soviet biosatellites (Cosmos 782, 936 and 1129) were analyzed by US investigators. The weight-bearing bones of the leg, the femur and tibia, reduced their rates of cortical bone growth. Both trabecular and cortical bone volumes decreased, although reduction of the trabeculae was more severe. Ash content of weight-bearing bones decreased, while marrow fat increased. Forelimb bones lost mineral, and the spinal column lost strength. The weight-bearing skeleton did not fully recover by 29 days postflight.

The naturally-occurring, ongoing processes of skeletal modeling also changed. Bone formation stopped almost completely, and bone resorption was virtually unchanged. Because bone formation was the larger of the two effects, spaceflight caused a net bone loss. Some impaired growth was noted in the jaws. Other skeletal elements, that undergo less active use by the organism and model at a slower rate, may show changes after periods of weightless flight longer than 20 days.

On Cosmos 936 a group of rats was subjected to artificial gravity (1 G) on a small centrifuge. This group's decrease in bone formation was similar to the weightless group, but bone mass recovered more rapidly postflight in the centrifuged group, and their femurs maintained normal strength. Centrifuges on Earth, as well as in space, are necessary for the scientific study of gravitational biology; they provide a way to investigate how and why organisms respond to alterations in the normal load of gravity. Expertise from two decades of biological studies using the centrifuge facilities at Ames Research Center (ARC) allowed investigators of the Biomedical Research Division to contribute in design studies of a space centrifuge, or Variable Gravity Research Facility (VGRF). Since the early 1960's the Space Science Board of the National Academy of Sciences repeatedly encouraged NASA to develop such a national research facility in space as a counterpart to the centrifuges on Earth at ARC. A VGRF on board Spacelab, or on a space station (Fig. 32), would permit experiments designed for less than 1 G but greater than zero G. Work began in cooperation with ARC's Biosystems Division for the determination of vibration tolerances and undesirable coriolis effects for different species. Some engineering problems were similar to those in the development of Ames' Vestibular Research Facility, although the vestibular spinning and control mechanism was more complex, requiring variable speeds and two-axis gimbals.

On Earth, investigators simulate the physiological effects of weightlessness on organisms using systems that lift and partially unload weight from the hindlimbs of rodents. Such a laboratory model produces results to compare with spaceflight data and allows researchers to investigate the underlying causes of changes in the major weight-bearing bones of the body. In this way a data base is created of results from flight and ground experiments to aid in the careful design of future research.

All biological flight studies thus far have been limited by a minimal number of specimens, and weightlessness exposures for brief periods of time, usually less than 20 days. Of particular interest in the future is the effect of long-term exposures of weightlessness on various animal and plant species over many months and spanning many generations. As an example, carrot cells have been able to divide and develop in weightlessness, but whether continuous generations could continue to grow is unknown. Except for missions of the Soviet Salyut space station, spaceflights are too short to see if plants can flower in weightlessness, or to see if animals can produce successive generations in weightlessness. Only biological experiments on long-term flights will permit scientists to finally understand the role of gravity on biological adaptation and function.

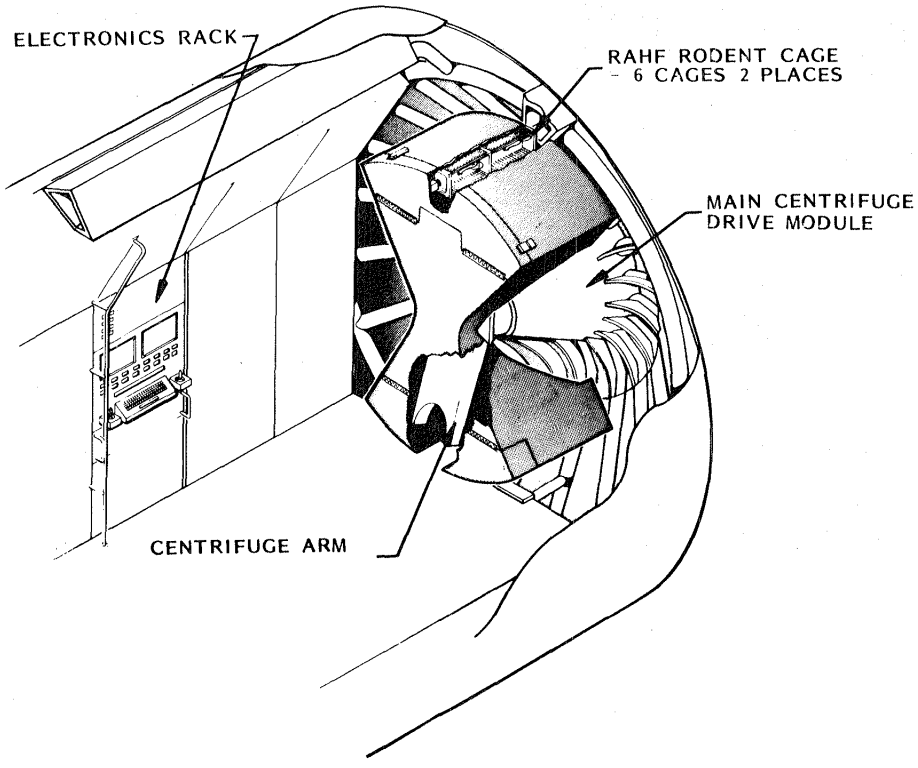

Fig. 32. Artist's conception of a large biological centrifuge on Spacelab or on Space Station. Rodent cages are of a design similar to cages built by Ames' Life Sciences Flight Experiments Project Office as part of the flight-qualified Research Animal Holding Facility (RAHF) scheduled for flight in 1985 on Spacelab 3.

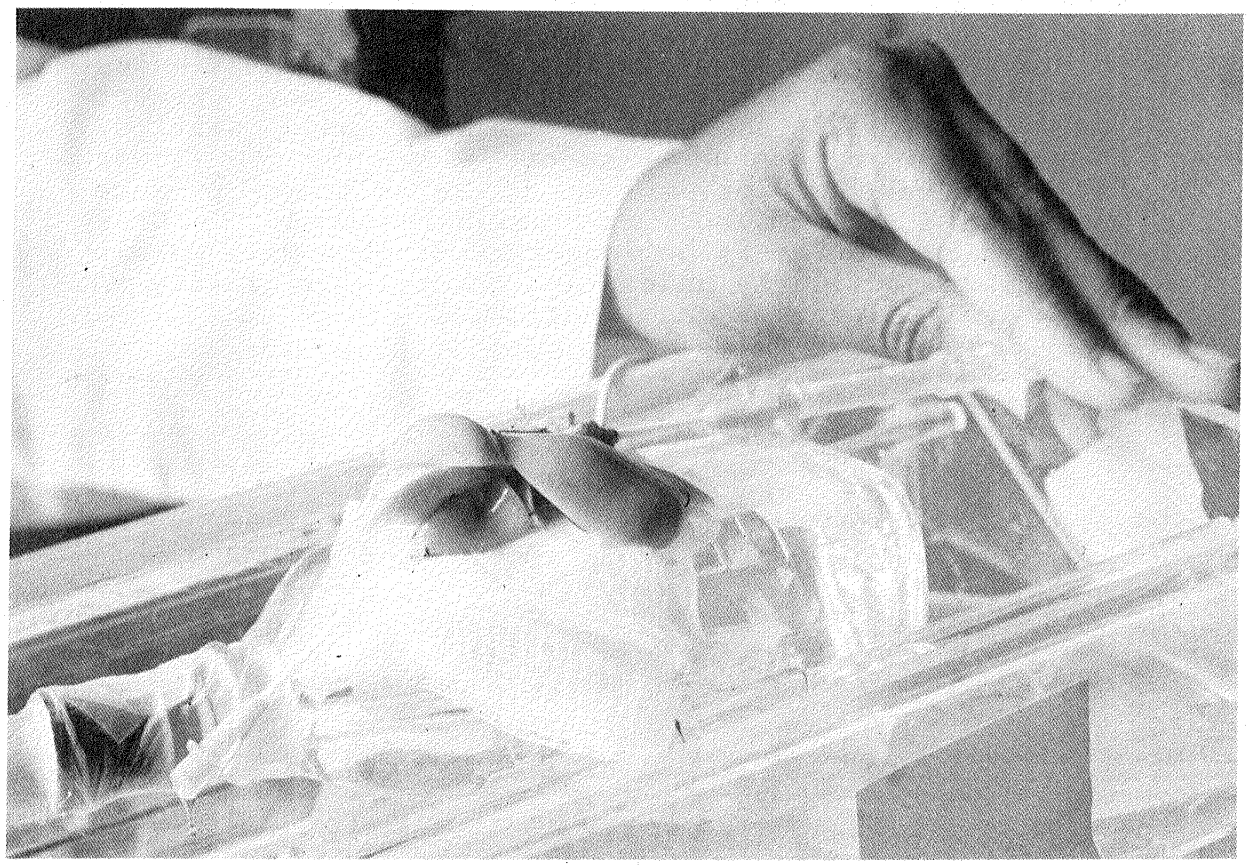

Fig. 33. The reverse liver perfusion technique (via the superior vena cava) used to prepare isolated hepatocytes from hyper-G stressed rats. This technique enables the perfusion of the liver in situ within 15 seconds after decapitation of the animal. The perfusate is shown leaving from the portal vein cannula. (Oyama 199-40-32-01)

Hyper-gravitational Effects on Metabolism and Thermoregulation 199-40-32-01

J. Oyama, Biomedical Research Division, Ames Research Center
C.B. Monson, National Research Council Associate, Ames Research Center

Comparative studies of gluconeogenic rates by isolated hepatocytes (Fig. 33) from hyper-G stressed and noncentrifuged control rats have shown the rates of the stressed rats to be more than twice the controls. These results are similar to previous in vivo studies and lend support to the usefulness of the hepatocyte preparation for investigations on the mechanisms of hyper-G stress effects on hepatic gluconeogenesis. These studies are aimed at obtaining a better understanding of the mechanisms involved with the stress effects induced when animals exposed to spaceflight are returned to normal earth's gravity.

During the past year, research has gradually shifted from investigations dealing with acute stress effects to the role which abnormal gravitational forces, i.e., hyper-G and zero-G, have on growth and developmental processes in mammals. Results obtained to date indicate that graded hyper-G intensities ranging from 1-2 G have virtually no effect on the growth rates of mice and rats in utero and that a minimum or critical body size must be reached before gravitational forces will exert a significant effect on growth and development postnatally. This critical body mass tentatively determined to be approximately 50 grams. Further studies on growth and development of various animal species are currently underway to validate this proposed minimum mass value for gravitational effects. If the proposed minimum body mass is validated, it would mean that animal species such as the mouse, which do not grow beyond 50 grams body mass, would not be affected by fractional-G or zero-G with respect to their growth and development postnatally; hence, they would not be suitable experimental subjects for future spaceflights involving these processes.

Publications: (1) Megory, E. and J. Oyama. 1984. "Hypergravity effects on litter size, nursing activity, prolactin, TSH, T3, and T4 in the rat." AVIATION, SPACE AND ENVIRONMENTAL MEDICINE 55: 1129-1135. (2) Monson, C.B. and J. Oyama. 1984. "Core temperature of tailless rats exposed to centrifugation." PHYSIOLOGIST 27(6, Suppl.): S97-S98.

Renal Function, Water, Electrolyte Balance, and Intestinal Transport in Hypokinetic Animals
199-40-32-02

X.J. Musacchia and J.M. Steffen, Department of Physiology and Biophysics, University of Louisville School of Medicine
E.M. Holton, Ames Technical Monitor

Cardiovascular responses and fluid/electrolyte shifts seen during spaceflight have been attributed to cephalad redistribution of vascular fluid. The antiorthostatic (AO) rat (suspended head-down, tilted 15-20 deg) was used to model these responses. Current studies showed that elevated blood pressures in AO rats are sustained for periods up to seven days. Comparisons were made with presuspension rats. Increased blood pressure in headdown tilted subjects suggests a specific response to AO positioning, potentially relatable to cephalad fluid shift. To assess a role for hormonal regulation of sodium excretion, serum aldosterone levels were measured. Circulating aldosterone levels were seen to increase about 100% during seven days of AO suspension. Sodium excretion also increased significantly during AO suspension and potassium excretion increased during the last day. These results suggest that aldosterone may not be involved in the long-term regulation of increased sodium excretion in AO rats.

Publications: (1) Steffen, J.M. and X.J. Musacchia. 1984. "Thymic involution in the suspended rat model for weightlessness: Decreased glucocorticoid receptor concentration." PHYSIOLOGIST 27(6, Suppl.): S39-S40. (2) Steffen, J.M., R. Robb, M.J. Dombrowski, X.J. Musacchia, A.D. Mandel, and G. Sonnenfeld. 1984. "A suspension model for hypokinetic/hypodynamic and antiorthostatic responses in the mouse." AVIATION, SPACE AND ENVIRONMENTAL MEDICINE 55: 612-616

Structural Development and Gravity 199-40-32-04

E.M. Holton, Biomedical Research Division, Ames Research Center

This research task is designed to elucidate the mechanisms by which gravity loading and/or fluid distribution alter bone formation and/or resorption in rat bone. The research projects completed this year include: (1) analysis of bone parameters in rats from 6 weeks to 68 weeks of age, (2) restricted access area in which rats on the model were not allowed to touch any side of the cage, and (3) the effect of dietary calcium levels on bone formation and resorption rates in controls and head-down rats.

