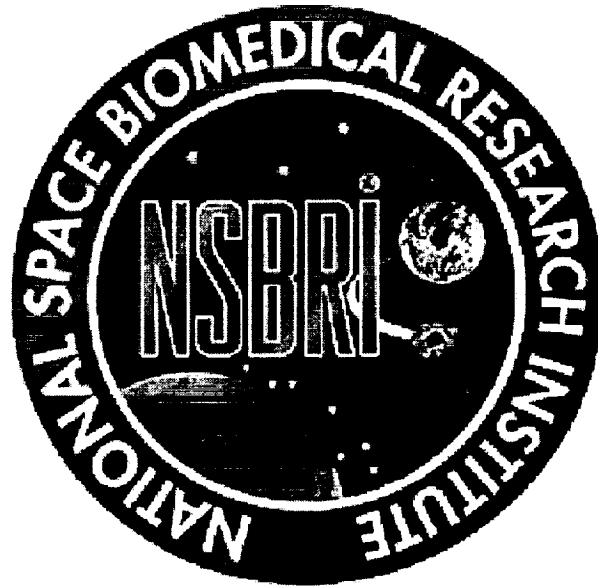


**NATIONAL SPACE BIOMEDICAL RESEARCH
INSTITUTE**

Annual Report

October 1, 1998 – September 30, 1999



Cooperative Agreement NCC 9-58

with the

**National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas**

September 30, 1999

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

ANNUAL REPORT
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1.0 INTRODUCTION

This report summarizes the activities of the National Space Biomedical Research Institute (NSBRI) during FY 1999, the second full year of existence of the NSBRI's research program, and is prepared in accordance with Cooperative Agreement NCC 9-58 between NASA's Lyndon B. Johnson Space Center and Baylor College of Medicine (NSBRI).

2.0 BACKGROUND

The NSBRI is responsible for the development of countermeasures against the deleterious effects of long-duration space flight and performs fundamental and applied space biomedical research directed towards this specific goal. Its mission is to lead a world-class, national effort in integrated, critical path space biomedical research that supports NASA's Human Exploration and Development of Space (HEDS) Strategic Plan by focusing on the enabling of long-term human presence in, development of, and exploration of space. This is accomplished by:

- designing, testing and validating effective countermeasures to address the biological and environmental impediments to long-term human space flight;
- defining the molecular, cellular, organ-level, integrated responses and mechanistic relationships that ultimately determine these impediments, where such activity fosters the development of novel countermeasures;
- establishing biomedical support technologies to maximize human performance in space, reduce biomedical hazards to an acceptable level, and deliver quality medical care;
- transferring and disseminating the biomedical advances in knowledge and technology acquired through living and working in space to the general benefit of mankind, including the treatment of patients suffering from gravity- and radiation-related conditions on Earth; and
- ensuring open involvement of the scientific community, industry and the public at large in the Institute's activities and fostering a robust collaboration with NASA, particularly through NASA's Lyndon B. Johnson Space Center.

The NSBRI was established in April 1997 following competitive selection by NASA. Primary support for the NSBRI's activities is furnished by NASA through a cooperative agreement although funds to support Institute activities also come from several sources, including the institutions involved in carrying out the NSBRI's programs. The cooperative agreement award is for a five and one-half year base period, lasting until September 30, 2002, and three five-year optional extensions. Base funding for FY 1998 and FY 1999 was approximately \$10 million annually.

At the end of FY 1999, the NSBRI is governed by a consortium of twelve institutions that includes Baylor College of Medicine, Brookhaven National Laboratory, Harvard Medical School, The Johns Hopkins University School of Medicine and the Applied Physics Laboratory, Massachusetts Institute

of Technology, Morehouse School of Medicine, Mount Sinai School of Medicine, Rice University, Texas A&M University, the University of Arkansas for Medical Sciences, the University of Pennsylvania Health System, and the University of Washington. Five new institutions were added to the consortium by action of the NSBRI Board of Directors during their September 1999 meeting; the process used to enlarge the consortium is described in Section 5.0. The Institute's headquarters are located in Houston at Baylor College of Medicine.