(1) The major findings of this project, using Sprague-Dawley derived male rats, are a) the tibia and the vertebral column increase about 35% in length from 6 to 18 weeks of age, but elongate very little (about 5%) over the next 50 weeks; b) bone apposition rate at the tibiofibular junction (TFJ) decreases linearly from 9.4 microns/day at 6 weeks of age to about 1.9 microns/day at 14 weeks, 1.0 micron/day at 18 weeks, 0.4 micron/day at 28 weeks, and 0.13 micron/day at 53 weeks of age; c) marrow area at the TFJ remains constant from 6 to 10 weeks, then increases from about 0.8 sq. mm to 1.16 sq. mm by 68 weeks of age suggesting that formation and resorption are comparable at this sampling site until 10 weeks of age when resorption predominates; d) body mass increases linearly from about 150 gm at 4 weeks of age to 310 gm by 8 weeks, 400 gm by 15 weeks, 550 gm by 43 weeks, and 580 gm at 68 weeks of age. (2) Restricting the rats on the model so that they could not touch the plexiglas sides of the cage did not further decrease bone formation rates following two weeks of experimentation. (3) Marrow area in head-down rats was very similar to control rats; in both groups, marrow area was inversely related to dietary calcium suggesting that bone resorption at the tibial endosteum at the TFJ is more responsive to metabolic factors than to load-bearing. Bone formation at the periosteal surface of the tibia at the TFJ was not affected by diet in head-down animals, while control rats showed a suppression of formation only at the very low level of dietary calcium (0.1% Ca., 0.3% P); bone formation in head-down rats was significantly lower than controls (40%) except in the very low Ca diet when the difference between groups was not significant (Fig. 34).

Publications: (1) Doty, S.B. and E.M. Holton. 1984. "Alterations in bone forming cells due to reduced weight bearing." PHYSIOLOGIST 27(6, Suppl.): S81-S82. (2) Globus, R.K., D.D. Bikle and E. Morey-Holton. 1984. "Effects of simulated weightlessness on bone mineral metabolism." ENDOCRINOLOGY 114: 2264-2270. (3) Montgomery, L.D., G.N. Mc Ewen, R.L. Gerber, C.E. Cann, and E.R. Morey. 1984. "Use of impedance plethysmography to continually monitor bone marrow blood flow." AVIATION, SPACE AND ENVIRONMENTAL MEDICINE 55: 604-611. (3) Wronski, T.J. and E.R. Morey. 1983. "Inhibition of cortical and trabecular bone formation in the long bones of immobilized monkeys." CLINICAL ORTHOPAEDICS 181: 269-276. (4) Simmons, D.J., B. Grazman, J.E. Russell, W.V. Walker, D.D. Bikle, and E.R. Morey. 1983. "Simulating certain aspects of hypogravity: Effects on bone maturation in the non-weight bearing skeleton." AVIATION, SPACE AND ENVIRONMENTAL MEDICINE 54(12): 1080-1084.

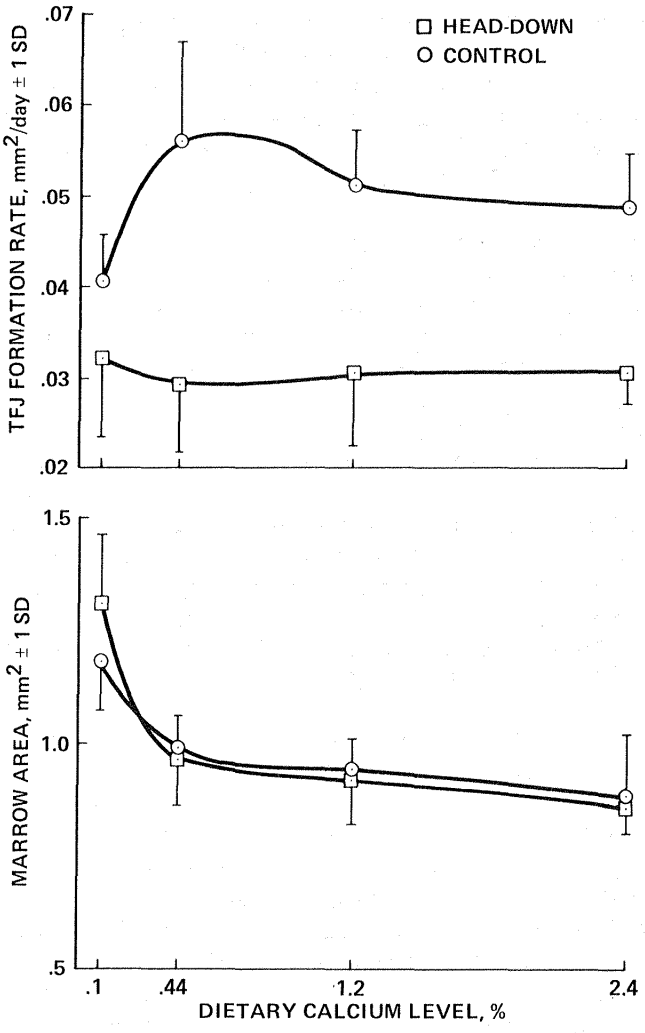

Fig. 34. Bone formation rate at the tibiofibular junction (TFJ) was significantly lower in rats undergoing head-down suspension to simulate certain effects of weightlessness (top), and was not influenced by dietary calcium level. Marrow area was not significantly different in head-down and control groups, and the response to dietary calcium was similar in both groups. (Holton 199-40-32-04)

(5) Spector, M., R.T. Turner, E.M. Holton, D.J. Baylink, and N.H. Bell. 1983. "Arrested bone formation during spaceflight results in a hypomineralized skeletal defect." PHYSIOLOGIST 26(6, Suppl.): S110-S111. (6) Spengler, D.M., E.R. Morey, D.R. Carter, R.T. Turner, and D.J. Baylink. 1983. "Effects of spaceflight on structural and material strength of growing bone." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY 174: 224-228.

Effect of Decreased Gravity on Circulation in the Rat 199-40-32-10

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E.M. Holton, Ames Technical Monitor

During the past year, the following data were obtained from chronically-cannulated rats (aortic and right atrial cannulas implanted about two weeks prior to the study) in a hypokinetic antiorthostatic model with a rat tilted at about 20 deg head-down. Immobilized (space restricted) animals did not adapt to repeated immobilization as indicated by levels of stress hormones. Rats on the model adapted after three to four days, and when negative tilt was eliminated, they adapted within a couple of hours. Adaptation was determined by measuring stress hormones, such as plasma prolactin, ACTH and corticosterone. Preliminary findings indicate that the antidiuretic hormone (ADH) in plasma decreased on the first day of exposure, but the angiotensin II level was only slightly elevated. Circadian variation in colonic temperature was absent during the initial exposure to the negative tilt model. Abnormal temperature regulation, and often hypothermia, were measured. Circadian patterns for cardiac output were undisturbed.

Weightlessness Simulation: Physiological Changes in the Fast and Slow Muscle 199-40-32-12

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E.M. Holton, Ames Technical Monitor

No reports are available studying the cholinergic system of nerve and muscle such as choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) and the acetylcholine receptor (AChR) during suspension induced hypokinetic conditions. The key enzymes involved in the synthesis and hydrolysis of the neurotransmitter, acetylcholine (ACh), ChAT and AChE are reported to be synthesized in the cell bodies of cholinergic motor nerves which innervate skeletal muscles.

Following synthesis these enzymes are transported by axoplasmic flow to the nerve terminals. ChAT is thought to remain highly localized in nerve terminals with low concentration in the muscles proper, whereas AChE is present in the axon and its activity is equally high in soleus (SOL) and higher in extensor digitorum longus (EDL). Its presence in mature muscle depends to a large extent on innervation and muscle activity. Among various reported models for studying disuse and stimulation of weightlessness, hindlimb suspension was used as a model of disuse to evaluate the effects of decreased activity on muscle characteristics.

Experiments were initiated to study the effects of reduced muscle activity on AChE and its molecular forms, choline acetyltransferase and nicotinic receptor binding in innervated slow and fast muscle. The weight of SOL was reduced to 64% within one week and continued to decrease progressively up to the third week when the weight was reduced to 40% as compared to controls. EDL showed a significant decrease in its weight only at the end of three weeks hypokinesia when it was reduced to 71% of control.

Hypokinesia caused a significant increase in ChAT activity in both sciatic nerve and in hinlimb muscles. Recovery was complete within one week after removal of suspension in nerve and muscles. In hypokinetic animals, EDL-AChE did not show a significant change when activity was calculated per g of muscle or per mg of protein. However, AChE activity in soleus increased by 161% and 261% when calculated on the basis of per g of muscle or per mg of protein, respectively. When individual molecular forms of AChE were assayed an increase of all four major forms: 16S, 12S, 10S and 4S were found in SOL, whereas in the EDL, no significant change was observed in the 4S and 16S while the 10S was increased. AChE activity in sciatic nerve was not affected significantly up to three weeks of hypokinesia from that of controls. Data on nicotinic acetylcholine receptor binding using ^{3}H-ACh as ligand indicate that two weeks hypokinesia caused a twofold increase ($p < 0.05$) in receptor binding in solubilized membrane preparations from both EDL and SOL compared to control.

LIFE SCIENCES FLIGHT EXPERIMENTS

LIFE SCIENCES FLIGHT EXPERIMENTS PROGRAM

The goal of the Life Sciences Flight Experiments Program is to establish a multi-use, multi-mission life sciences laboratory using the European-built Spacelab (SL). This will provide an opportunity for investigations of the effects of the space environment on biological systems that cannot be performed on the ground. A major feature of the program is the development of an inventory of commonly used scientific equipment which may be flown on many missions and serve the needs of multiple investigations. The near-term objective is to fly dedicated Life Science Spacelab missions at two-year intervals. Dedicated missions allow a maximum number of integrated experiments to be flown at one time, thus permitting extensive, simultaneous measurements on the limited set of specimens available on each flight. Such broad coverage provides numerous opportunities to correlate measurements from diverse experiments to characterize the biological effects of microgravity. Approximately 15 to 20 investigations will be carried out on each mission, with the first laboratory dedicated to the life sciences, Spacelab Life Sciences 1, scheduled for a 1986 launch. A double rack of experiments was successfully flown on SL-1 and three racks of equipment are scheduled for flight on SL-3. Smaller scale experiments have been flown on STS-2 and STS-3 and will be flown on SL-2.

Tom Perry
Program Manager

LIFE SCIENCES FLIGHT EXPERIMENTS PROGRAM

The near weightlessness of spaceflight remains the definitive environment to test hypotheses developed during ground-based research in gravitational biology and space medicine. Over the past two decades the Life Sciences Directorate at Ames Research Center has developed a multitude of experiments for spaceflight programs, such as Biosatellite (unmanned Earth orbital), Gemini, Apollo, Skylab, the Viking mission to Mars, joint US-USSR Cosmos biosatellites and the Space Shuttle. In the near future, life sciences experiments are scheduled primarily for flights of the Space Shuttle and Spacelab. These experiments only require seven to ten days of weightlessness that the Shuttle-Spacelab flights provide. Experiments requiring weightlessness for many weeks, months or years must wait for long-duration, unmanned satellites or a manned space station.

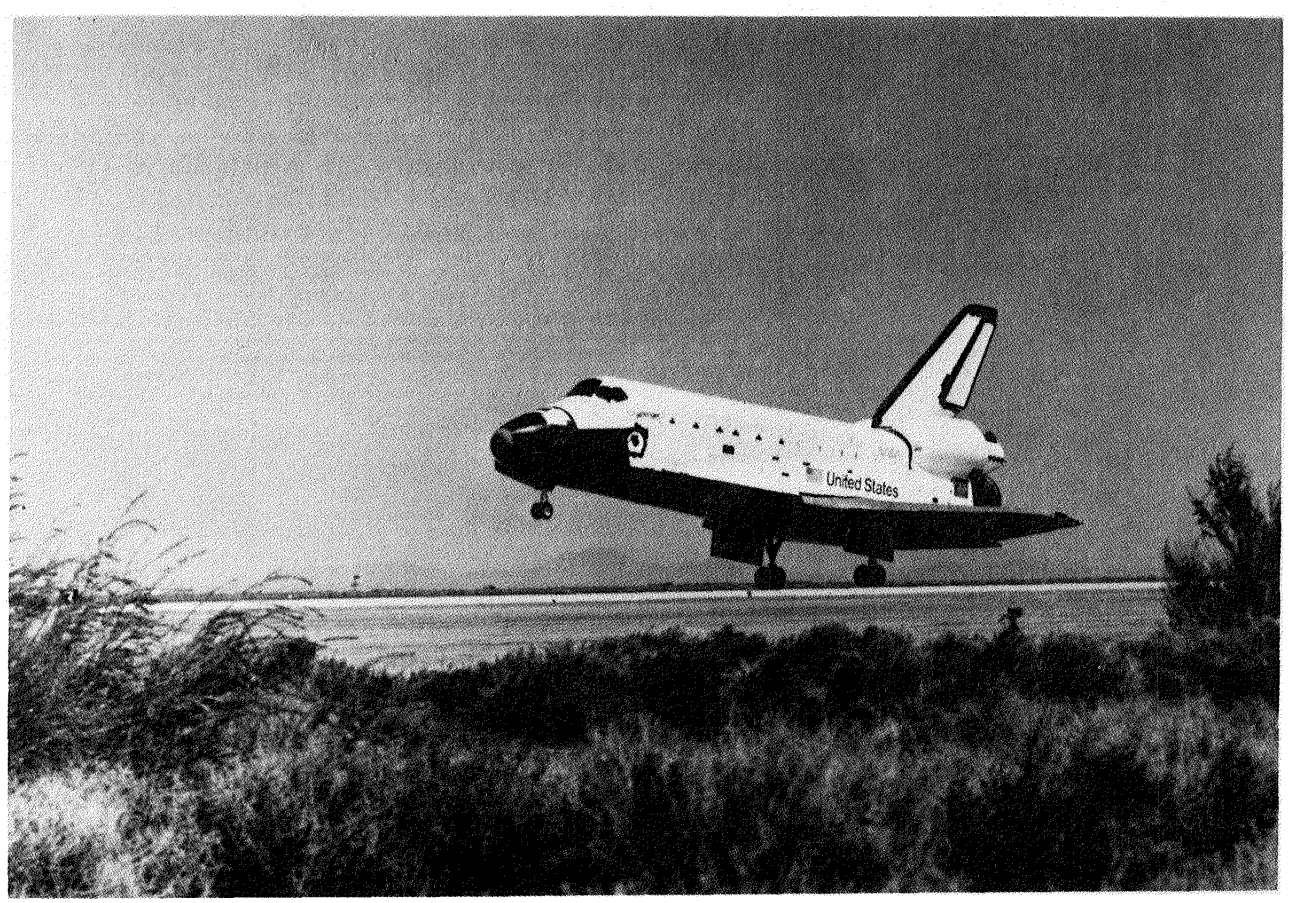

Fig. 35. The Space Shuttle provides scientists with a controlled environment to conduct biological and medical experiments in space.

Spacelab, a pressurized module carried in the cargo bay of the Space Shuttle, provides the crew with a shirt-sleeve environment, and sea-level atmospheric pressure and composition. Spacelab, built jointly by ten European nations through the European Space Agency (ESA), provides an environment where scientists can conduct biological experiments under standard laboratory conditions. Some of the necessary, specialized equipment for Spacelab is being designed and built by the Life Sciences Flight Experiments Project Office (LSFEP) at Ames Research Center.

Among the hardware projects for NASA's many plant and animal experiments, LSFEP has built a Research Animal Holding Facility to provide housing cages, environmental control, food, water, light, and waste management for various animal species. In the cages, wastes are blown down through a coarse grill in the floor onto a screen for drying. Urea and ammonia are trapped on a chemically treated pad and a charcoal bed to control odors. Controlled lighting and air flow permit an environment for animals that is separate from humans. Another unique piece of equipment is the General Purpose Work Station (GPWS), an enclosed workbench to be used for animal surgery and any other laboratory techniques. Like a fume hood in laboratories on Earth, the GPWS provides air flow within a confined area. The GPWS can be accessed by a sliding door, or by a laboratory glove box to completely isolate the working space from the spaceflight cabin. Such equipment is designed to perform those laboratory procedures in space that cannot be delayed until return to Earth.

Life science investigations on Spacelab are performed by scientists from many countries including Canada, Italy, Switzerland, U.K., U.S.A., Australia, Spain, Netherlands and West Germany. Spacelab missions carrying biological experiments will be either multidisciplinary (Spacelab 2 and 3 in 1985), or will be completely dedicated to life sciences (Spacelab Life Sciences 1 and 2 in the mid 1980's). Typical questions addressed on flight experiments are: (1) what is the role of gravity in a variety of biological processes, such as reproduction, growth and development, spatial orientation, and perception; and (2) how does the human body react to spaceflight? The following flight activities describe the current involvement of the Biomedical Research Division (LR) in basic biomedical and gravitational biology experiments using various species on flights of the unmanned Cosmos biosatellite, the Space Shuttle and Spacelab.

Shuttle Student Involvement Program

D.J. Weber, Student Investigator, Cornell University, Ithaca, NY
E.M. Holton, Project Manager/Scientist, Biomedical Research Division, Ames Research Center
D. Larson and M. Ernest, Scientific Sponsors, Pfizer, Inc.
T. Kessler and G. Huston, Engineering Sponsors, General Dynamics, Inc.

A student experiment to study the effects of weightlessness on arthritis was successfully flown on STS-41B in February 1984. This experiment was among those chosen in a nationwide competition, the Shuttle Student Involvement Program (SSIP) sponsored by NASA and the National Science Teachers Association. The experiment was designed by Daniel J. Weber while attending Hunter College High School in New York City. This flight tested the hypothesis that the development of adjuvant-induced arthritis is affected by gravity. Studies with rats on Earth, simulating some aspects of spaceflight by suspending the rear limbs (gravity unloading) and shifting fluids toward the head, inhibited the systemic portion of the disease. This result was not confirmed in the flight experiment. Immunologically different animals were flown compared to those rats used on Earth: gnotobiotic (completely germ-free) animals were used for flight while specific pathogen-free (SPF) animals were used for all ground-based studies. The two different animals had slightly different time courses for the disease: 14 days in the gnotobiotic flight animals compared to 10 days in SPF animals. Shuttle reentry taking place at the time when the systemic disease occured may have significantly affected the data. The difference in time course of the disease was unanticipated prior to flight. The normal control rats carried on STS-41B ate more food and gained more weight compared to controls on the ground. However, both groups added body mass at the same rate.

The rats were housed in colony-type cages with three rats per cage. An Animal Enclosure Module (AEM) was designed for colony housing in flight. Rats are communal and normally live in colonies. STS-41B was the second flight to demonstrate that the AEM could adequately support rats during flight in a Shuttle middeck locker. The Life Sciences Flight Experiments Project Office at Ames is currently investigating an upgrade of the AEM for future biology experiments on the Shuttle.

Joint US-USSR Cosmos Biosatellite: Cardiovascular Measurements

Cooperation between the US and the USSR in the area of space biology and medicine began in 1971 with the signing of the US-USSR Science and Applications agreement. Annual meetings between the two countries created a joint program to fly biological satellites. The principal objectives of these flights were to determine how stresses of spaceflight affect biological systems with particular attention on biomedical problems common to humans and animals. Experiments in space biology and radiation physics were also conducted on these flights. Payloads contained rats, plants, insects, and a variety of other organisms.

This cooperative venture gleaned valuable data for all researchers involved, and was especially useful at a time when independent American biological flight experiments were not possible, due to the Space Shuttle being in the developmental stage. Considerable insight was also gained into Soviet experimental techniques and spaceflight operations. The flights included Cosmos 782 (1975), Cosmos 936 (1977), Cosmos 1129 (1979), and Cosmos 1514 (1983).

"Krovotok"-Cardiovascular Parameters during Spaceflight

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B.S. Kulaev, Institute of Biomedical Problems, Moscow
H. Sandler, Biomedical Research Division, Ames Research Center
H.L. Stone, Health Sciences Center, University of Oklahoma

Cardiovascular measurements from one small rhesus monkey were recorded during Cosmos 1514, a joint US-USSR biosatellite flight test from December 14-19, 1983. Analysis of the data from an implanted combined pressure and flow cuff (CPF) confirmed an increase in blood velocity to the head during spaceflight, as well as lowered blood pressure and peripheral resistance in the vessels. The CPF cuff was designed for implantation around the carotid artery in the neck of small (3-4 kg) rhesus monkeys (Macaca mulatta). Both the American and Soviet research groups implanted a total of 65 rhesus during developmental studies to refine transducer design, surgical procedures and data analysis techniques. In November 1983, US investigators assisted Soviet engineers during a bioengineering simulation in the USSR.

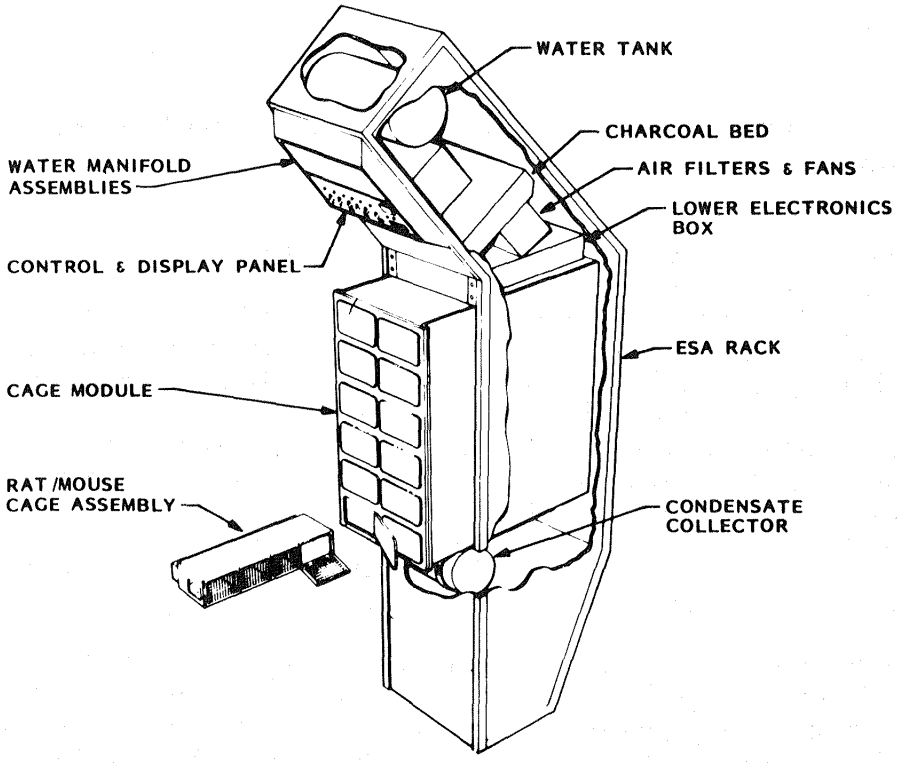

Fig. 36. The Research Animal Holding Facility (RAHF), designed by Ames' Life Sciences Flight Experiments Project Office to house and provide life support for small mammals, will be flight tested on the Spacelab 3 mission with rats and squirrel monkeys. For flexibility of use, the RAHF can be housed in either single or double European Space Agency (ESA)-designed racks inside the pressurized Spacelab.

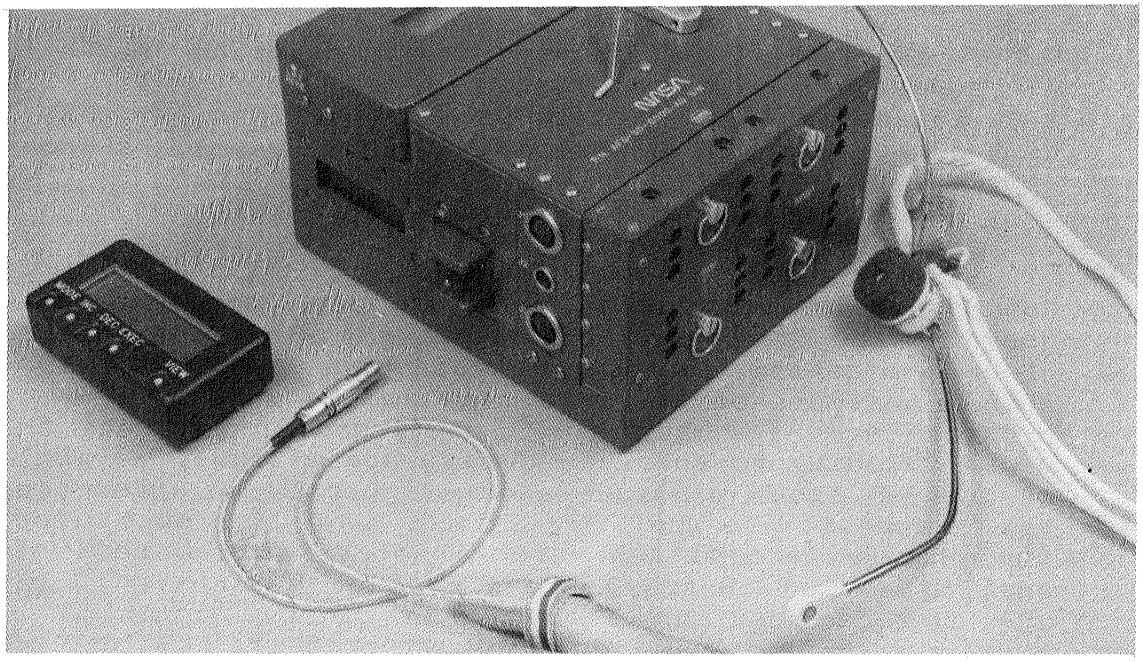

Fig. 37. A belt-size biofeedback unit and recorder with wrist display will permit Spacelab 3 astronaut-scientists to monitor their physiological responses during experiments using Ames-developed Autogenic Feedback Training to counteract motion sickness symptoms.

Soviet investigators then decided to fly a rhesus, nicknamed Bion, in the Cosmos (a modified Vostok spaceship) in December. Another animal, Abrek, served as a synchronous control on the ground. Data were collected for one day on the launch pad, for five minutes every two hours in orbit, and during one postflight test. The flight animal died 69 hours after landing due to a strangulated bowel, possibly a congenital defect, and was not attributable to the instrumentation. Data were transferred from Soviet to American recorders in February 1984.

Spacelabs 2 and 3: Animal Facility Flight Test, Human Motion Sickness Experiment (SL-3) and Calcium Metabolism Study (SL-2)

Research Animal Holding Facility (RAHF)

On the Spacelab 3 mission, a research team led by P.X. Callahan of Ames' Life Sciences Flight Experiments Project Office with R.E. Grindeland, L.M. Kraft and P.R. Lundgren of the Biomedical Research Division (LR), will record animal growth, body composition, organ weights, and concentrations in blood plasma of electrolytes, hormones and cells. These results, with additional data from flight and ground-based studies on food and water consumption, biological rhythms, environmental conditions, and behavior, will enable an assessment of the performance of the RAHF (Fig. 36).