Because of the nature of the competitive process used by NASA to select the NSBRI, most of the Institute's initial three-year research program is carried out at the consortium institutions. There are, however, no restrictions concerning institutional participation in Institute activity. In fact, the current program is carried out by 130 investigators at twenty-seven institutions and government laboratories (see Appendix A). The management plan for the Institute is based on the model used by the National Institutes of Health. An independent Board of Scientific Counselors is responsible for assuring excellence in the Institute's intramural program through independent external peer review, and an External Advisory Council is responsible for advising Institute management concerning programmatic effectiveness. The NSBRI also has a User Panel of former and current astronauts and flight surgeons responsible for assuring that the research program is focused squarely on astronaut health and safety. An Industry Forum of representatives of space and biomedically-related industries assists the Institute in developing industry participation in NSBRI and in timely technology transfer. In addition to its research program, the NSBRI has developed a vital education and outreach program which takes advantage of the Institute's core research activities.

3.0 RESEARCH PLAN

As described in the original proposal to establish the NSBRI, the Institute's initial strategic research agenda involves eight teams of scientists focused on:

- *Bone Loss* – Addressing the loss and weakening of bone during space flight with the inherent fracture risks;
- *Cardiovascular Alterations* – Addressing inflight increase of cardiac dysrhythmias and postflight impairment of the cardiovascular response to orthostatic and exercise stress;
- *Human Performance* – Addressing maintenance of high cognitive performance and vigilance despite environmental stress and sleep disturbances;
- *Immunology, Infection and Hematology* – Addressing the potential for immune system impairment and altered susceptibility to infection, increased allergic response, decreased blood volume and postflight anemia;
- *Muscle Alterations and Atrophy* – Addressing the loss of skeletal muscle mass, strength and endurance that accompanies space flight;
- *Neurovestibular Adaptation* – Addressing the problems of space motion sickness and disorientation during flight and the postflight problems of balance and gaze disorders;
- *Radiation Effects* – Addressing the problem of increased cancer risk caused by the natural space radiation environment; and
- *Technology Development* – Developing instrumentation that will enhance the research of the other teams and transferring the technology to industry for the benefit of society.

Each research team consists of investigator groups working on complementary projects focused on a common theme. Team management and coordination is the responsibility of a program director called a Team Leader while overall scientific direction is the responsibility of the Institute Director and Associate Director. The total current intramural research program, includ-

ing all eight research areas, involves 41 projects, with an average funding per project of approximately \$200,000 (Direct + Indirect Costs). Appendix B provides a summary of each project, as well as FY 1998 and 1999 funding information. Further details concerning the current intramural projects and team leaders are provided on the web: www.nsbri.org/research/newresearch.html.

In addition to this core intramural research program, the NSBRI has developed a joint program with the National Institute on Deafness and Other Communication Disorders (NIDCD) that jointly funds six competitively awarded extramural grants related to the dynamic adaptation of central vestibular function, an area of common interest. Appendix C provides funding information for this five-year joint program; NIDCD is contributing over \$1.1 M to this program in FY 99, while the NSBRI is contributing \$245 K from private sources.

During FY 1998, the NSBRI began to develop non-U.S. partnerships with the objective of enlarging the core research program by including projects carried out in other countries and supported by those countries, and signed an agreement of affiliation with the Institute of Aerospace Medicine of the German Aerospace Center in Cologne (Deutsches Zentrum für Luft- und Raumfahrt e.V., DLR). During FY 1999, the Institute continued to develop its partnerships by signing an agreement of cooperation with the Institute for Space Physiology and Medicine in Toulouse, France (Institut de Médecine et de Physiologie Spatiales, MEDES), and a framework agreement with the Politecnico di Milano. Appendices D and E provide those agreements. As part of its project activity (see Section 8.0), the NSBRI has developed a contractual relationship with the Russian Institute for Biomedical Problems in Moscow. Appendix F provides a copy of this initial contract.

Table 1 presents the summary schedule of major NSBRI activities taking place in FY 1999. The activities ranged from workshops to management-related meetings designed to provide guidance and oversight to the Institute's programs.

3.1 Research Highlights

All of the NSBRI's 41 funded research projects were initiated in FY 98 and continued through FY 99; no new research projects were added in FY 99. Included in this total are four "synergy" projects providing seed money for one year to enable investigator teams to develop cross-disciplinary research. This section presents a brief summary of project results and findings for FY 99. They are presented here for NASA internal use only. Results are privileged and should not be published or quoted from directly until the investigators have had the opportunity of publishing them in peer-reviewed journals. Appendix G provides a list of papers, reports, abstracts and presentations resulting from full or partial NSBRI support.

Bone Loss Research Team

(O'Malley) Using *in vitro* cell studies, we have:

- Established assays to measure vitamin D receptor (VDR) and estrogen receptor (ER) function in bone cells using transiently transfected reporters as well as endogenous targets including alkaline phosphatase and osteocalcin. Using these assays, we have tested several less calcemic VDR agonists including EB1089 from Leo Pharmaceuticals and LG10119 from Ligand Pharmaceuticals.