A Preventive Method for the Zero-gravity Sickness Syndrome: Autogenic Feedback Training for Vestibular Symptomatology

Biomedical results from Skylab indicated that, while individuals experienced different susceptibility to space motion sickness, they adapted to weightlessness within five to seven days. Since current Shuttle missions are of this duration, it is desirable to ameliorate space motion sickness during the susceptible period. On Earth, human subjects successfully suppressed their own motion sickness symptoms using a technique developed by P.S. Cowings (LR) called Autogenic Feedback Training (AFT). Scheduled for Spacelab 3, crew members during preflight training will be instructed in specific exercises (operant conditioning) to volitionally control a variety of physiological parameters, e.g., heart rate, respiration rate, galvanic skin response. The subject's degree of control will then be tested during ground-based motion sickness tests, e.g., while moving the head during angular acceleration in a rotating chair. During flight a small instrument package on the body (Fig. 37) will monitor and display to the crew member the same physiological parameters used during training.

AFT effectiveness in controlling any space motion sickness symptoms experienced by the crew members will be determined. In addition, important physiological data accompanying the onset and control of symptoms will be collected.

Vitamin D Metabolites and Bone Demineralization

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H.F. DeLuca, Department of Biochemistry, University of Wisconsin
E.M. Holton, Biomedical Research Division, Ames Research Center

Active metabolites of Vitamin D increase the transport of calcium across the intestine, as well as mobilize calcium from old bone. The alteration of this function during spaceflight will be monitored by measuring Vitamin D_2/D_3 (D_2: ergosterol, from plants used to fortify milk; D_3: cholecalciferol, in animals) and its active metabolites: 25-hydroxyvitamin D; 24,25-dihydroxyvitamin D; and 1,25-dihydroxyvitamin D. For this purpose blood samples will be taken from astronauts preflight, soon after entering orbit, just prior to reentry, and postflight on Spacelab 2.

Spacelab Life Sciences 1: Skeletal Experiment

Bone, Calcium, and Spaceflight

E.M. Holton, Principal Investigator, Biomedical Research Division
C.E. Cann, Department of Radiology, University of California Medical Center
W.E. Roberts, University of the Pacific Dental School

In growing rats flown for three weeks aboard the Soviet biosatellites, Cosmos 782, 936 and 1129, bone formation ceased in the diaphyseal (long portion of the limb bone) tibia, probably sometime after the eleventh day of flight. The proposed Spacelab experiment will use rats to expand our current understanding of calcium turnover in the body and alteration of bone formation occurring during spaceflight. The rate of bone formation will be determined by using a fluorescent, bone-labelling technique. The histology of specific bones, such as the weight-bearing tibia, and the nonweight-bearing humerus and radius, should indicate growth rates of bone at these various, individual sites compared to the total skeleton. Isotope studies immediately after spaceflight will define those cells which are active. Total bone resorption by the body will be measured using a stable calcium isotope released from the bone.

Spacelab Life Sciences 2: Muscle Experiment and Embryology

Spacelab Life Sciences 2 (SLS-2) will be the second flight of Spacelab exclusively dedicated to life science experiments. Along with a reflight opportunity for selected experiments flown on SLS-1, muscle physiology experiments, a plant experiment, and a frog embryology experiment will be flown for the first time.

Electron Microscopy Electromyography, Protease Activity of Rat Hind Limb Muscles

D.A. Reilly, Principal Investigator, Department of Anatomy, University of California Medical Center,
S. Ellis, Biomedical Research Division, Ames Research Center

Astronauts in space experienced a loss of muscle mass and strength, particularly in the calf of the leg. Muscles of rats also showed atrophy during Soviet space flights. Ground studies of muscle disuse in rats revealed a 30% loss of hind limb muscle mass in three to four days, and a 60% loss in 14 days. Spacelab will provide an essentially weightless environment to study atrophy, as opposed to such Earth-bound methods as immobilization, or denervation (severing the nerve to the muscle). This experiment proposed for the first time to assess changes due to weightlessness alone by removing the soleus and gastrocnemius muscles of some rats during spaceflight to prevent the body's repair processes when the animals are returned to Earth. While in orbit, tissue will be fixed for electron microscopy or frozen for histochemical and biochemical analysis on the ground. Other rats will be autopsied on the second and 22nd days postflight, the latter of which will also be implanted with electromyographic (EMG) transmitters prior to launch of the Shuttle. The number of muscle impulses monitored by EMG should decrease by 5% to 15% per day, reflecting the change in muscle workload. Among other measures of the atrophy process, studies will include determining the number of cellular lysosomes, which contain enzymes (proteases) to break down protein, and assessing the degeneration of energy-producing mitochondria in cells. Results should establish or define any unique changes induced in skeletal muscle due to the weightless environment, and the rate that muscle atrophies in weightlessness as compared to atrophy produced on Earth by disuse, denervation, or cast immobilization.

Ground-based studies have led to the development of a more sensitive method for the measurement of calcium-activated protease in rat muscles using much smaller samples than previously possible. Atrophying soleus muscle has sustained a 50% increase in the calcium-activated protease after four days of inactivity.

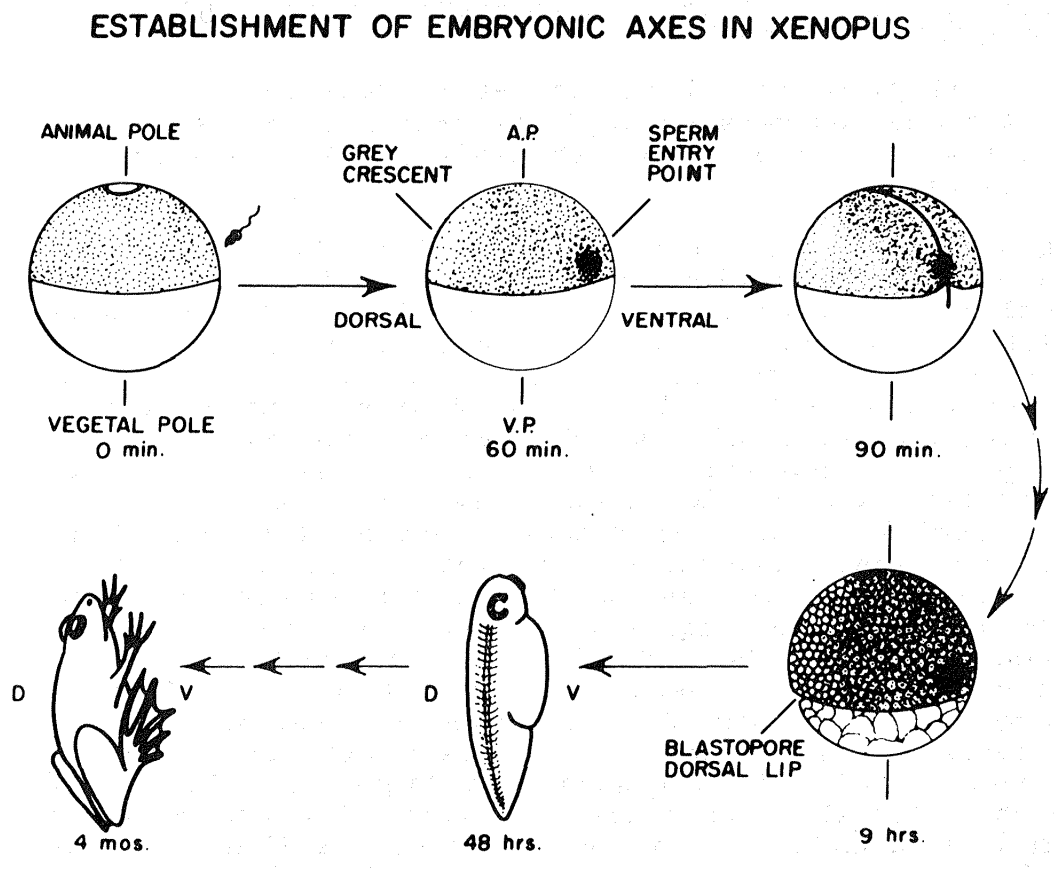

Fig. 38. A Spacelab experiment will investigate if the establishment of embryonic axes in Xenopus eggs and their development as tadpoles is gravity-dependent.

Frog Egg Fertilization and Development during Spaceflight

K.A. Souza, Principal Investigator, Ames Research Center
G. Nace and M.D. Ross, Department of Biological Sciences, University of Michigan

Although mature orgaisms can survive in the weightlessness of space, it is unknown if the fertilization of eggs and the initial stages of embryogenesis will occur without gravity. The African clawed frog (Xenopus laevis) was chosen as the experimental species, and male and female gametes will be combined on SLS-2. A colony of Xenopus has been established at Ames Research Center for preflight studies.

Animal embryos rotate into a definite position with respect to the Earth's gravity. Chicken embryos turn over during the early stages of incubation. In amphibians the unfertilized egg has an unequal distribution of yolk, with most of the mass at the designated vegetal pole of the egg. Within minutes after fertilization the egg orients itself by rotation, so that the heavier vegetal pole turns downward, and the darkly-pigmented animal pole opposes gravity. Under normal terrestrial conditions the dorsal-ventral (back-to-belly) axis correlated with the sperm entry point (Fig. 38), i.e., the dorsal side of the embryo forms opposite the site of sperm entry. This correlation is known to be influenced by gravity and will be investigated in the flight specimens.

During the flight of SLS-2 one of four live female frogs will be selected as an egg donor. These frogs will be held in a specially-designed frog container: an enclosed box lined with damp foam and supplied with a regulated air flow. Eggs will be stripped from the frog and placed in egg chambers, where they will be fertilized with sperm that will be carried aloft. The egg chambers are made of clear injection-molded acrylic, and will contain the developing eggs throughout the experiment. Some chambers will remain in zero-G, and others will be placed in a one-G centrifuge as controls. Fixation to preserve the embryos and tadpoles at different stages of development will be performed at set intervals throughout the flight.

ADDITIONAL ACTIVITIES

ADDITIONAL ACTIVITIES

Director's Discretionary Fund

The nature of scientific problem solving requires freedom for the investigator to explore areas for fresh insights into complex research questions. Often research in seemingly unrelated areas inspires a practical solution to a pressing problem. Yearly at Ames Research Center, a discretionary fund distributed through the Office of the Center Director offers just such an opportunity for investigators to develop new ideas that are otherwise difficult to pursue through normal funding sources. Demanding standards are used to judge proposals on technical and scientific merit, and compatibility with the goals of Ames and NASA. The six-member Basic Research Council, consisting of a representative from each of the technical directorates at Ames, submits funding recommendations to the Center Director twice yearly.

Scientists in the Biomedical Research Division have made progress in important areas of research thanks to the Director's Discretionary Fund. A description of findings from research funded in FY 1984 follows.

"Elucidation of the Role of Brain Peptides in Motion Sickness"
N.G. Daunton, Principal Investigator

The hypotheses to be evaluated centers on the concept that a chemical substance serves as a link between brain areas receiving information on motion, and brain areas involved in the production of motion-induced vomiting. Results showed that animals with complete blockage of the flow of cerebrospinal fluid to the fourth ventricle and area postrema of the brain did not get motion sick. One catecholamine which is a possible candidate for the chemical link is dopamine.

"Computer Model of Insulin Resistance"
C.B. Dolkas, Principal Investigator

A large computer simulation was developed on an IBM 360/67 of a normal glucose tolerance test. The model is composed of serveral sections representing systems, such as liver, adipose, muscle, heart, gastro-intestinal, blood, and respiration. Modeled within these sections were the important biochemical pathways in the form of equilibrium equations and speed of reactions.

"Atrophy of Skeletal Muscles in Simulated Weightlessness"
H.J. Ginoza, Principal Investigator

The antigravity muscles of suspended rats lost between 35% and 45% mass in seven days, which is comparable to rats returned from spaceflight in the US-USSR Cosmos biosatellite experiments. Rats were also temporarily removed from this model and allowed to exercise freely. The results showed that eight hours of continuous exercise was required for completely alleviating loss of muscle mass.

"Physiological and Biochemical Studies of Growth Hormone
Releasing Factor"
R.E. Grindeland, Principal Investigator

A sensitive bioassay was developed for bioassayable growth hormone. Other existing assays require 100-200 micrograms of growth hormone, but the new assay can measure 0.01-0.1 microgram quantities of growth hormone. Pituitary cells were separated by free flowing electrophoresis on Earth and in space. Without the effects of cell density under gravity during electrophoresis, it was demonstrated for the first time that various cell types have different surface charges. Also, growth hormone secretion in flight was about 10% of the amount secreted at 1 G, whereas prolactin secretion was increased in microgravity, which is the first hard evidence that a defect in cell physiology can occur in flight.

"Experimental Test of Current Theories of Aging by Long-Term Mouse Centrifugation"
D.E. Philpott, Principal Investigator

Fifty-four mice, exposed to acute centrifugation at 3.14 G, were treated with a combination of nutrients that show potential in countering the negative effects of stress. These supplements included inositol, carnitine, mixed tocopherols, pyridoxine, ascorbic acid, and chromium. The chemical treatment was associated with a 14% higher survival rate, and a larger number of viable mitochondria, the energy-producing organelles in the cells.

Appointments, Awards and Meetings

M.M. Cohen: Lecturer in Astronautics and Aeronautics, Stanford University, Stanford, CA.

Member, National Research Council/National Academy of Sciences Working Group on Simulator Sickness.