Table 1. MAJOR NSBRI ACTIVITIES

October 1, 1998 – September 30, 1999

DATE	ACTIVITY	LOCATION
November 5, 1998	Mr. Goldin Visits NSBRI	Houston
November 12	NSBRI Presentation to NASA/NIH Advisory Committee	Washington
November 14	Baylor President Presents NSBRI to NAS Presidents' Circle	Houston
December 7	NSBRI Presentation to NRC Committee on Space Biology & Medicine (CSBM)	Washington
December 23	Dr. Nicogossian Visits NSBRI	Houston
January 11-13, 1999	NASA Biomedical Investigators Meeting	Houston
January 14-15	Artificial Gravity Workshop	Houston
February 18-19	Site Visit Review of JSC Medical Information System Plan	Houston
February 22-23	External Advisory Council Meeting	APL
March 3-5	NSBRI Status Presented to NRC CSBM During Review of JSC's Programs	Houston
March 25	Board of Directors Meeting	Houston
April 15	Signing of Framework Agreement with the Politecnico di Milano	Milan
May 10	Release of Announcement to Institutions Regarding Becoming a Consortium Member	N/A
June 16	Signing of Agreement of Cooperation with MEDES	Paris
June 21-22	WORKSHOP: Nutrition, Physical Fitness and Rehabilitation	Houston
June 29-30	WORKSHOP: Smart Medical Systems	Houston
July 12	Consortium Expansion Review – Phase I	Houston
July 13-14	WORKSHOP: Integrated Human Function	Houston
July 19-20	WORKSHOP: Neurobehavioral and Psychosocial Factors	Houston
August 24-25	WORKSHOP: Gender-Related Issues in Space Flight Research and Health Care	Houston
September 1-2	Consortium Expansion Review – Phase II	Houston
September 7-8	External Advisory Council Meeting	Houston
September 23	Board of Directors Meeting	Houston

- Determined that EB1089 and LG10110 were capable of efficiently inducing VDR targets at concentrations that should not cause hypercalcemia *in vivo*. EB1089 was chosen for further study because it is already in phase II trials for prostate cancer and is thus more likely to be accepted for human use.
- Determined that slow turning lateral vessels (STLV) are a suitable mimic to study the effects of microgravity on cells. By comparing the responses of MG-63 cells in an STLV with those of MG-63 cells flown on the Foton 10 satellite, the group observed similar changes in basal markers and similar reductions in the induction of target genes by calcitriol. This suggests that the STLV is an acceptable model.
- Found that, in comparing calcitriol and EB1089 in the STLV, EB1089 is both more potent and efficacious in inducing VDR targets. This suggests that EB1089 is a good candidate for reversing effects induced by microgravity.
- Found that, of several selective estrogen receptor modulators (SERMs) tested to date, Idoxifene is the most potent activator of synthetic ER target genes. Several SERMs have been tested for their ability to activate target gene expression in the MC3T3-E1 osteoblastic cell. As a SERM, Idoxifene should not stimulate ER activity in tissues, such as the breast, and may therefore be suitable for targeted treatment of bone loss.
- Established a model system of differentiated MC3T3-E1 cells, representative of a more mature osteoblast phenotype. This system responds to estrogen treatment by increased alkaline phosphatase production. This system will be used to examine the ability of estrogen and SERMs to stimulate osteoblastic gene and protein expression.
- Shown that the extracellular calcium-sensing receptor (CaR), a key mediator of the direct actions of extracellular calcium on numerous cell functions that serves as the body's "calcistat," is expressed in monocytes, which serve as precursors for bone resorbing osteoclasts. Elevated concentrations of calcium inhibit the formation of osteoclasts as well as the activity of mature osteoclasts, possibly providing a mechanism for inhibiting excess bone resorption in microgravity via the use of CaR activators.
- Shown that the CaR is expressed in several osteoblast-like cell lines, which are thought to represent models of bone-forming osteoblasts. Elevated concentrations of calcium, likely acting via the CaR, stimulate the proliferation and chemotaxis of these osteoblastic cells, possibly providing a mechanism for stimulating bone formation in microgravity via the use of CaR activators.
- Shown that the CaR is expressed in a bone marrow stromal cell line. Stromal cells can serve as osteoblastic precursors or communicate with other bone cells (e.g., osteoblasts and osteoclasts) in a paracrine manner. Elevated concentrations of calcium stimulate the proliferation and chemotaxis of these stromal cells, probably acting via the CaR, thereby potentially providing a mechanism for stimulating bone formation in microgravity via the use of CaR activators.