Member, NASA Space Station Crew Systems Safety Study, an informal advisory and review committee.

Member, Space Adaptation Working Panel, which coordinates studies of biological sensory processing on Space Shuttle missions.

Member, American Institute of Biological Sciences (AIBS), Space Medicine Advisory Panel to NASA, which conducts peer reviews of research proposed for NASA funding.

Chaired the session entitled, "Acceleration," at the 55th annual scientific meeting of the Aerospace Medical Association, San Diego, CA.

M.L. Corcoran: Participated in planning meetings at NASA Headquarters and Harpers Ferry, W.VA to organize a Workshop on Gravity Perception.

P.S. Cowings: "Autogenic-feedback training as a treatment for motion sickness" presented at the 15th annual meeting of the Biofeedback Society of America, Albuquerque, NM.

N.G. Daunton: Project Scientist, Vestibular Research Facility (VRF), which is designed to provide motion and visual stimuli in various animal species for research on the operation of the vestibular system.

Member, Animal Care and Use Committee, Ames Research Center.

Member, Space Adaptation Working Panel, which coordinates studies of biological sensory processing on Space Shuttle missions.

Member, Space Biomedical Research Institute peer review panel to NASA, which reviews research proposed for NASA funding.

Presented a paper and chaired a symposium session on Vestibular and Visual Control of Posture and Equilibrium, Baylor College of Medicine, Houston, TX.

"Sensory-motor rearrangement and motion sickness: Is there evidence for their relationship?" presented at the International Symposium on Space Medicine, Nagoya, Japan.

"Susceptibility of cat and squirrel monkey to motion sickness induced by visual stimulation: Correlation with susceptibility to vestibular stimulation" presented at the AGARD Aerospace Medical Panel Symposium on Motion Sickness, Williamsburg, VA.

D.J. Goldwater: Clinical Instructor of Medicine and Cardiology; Lecturer in Astronautics and Aeronautics, Stanford University, Stanford, CA.

Instructor of Advanced and Basic Cardiac Life Support (CPR), Stanford University Medical Center.

"Exercise capacity following repeat simulated Shuttle flight," and "Shuttle flight-related echocardiography" presented at the 55th annual meeting of the Aerospace Medical Association, San Diego, CA.

A.L. Goodwin: Participated in resource management meeting for the Office of Space Science and Applications, NASA Headquarters, Washington, D.C.

Received the NASA Special Achievement Award.

J.E. Greenleaf: "Effects of drinking on plasma vasopressin, renin and aldosterone in dehydrated humans" presented at the Federation of American Societies for Experimental Biology (FASEB) meeting, St. Louis, MO.

R.E. Grindeland: Chairman, Animal Care and Use Committee, Ames Research Center.

Received training at payload operation control center at Marshall Space Flight Center, Huntsville, AL in preparation for Spacelab 3.

E.M. Holton, Lecturer in Astronautics and Aeronautics, Stanford University, Stanford, CA.

Member, Spacelab Life Sciences 1 and 2 Investigators Working Group.

Presented research progress and the results from the first successful test of the middeck Animal Enclosure Module on Space Shuttle STS-8 at the Space Biology Symposium sponsored by the American Institute of Biological Sciences (AIBS) in Arlington, VA.

Performed NASA project manager/scientist duties at Kennedy Space Center during the Shuttle STS-41B student experiment, The Effects of Weightlessness on Arthritis.

Attended Workshop on the Space Shuttle Experimental Environment, New England College, Henniker, NH.

Member of the panel entitled, "Calcified structures and gravity," at the 55th annual meeting of the Aerospace Medical Association, San Diego, CA.

E.M. Huff: Participated in development meetings for the Emergency Medical Services Helicopter program and for the Space Station program, NASA Headquarters, Washington, D.C.

L.C. Keil: Member, Academic Affairs Committee, Ames Research Center, which reviews proposals from outside institutions.

"Radioimmunoassay of fluid and electrolyte hormones" presented at the Workshop on Advances in NASA-Relevant Minimally Invasive Instrumentation, Pacific Grove, CA.

L.M. Kraft: Member, Animal Care and Use Committee, Ames Research Center.

Member, Administrative Panel on Laboratory Animal Care, Stanford University, Stanford, CA.

Participated in the Space Radiation Effects Workshop, Lunar and Planetary Institute, Houston, TX.

A.D. Mandel: Member, NASA Space Station Crew Systems Safety Study, an informal advisory and review committee.

W.R. Mehler: Adjunct Associate Professor of Anatomy, University of California Medical School, San Francisco.

Editorial Board: Brain, Behavior and Evolution.

J. Oyama: Member, NASA Variable Gravity Research Facility Advisory Committee to develop requirements for the establishment of a large centrifuge for spaceflight.

Consultant, Swiss National Science Foundation.

Consultant, Regulatory Biology Program, National Science Foundation.

Reported at the Space Biology Symposium sponsored by AIBS in Arlington, VA on the changes in metabolism of animals under increased G-forces produced in the centrifuge facilities at Ames Research Center.

D.E. Philpott: Consultant, Department of Pathology, Presbyterian Hospital, San Francisco, CA.

Consultant, Electron Microscopic Methods and Interpretation, Veterans' Administration Hospital, New York, NY.

Charter and Current Member of the National Board for Certification of Electron Microscopists, Electron Microscope Society of America.

Member of the board to set curriculum requirements for electron microscope technicians, San Joaquin Delta College, Stockton, CA.

Science Coordinator, Students Space Biology Research Program, Ames Research Center.

Member, NASA Space Station Crew Systems Safety Study, an informal advisory and review committee.

Contributed to the Space Radiation Effects Workshop at the Lunar and Planetary Institute, Houston, TX.

"The response of a single spermatogonial cell type in mouse testes to HZE irradiation" presented at the joint meeting of the Electron Microscope Society of America and the Microscopical Society of Canada in Detroit, MI.

Organized the program on "The ultrastructural/ morphologic effects on cells and tissues of radiation and multi-modality therapies" for the annual Scanning Electron Microscopy meeting.

H. Sandler: Clinical Professor of Medicine, Stanford University, Stanford, CA.

Adjunct Associate Professor of Medicine, Wright State University, Dayton, OH.

Consultant, Presbyterian Medical Center, San Francisco.

Consultant, Mt. Zion Hospital, San Francisco.

Consultant, Cardiovascular Research Institute, University of California Medical Center, San Francisco.

Editorial Boards: Circulation Research; and the Journal of Biotelemetry.

Fellow of the Aerospace Medical Association; American College of Angiology; American College of Cardiology; and the American Heart Association's Council on Circulation.

"Cosmos primate cardiovascular measurements" presented at the 14th Intersociety Conference on Environmental Systems in San Diego, CA.

Co-chaired the session entitled, "Basic Research: Ventricular Function," at the 56th scientific session of the American Heart Association, Anaheim, CA.

K.A. Souza: Participated in the space biology program review sponsored by AIBS in Arlington, VA.

Member, Spacelab Life Sciences 1 and 2 Investigators Working Group and Payload Steering committee.

Participated in NASA Management Education Program, Wallops Island, VA.

Chaired the NASA-AIBS Workshop on Developmental Biology, Arlington, VA.

Chaired the session entitled, "Results of Cosmos 1514 Experiments," at the 14th Intersociety Conference on Environmental Systems, San Diego, CA.

M.J. Stevenson: Science Coordinator, Students Space Biology Research Program, Ames Research Center.

Member, Source Evaluation Board, Ames Research Center, to evaluate major negotiated procurements for the Center.

J.A. Williams: Collaborator at the Memorial Sloan Kettering Cancer Center, New York, NY using monoclonal antibody techniques developed at NASA-Ames' immunology research laboratory.

C.M. Winget: Lecturer in Animal Physiology, University of California, Davis.

Lecturer in Biological Sciences, San Jose State University, San Jose, CA.

Professor of Pharmacology and Toxicology, Florida Agricultural and Mechanical University, Tallahassee, FL.

Consultant, US Olympic Committee, Sports Medicine Division.

Presented "Chronobiology and athletic performance," and co-chair of session at the fall meeting of the American Physiological Society, Lexington, KY.

D.R. Young: "Space travel osteoporosis: A model of adult-acquired reversible osteoporosis" presented at Johnson Space Center, Houston, TX.

Seminar Speakers Sponsored by the Biomedical Research Division in FY 1984

Gerry Herbison, Department of Rehabilitation Medicine, Thomas Jefferson University Hospital, Philadelphia, PA
STRENGTHENING AND ENDURANCE EXERCISE IN NORMAL MUSCLE

Herman H. Vandenburgh, Department of Pathology and Laboratory Medicine, The Miriam Hospital and Brown University, Providence, RI
CELL SHAPE AND GROWTH REGULATION IN SKELETAL MUSCLE: EXOGENOUS VS. ENDOGENOUS FACTORS

George H. Crampton, Department of Psychology, Wright State University, Dayton, OH
THE ROLE OF CATECHOLAMINES IN MOTION SICKNESS IN CATS

Kenneth R. Brizzee, Delta Primate Research Center, Tulane University, Covington, LA
THE VOMITING CENTER REVISITED

Emily Morey-Holton, Biomedical Research Division, Ames Research Center
DETAILED SUPPLEMENTARY OBJECTIVE (DSO) 0421: RATS IN SPACE, SUMMARY OF THE RAT HARDWARE TEST ON SPACE SHUTTLE STS-8

Ary L. Goldberger, Cardiology Section, University of California, San Diego
NON-LINEAR DYNAMICS OF SUDDEN CARDIAC DEATH

John T. Lett, Department of Radiology and Radiation Biology, Colorado State University, Fort Collins
DAMAGE OF OPTICAL SYSTEMS OF THE RABBIT BY HEAVY IONS

Wesley C. Hymer, Department of Biochemistry, Pennsylvania State University, University Park
NEW APPROACHES TO THE STUDY OF PITUITARY CELL FUNCTION

Bonifacio C. Daligcon, Biomedical Research Division, Ames Research Center
EFFECTS OF HYPERGRAVITY ON GLUCONEOGENESIS AND BLOOD REGULATION IN RATS

Geert A. Ubbels, Hubrecht Laboratory, The Netherlands
FERTILIZATION AND EARLY DEVELOPMENT OF XENOPUS LAEVIS EGGS UNDER MICROGRAVITY; BIORACK EXPERIMENT ON THE SHUTTLE/ SPACELAB D-1 MISSION

W.T. Stauber, Department of Physiology, West Virginia University Medical Center, Morgantown
LYSOSOMES IN MUSCLE ATROPHY

Philip Person, Department of Biochemistry, New York University College of Dentistry, New York City
INVERTEBRATE AND LOWER VERTEBRATE CARTILAGES

Victor Schneider, University of Texas Public Health Service, Houston
DISUSE OSTEOPOROSIS: A MODEL FOR THE EFFECT OF SPACE TRAVEL ON BONE

John Maloney, Chairman of the Reproductive Medicine Research Group, University of Calgary, Alberta
DEVELOPMENT OF THE RESPIRATORY SYSTEM AND BIRTH: FROM A MICROGRAVITATIONAL ENVIRONMENT TO A GRAVITATIONAL ENVIRONMENT

Leonard Martin, Department of Psychology, Columbia University
EXTRA-RETINAL EYE POSITION INFORMATION AND SPATIAL LOCALIZATION OF VISUAL OBJECTS

H. Mettelstaedt, Max Planck Institute fur Verhaltenphysiologie, Seewiesen, West Germany
THE ROLE OF GRAVITY IN SUBJECTIVE ORIENTATION

FACILITIES

FACILITIES

Ames Research Center has facilities that are unique throughout the world for the study of biomedical issues in aerospace medicine and gravitational biology. Many of these facilities simulate the aerospace environment for investigators to study the biological effects of simulated weightlessness, acceleration, and even the rarified atmosphere of other planets. While the aeronautical facilities give Ames the reputation as "a city of wind tunnels," it is also "a city of centrifuges," which are used in both animal and human biological research. Tables and descriptions follow of the many specialized facilities at Ames used by investigators of the Biomedical Research Division.

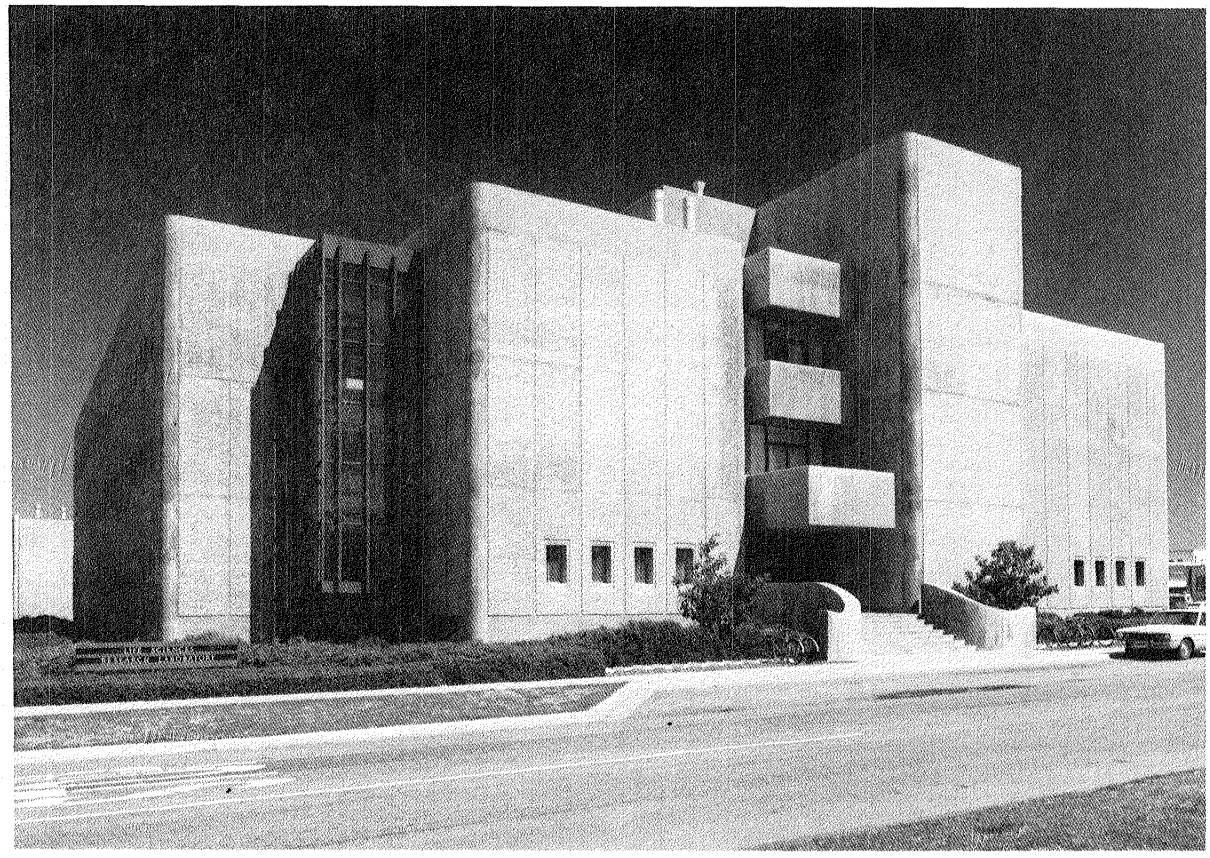

Fig. 39. One of the Life Sciences Research Laboratories at Ames Research Center, housing some of NASA's unique research facilities for space medicine, exobiology, aviation psychology, and bioregenerative life support systems.

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TABLE 1V. FACILITIES MANAGED BY BIOMEDICAL RESEARCH DIVISION (LR)

FACILITY	DESCRIPTION
Cardiovascular Research Lab (Bldg. 236)	
Surgical Suite	Used in the preparation of animals for biomedical research.
X-ray Room	Used in x-ray studies of the heart and blood vessels, using radioactive tracers and high speed film.
Angiography Suite	Used in radiological study of the heart and blood vessels.
Animal Water Immersion Facility	Used to reproduce many of the physiological changes accompanying microgravity.
Bioinstrumentation Lab	Develop and test advanced biomedical electronic equipment.
Data Processing Room	PDP 11/34 computer.
Neurosciences Lab (Bldg. 239)	
Surgical Area	Used in the preparation of animals for research of the anatomy and neural pathways affecting motion sickness.
Sensory Conflict Test Chambers	Test animal subjects using visual stimulation and physical agitation to establish visual and vestibular cues in motion sickness.
Data Processing	PDP 11/34 computer.
Psychophysiology Lab (Bldg. 239-A)	
Biofeedback Test Chambers	Used to train humans in self-control of motion sickness.
Data Processing	PDP 11/34 computer.

Bone Physiology Labs (Bldgs. 236 and 239, three labs)

Bone Biomechanics Area	Research to measure bone strength and mechanisms of disuse osteoporosis.
Bone Image Analysis System	Program on PDP 11/34 digitizes bone images to trace chemical labels quickly.

Animal Centrifuges (Bldg. 239-A)

8, 24 and 52 ft diameter centrifuges for short and chronic testing of gravity-sensitive biological systems.

Electron Microscopy Lab (Bldg. 239)

Conduct morphological studies of animal ultrastructures using two transmission electron microscopes, scanning electron microscope, and specialized tissue processing equipment.

Immunology/Tissue Culture Lab (Bldg. 239-A)

Clean room for growing tissue cultures.

Human Environmental Physiology Lab (Bldg. 239-A)

Human Water Immersion Tank	Used to simulate physiological alterations accompanying weightlessness in humans.
Environmental Test Facility	Perform psychological and physiological tests on humans during isolation, exercise, and changes in temperature, pressure and humidity.

Animal Biorhythm Lab (Bldg. 239)

Environmental Test Chambers	Monitor animal responses to changes in temperature, pressure and humidity.

Histochemistry/Histopathology Labs (Bldgs. 236 and 239)

Two labs to study vestibular function and radiation biology.

Biochemistry/Endocrinology Labs (Bldg. 239)

Six labs to study fluid and electrolyte biochemistry, and muscle biochemistry.

General Physiology Labs (Bldg. 239, five labs)

Vertical Acceleration and Roll Device (VARD) (Bldg. 239-A)

Human test simulator used in studies of spaceflight physiological changes, including tests for space motion sickness.

Trailers

Eleven trailers as temporary laboratory facilities.

TABLE V. RESEARCH FACILITIES USED BY LR AND MANAGED BY OTHER ORGANIZATIONS

FACILITY	DESCRIPTION
Human Research Facility (Bldg. 239)	Used to conduct human bedrest studies; managed by Biosystems Division, Life Sciences Directorate.
Human Centrifuge (Bldg. 221-A)	50 ft diameter, 20-G centrifuge; managed by Flight Systems and Simulation Research Division, Aeronautics and Flight Systems Directorate.
Man Carrying Rotation Device (Bldg. 239-A)	Evaluate performance of pilots and potential Shuttle passengers during physical agitation; managed by Flight Systems and Simulation Research Division, Aeronautics and Flight Systems Directorate.
Animal Colony (Bldg. 236)	Housing for test animals; managed by Biosystems Division, Life Sciences Directorate.
Ames Learjet	Used for parabolic flight and motion sickness experiments; managed by Science and Applications Aircraft Division, Operations Directorate.

Electrical Systems Branch (Bldg. 213)

Design and engineer bioinstrumentation for spaceflight and ground studies; managed by Systems Engineering Division, Engineering and Computer Systems Directorate.

Bevalac (U.C. Bereley)

Linear accelerator that produces heavy particles (similar to cosmic ray particles) to test their effects on animals; managed by Lawrence Berkeley Laboratories at the University of California, Berkeley.

ANIMAL CENTRIFUGES

A 2.44m dia animal centrifuge is used with small laboratory animals for acute exposures to hypergravity up to 24 hrs in duration. This centrifuge provides a 10 G field, but most studies do not exceed 5 G. Each of ten radial arms supports at least one cage assembly, and some hold two. The minimum radius to test specimens is approximately 457mm and the maximum radius is approximately 1.68m. Both rectal and tail temperatures of 18 rats can be monitored simultaneously. A thermally controlled holding cage, or metabolic chamber, can monitor the rate of oxygen consumption and carbon dioxide production from an individual rat during centrifugation.

7.31m dia chronic animal centrifuge (Fig. 40) is used primarily with small laboratory animals for long-term exposures to hypergravity up to three years. Each of ten radial arms supports two cages at an inner and an outer position. The centrifuge operates continuously, except for service stoppages twice weekly to change sawdust-lined cages and replenish the feed. Water is available at all times through an automated, nuzzle valve watering system. The animals are subjected to the resultant of the centrifugal and graviational forces as the cages swing outward when the centrifuge is operating. The centrifuge speed is 26.1 revolutions per minute (rpm), which subjects animals at the outer position to 3.1 G, and to 2.1 G at the inner position. Each suspended cage can hold six standard sized rat cages. Normally, a maximum of two adult rats per cage is used in chronic studies, for a total of 240 rats at one time. Non-centrifuged control rats are maintained under normal gravity in the centrifuge room to ensure that they are subjected to the same amount of noise, light (12 hrs on/12 hrs off), and handling as the centrifuged rats.

The platform of the 15.85m dia continuous centrifuge (Fig. 41) supports ten radial tracks, where one or two cage assemblies are positioned. Each cage assembly has its own waste removal system, and water and feed delivery system, which permits continuous operation of the centrifuge for indefinite periods of time. The centrifuge has operated for two months without any stoppage. With a maximum speed of 20 rpm the centrifuge can generate 3 G at the outermost position. An onboard television camera and videotape system can monitor and produce visual records of the physical activity of centrifuged animals. Heart rate and deep body temperature have been recorded from various species of animals, such as rats, rabbits and dogs, during chronic centrifugation. This centrifuge is unique in providing laboratory animals with long-duration, continuous exposures to hypergravity.

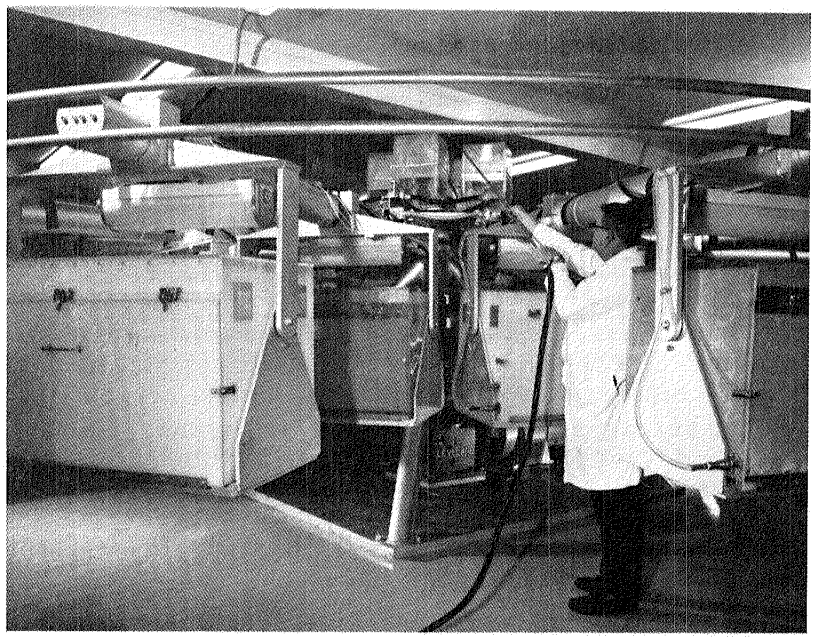

Fig. 40

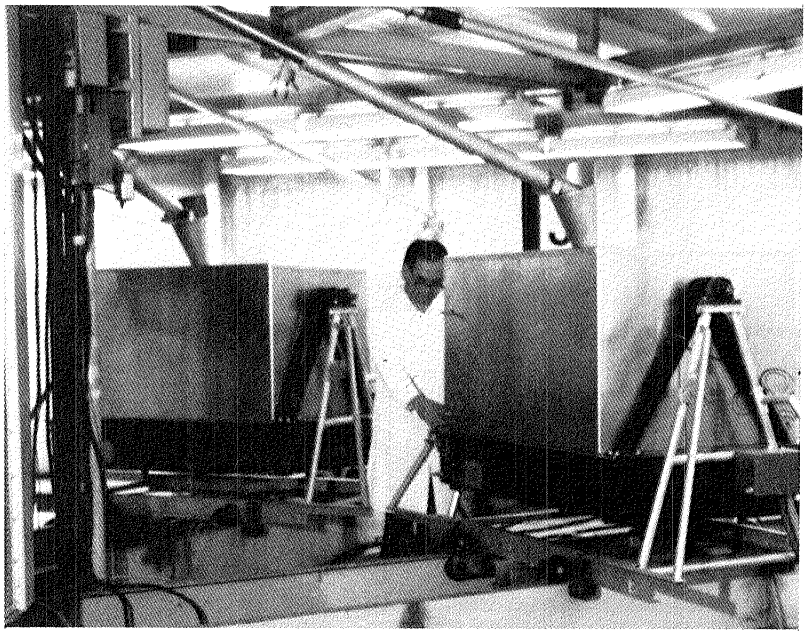

Fig. 41

20-G HUMAN CENTRIFUGE

The 20-G Human Centrifuge (Fig. 42) at Ames is the only facility of its kind in NASA. Investigators use the 20-G centrifuge to examine the effects of G-forces on biological subjects, specimens and instrument packages to determine their qualification for flight. This facility is useful in basic research studies of reactions, relating to the stress of reentry in flights of the Space Shuttle by both astronauts and cross sections of the population at large. Such studies establish criteria to provide the optimum health and safety for space travellers under the Operational Medicine Program.

Continuous centrifugation has been accomplished at this facility for 27 days at 2.5 G, useful for long-term biological experiments, and for more than 20 days at 16 G for hardware testing. The centrifuge has cabs at both ends to hold a maximum payload of 7,257 G kg at each end, e.g., 558 kg at 13 G or 362 kg at 20 G. The arm radius is 7.62m. Additional equipment weighing up to 907 kg can be mounted within 1.22m of the center of rotation. (Managed by Ames Flight Systems and Simulation Research Division, Aeronautics and Flight Systems Directorate.)

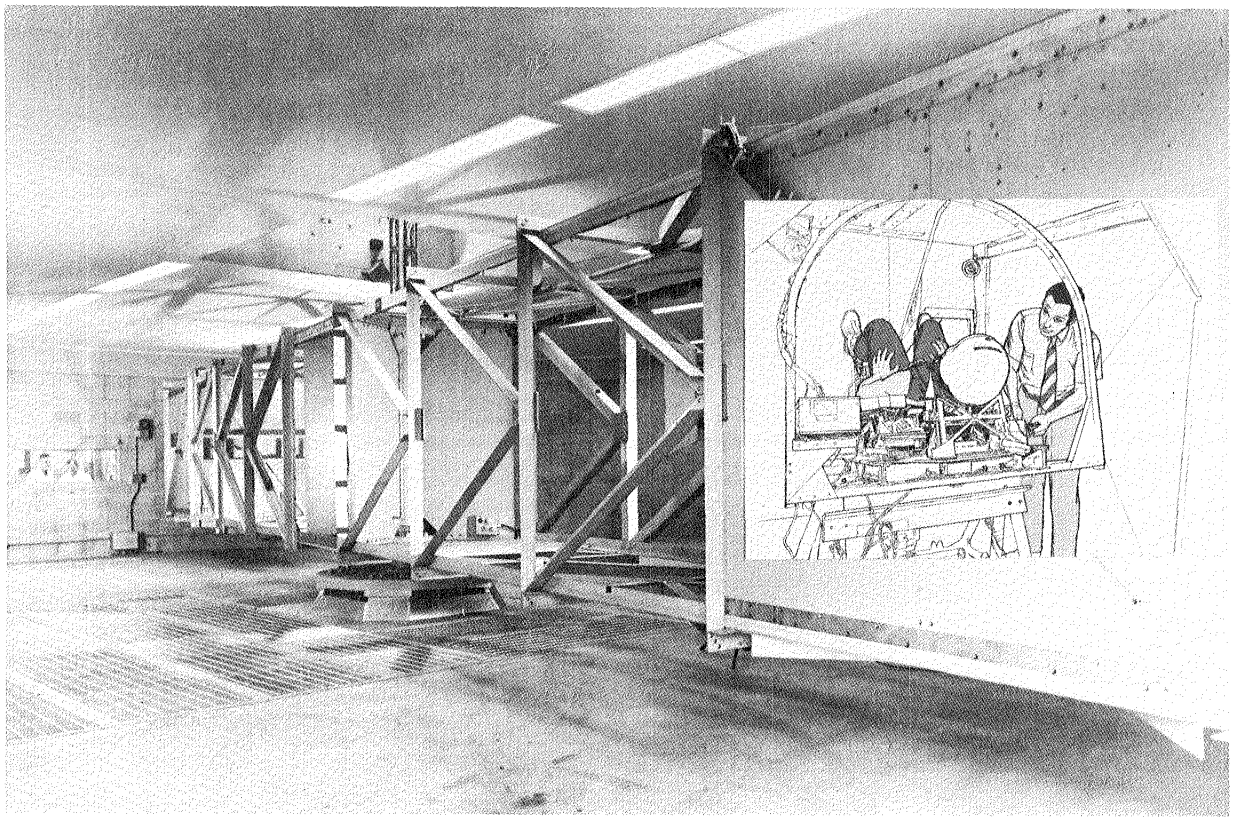

Fig. 42

HUMAN ENVIRONMENTAL PHYSIOLOGY LABORATORY

This laboratory allows LR researchers to produce various physical stresses for the study of human adaptability to altered environmental conditions and simulated weightlessness. Facilities include three environmental chambers (129.5 cu m, 32.5 cu m and 18.4 cu m) with controls for heating, cooling and pressure, a tilt table, exercise capacity testing equipment (treadmill and ergometers), and two water immersion tanks (4.0 cu m and 2.3 cu m). The smaller tank has a scale for measurement of body density.

Two large environmental chambers are used for more specialized studies of humans in a space environment. Both chambers can provide almost any atmospheric gas composition, which is useful in testing optimal mixtures of gases for breathing inside spacecraft. The smaller chamber is especially useful in studying the physiological and psychological responses of human subjects to the stresses of exercise or confinement. The two-story, 129.5 cu m chamber (Fig. 43) is suitable for tests of pressure suits and long-term studies of humans in a spacecraft environment. Both chambers have television monitors and voice intercommunication systems to a control room. Exercise equipment can be accommodated in both chambers. This facility can also support research involving closed ecological systems.

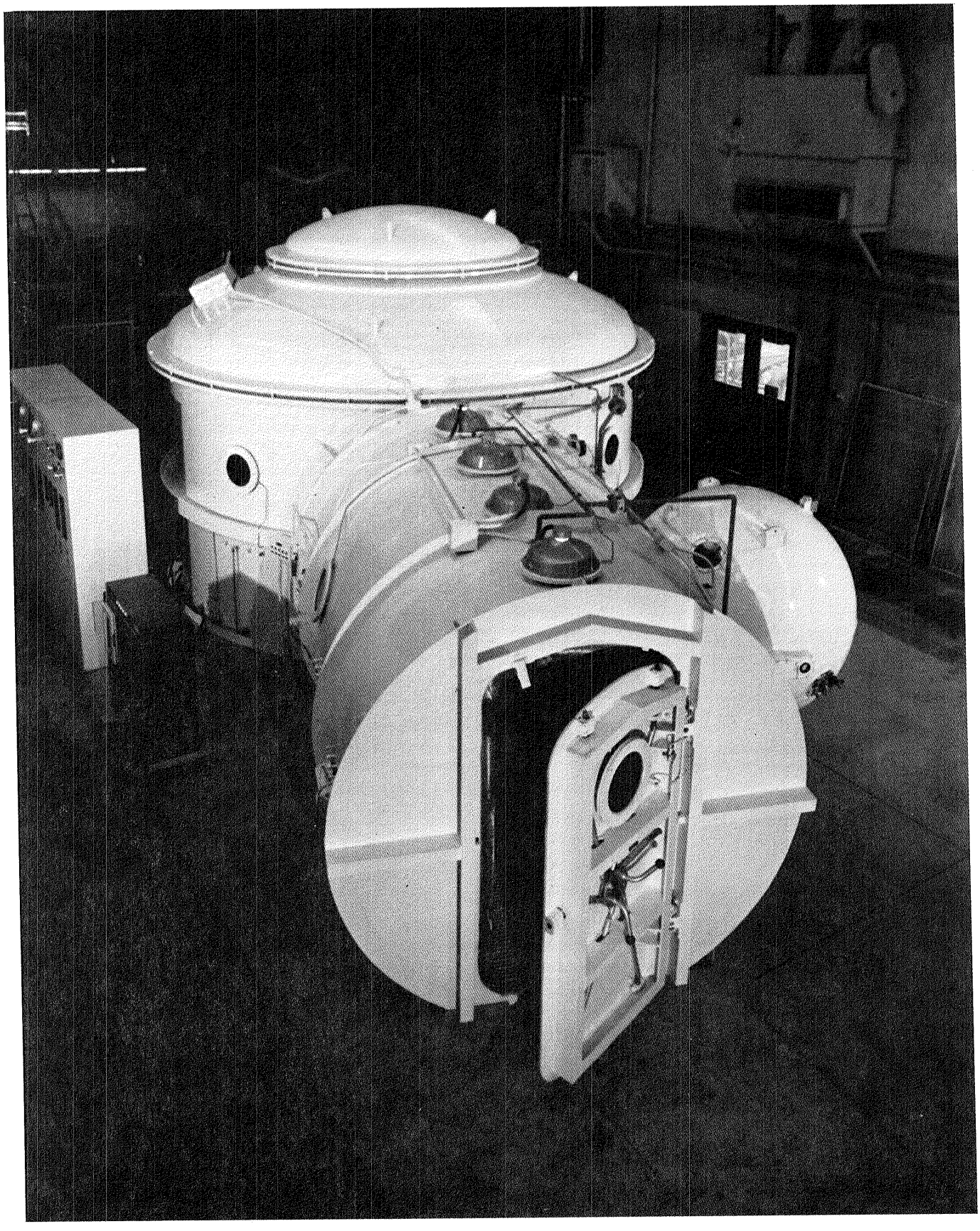

Fig. 43

HUMAN RESEARCH FACILITY

The Human Research Facility can accommodate up to 12 subjects during bedrest simulations of weightlessness, as well as other physiological testing and medical monitoring (Figs. 44 and 45). Basic research studies have been conducted here in support of both the Operational Medicine and Biomedical Research Programs.

Fig. 44

Studies examine the effects of weightlessness on living in space and the efficient operation of aircraft. A unique feature is a horizontal shower for subjects to maintain normal hygiene during bedrest studies of a week or longer. (Managed by Biosystems Division).

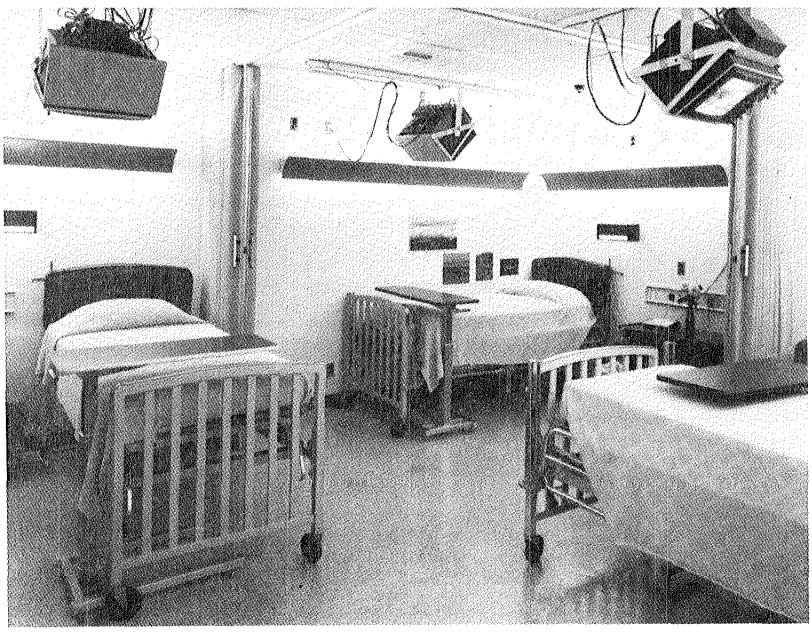

Fig. 45

ELECTRON MICROSCOPY LABORATORY

This facility is equipped with a scanning electron microscope (SEM), which produces pictures of the surface topography of specimens with a remarkable illusion of three-dimensionality. The SEM can magnify the surface of an object more than 100,000x with a superior depth of field.

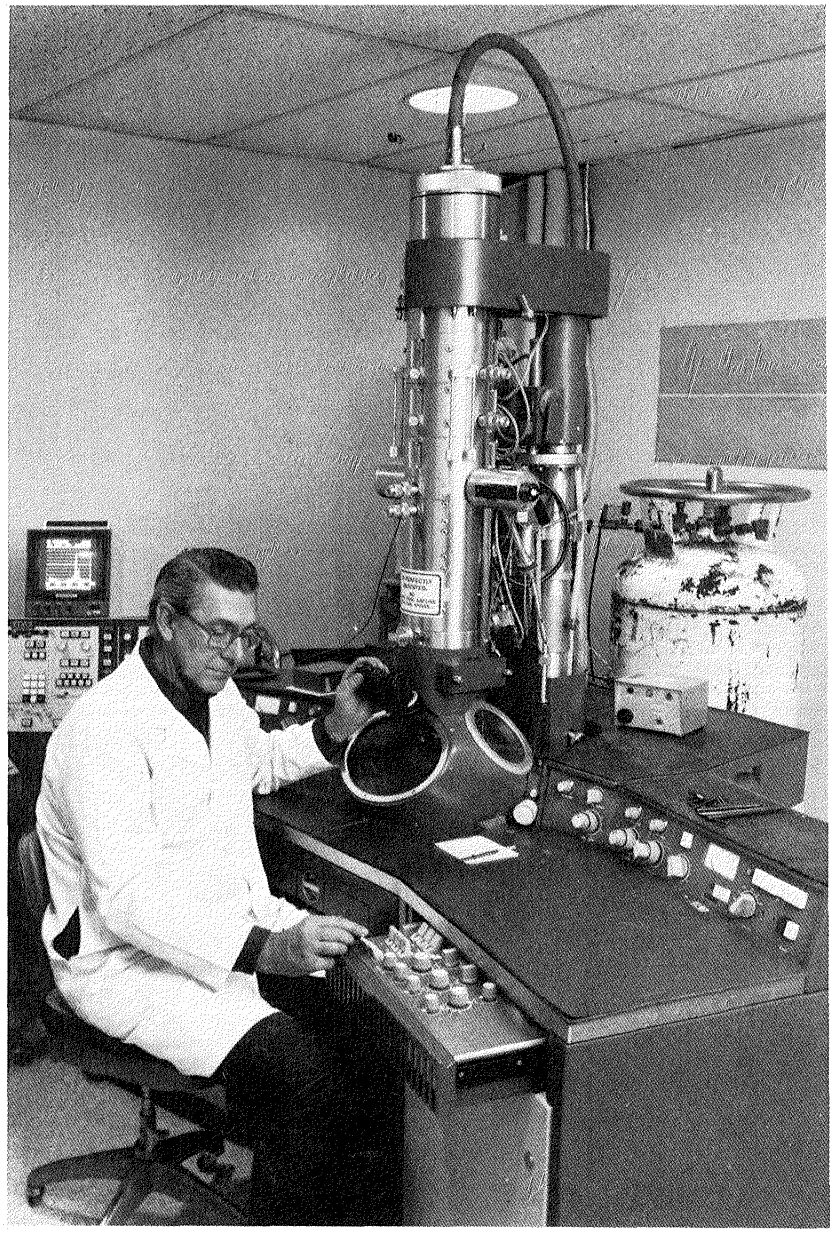

Fig. 46

Whereas a light microscope can focus only on one horizontal plane of a specimen, the SEM scans the entire surface uniformly. Two transmission electron microscopes, like the one in Fig. 46, produce pictures with very high contrast. Specialists in this facility have developed equipment and techniques for processing specimens for viewing. Morphological studies support numerous research efforts, including atrophy effects on cardiac and skeletal muscle, change in the number of receptors for steroids in target cells of the kidney, effects of radiation on neural and optical tissue, and morphological effects on animals flown on the Space Shuttle and Cosmos biosatellites, to name only a few studies.

LEAR 24B AIRCRAFT

The Lear 24B aircraft (Fig. 47) is a modified, twin-engine executive jet manufactured by Gates Learjet Corporation. This aircraft is used both as a high-altitude observation platform, and weightless simulator for brief periods during parabolic flight. Numerous studies into the cause of space motion sickness with both humans and animals (Fig. 48) have been conducted using the Lear Jet. It has a practical operating range of about 3,704 km at a 241.7 m per sec indicated airspeed, an operating ceiling of about 13.7 km and a useful payload of 453 kg. (Managed by Ames' Science and Applications Aircraft Division, Flight Operations Directorate).

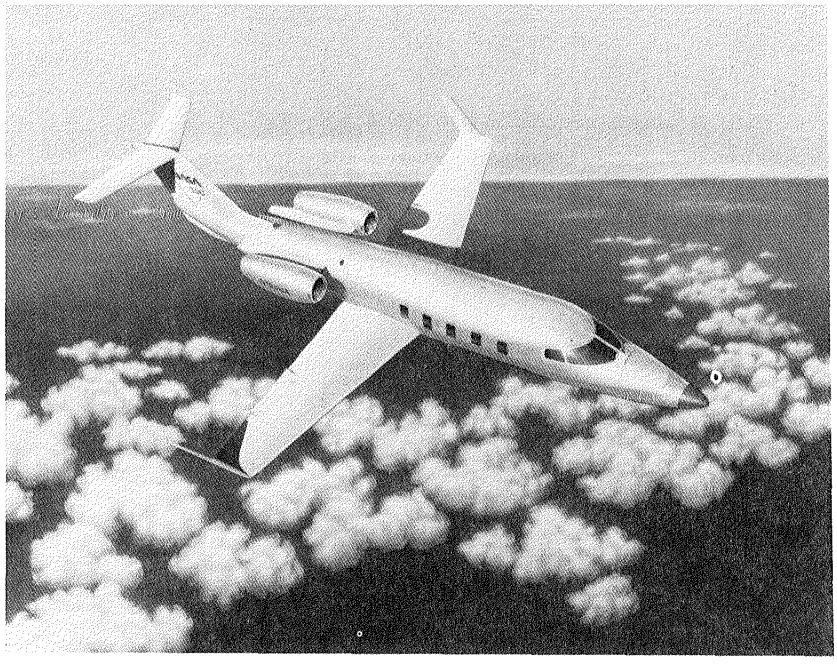

Fig. 47

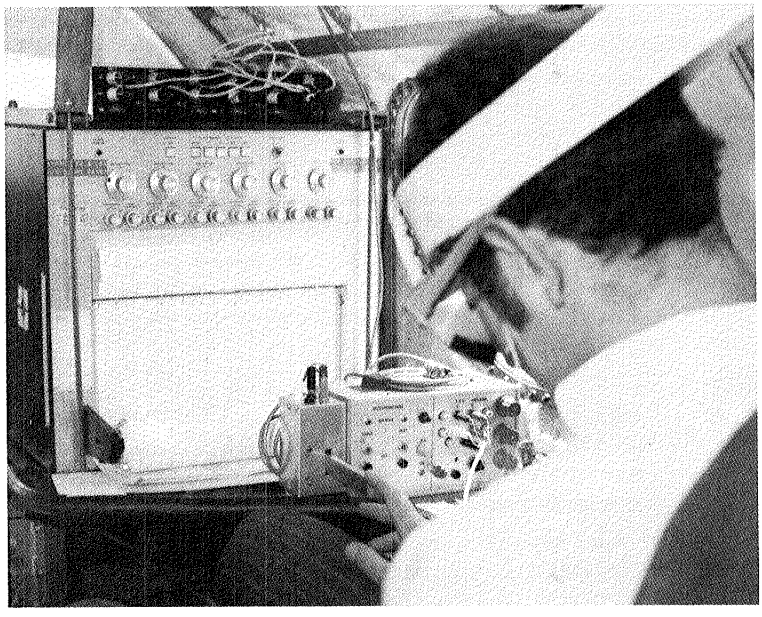

Fig. 48

PSYCHOPHYSIOLOGY LABORATORY

The Psychophysiology Laboratory is used to conduct basic research into the use of biofeedback to counteract undesirable effects of spaceflight, such as motion sickness, through learned control of cardiovascular and other bodily functions. One booth houses a bioinstrumented rotating chair surrounded by a rotating drum to produce optokinetic stimulus (Fig. 49). This system is used to induce Coriolis and pseudo-Coriolis acceleration in human subjects while monitoring their physiology. The second booth is the primary environment to administer Autogenic-Feedback Training to combat aerospace motion sickness. The environment is designed to induce complete relaxation in subjects while they undergo specific training procedures without distractions from outside activities. It contains a wide variety of biomedical equipment connected to an elaborate system, which outputs signals directly from the subject to the main lab for analysis, and immediately feeds specific information back for use by the trainer and the subject.

Fig. 49

VERTICAL ACCELERATION AND ROLL DEVICE (VARD)

The Vertical Acceleration and Roll Device (Figs. 50 and 51) is a dynamic flight simulator used for aircraft human factors studies, as well as for biomedical investigations that require vertical accelerations. It consists of a two-place, side-by-side cockpit supported on a vertical track. This simulator is normally driven open loop. It can be operated closed loop with flight dynamics generated on an analog or digital computer programmed to account for dynamic response of the vehicle to control inputs from the pilot. The VARD has proven useful in experiments on motion sickness.

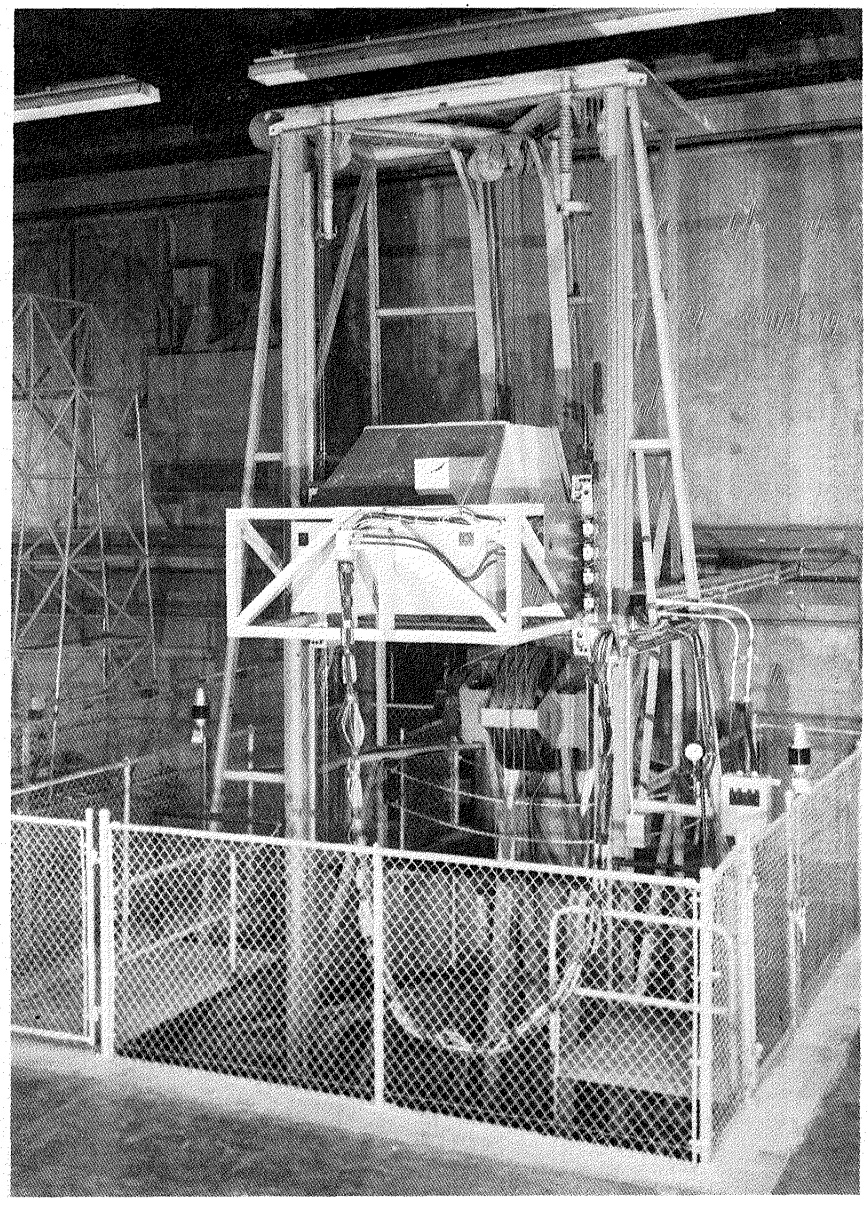

Fig. 50

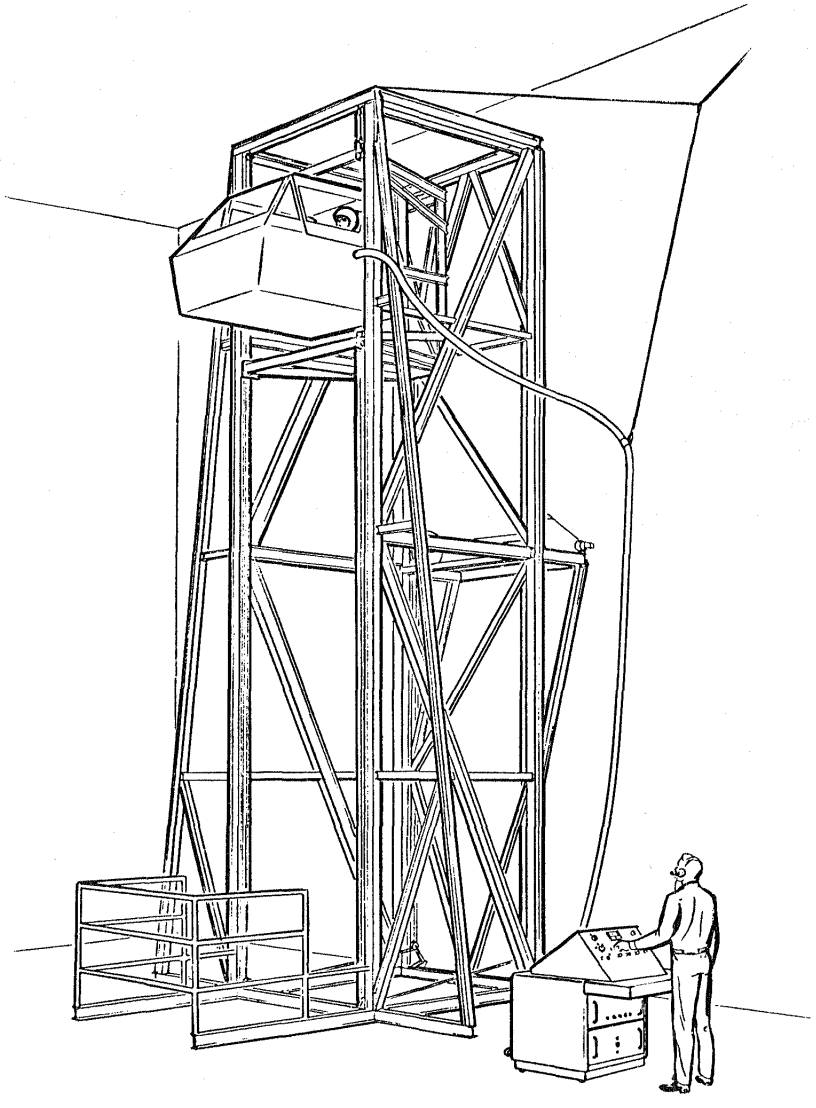

Fig. 51

1. Report No.	2. Government Accession No.	3. Recipient's Catalog No.
NASA TM-86692		

4. Title and Subtitle	5. Report Date
BIOMEDICAL RESEARCH DIVISION - SIGNIFICANT ACCOMPLISHMENTS FOR FY 1984	February 1985
	6. Performing Organization Code
7. Author(s)	8. Performing Organization Report No.
Norman Martello, Johnson Engineering	A-85144
	10. Work Unit No.
9. Performing Organization Name and Address	
NASA Ames Research Center Moffett Field, CA 94035	11. Contract or Grant No.
	13. Type of Report and Period Covered
12. Sponsoring Agency Name and Address	Technical Memorandum
National Aeronautics and Space Administration Washington, DC 20546	14. Sponsoring Agency Code 199-22-40

15. Supplementary Notes

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16. Abstract

This report describes various research and technology activities at Ames Research Center's Biomedical Research Division. Contributions to the Space Administration's goals in the life sciences include descriptions of research in operational medicine, cardiovascular deconditioning, motion sickness, bone alterations, muscle atrophy, fluid and electrolyte changes, radiation effects and protection, behavior and performance, gravitational biology, and life sciences flight experiments.

17. Key Words (Suggested by Author(s))	18. Distribution Statement
Biomedical research Gravitational biology Spaceflight experiments Life sciences Space research	Unlimited Subject category - 51

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price*
Unclassified	Unclassified	162	A08

*For sale by the National Technical Information Service, Springfield, Virginia 22161

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