(*Bloomfield*) Using an adult rat hindlimb unloading model, we have found that:

- Blood flow to hindlimb bone declines by 50 percent after 7 days of hind limb unloading. These changes are somewhat site specific. For example, no change in flow was noted in the distal tibia. Much of the change in blood flow (up to 60%) appears to occur in the first 10 minutes of hind-limb unloading as measured in control animals suspended briefly.
- Blood flow to the weighted humerus increases briefly at the onset of hindlimb unloading. This increase ranges from 50-100 percent, depending on the region of the humerus. Blood flow normalizes after seven days of hindlimb unloading. One

possible interpretation is that the forelimb vasculature may be adapting to the change in fluid shifts and hydrostatic pressure after seven days of unloading.

- In the unloaded femur, growth factors favoring bone formation are down-regulated early in the unloading period, whereas cytokines favoring resorption are up-regulated. Gene expression for the growth factors, TGF- β_1 and TGF- β_2 , declines in the unloaded femoral bone after three days. Simultaneously, gene expression for these growth factors increases in the humerus. Gene expression for several cytokines affecting bone resorption (IL-6 and IFN- γ) tended to increase in femoral bone after three days unloading.

(Schultheis) Using a suspended rat model of chronic partial weightbearing, we have determined that:

- Preliminary analyses of bone by pQCT, histomorphometry, mechanical testing and biochemistry suggest that chronic exposure to half of Earth gravity is insufficient to prevent severe bone loss.
- Similarly, preliminary analyses indicate that 2 hours daily of full weightbearing was insufficient to prevent the bone loss observed in 50% weightbearing animals.
- Ibandronate, a long-acting potent bisphosphonate proved more effective in preventing bone loss and associated functionality based upon structure than our first efforts at mechanical countermeasures, independent of generalized systemic stress imposed by the suspension paradigm.
- High frequency components of impact forces (generated by servo-controlled force plates on suspended rats with implanted strain gauges) are particularly potent in producing bone strain independent of the magnitude of the peak force or peak energy applied to the leg and passive vibration may also be effective, but passive vibration may or may not increase bone in the appropriate architectural pattern to oppose the forces of normal ambulatory activity.

(Ruff) Using a suspended rat model, we found preliminary evidence that:

- Tail-suspension has a negative effect on bone structural properties, particularly trabecular density. This is just as true for the .5 G loaded humerus as for the unloaded femur, i.e., partial loading (to half gravitational force) does not protect against bone loss.
- Ibandronate is a very effective countermeasure to bone loss induced by a low gravity environment. This is particularly true for trabecular bone loss. In addition, free-ranging rats treated with ibandronate had higher trabecular bone densities than free-ranging controls.
- Periodic full weight-bearing had much smaller, if any, effect on bone loss and bone strength. A possible explanation for this is that during the full weight-bearing periods rats were relatively inactive, and thus not subjecting their bones to substantially increased mechanical loads. Future studies will incorporate more controlled increases in mechanical loads (strains) as a potential countermeasure.

Using DEXA (dual energy x-ray absorptiometric) scans of 19 Russian cosmonauts subjected to 126 to 312 days of space flight on Mir, we found evidence that:

- There was a greater loss of bone mass than in corresponding bedrest subjects.
- Declines in the section modulus, an index of bending and torsional strength, averaged about 8% in the femoral neck and about 4.5% in the femoral shaft, suggesting that the countermeasures used on Mir to maintain bone integrity are inadequate. The magnitudes of declines in section modulus were weakly but significantly associated

with duration of space flight at both locations, accounting for 17% and 13% of the variability in these parameters in the neck and shaft, respectively.

- Data from eight cosmonauts taken an average of 481 days after return to Earth indicated that, on average, neck and shaft BMD returned to within 3% and 2% of preflight levels, respectively. The more strength-relevant neck and shaft section moduli on average returned to within 2% and 1%, respectively, of pre-flight values.

Using Finite Element Modeling, we have found that:

- Hip loading anticipated during Mars-gravity locomotion and falls may be as severe as Earth-based activities due to the additional mass and inertia of a spacesuit, particularly the backpack life support system. Loads of two to three times body weight are experienced during locomotion, while impact loading of as much as eight times body weight would occur during a fall.

Cardiovascular Alterations Research Team

(*Cohen*) Using a human bed-rest model, we have:

- Detected alterations in cardiovascular control during and after bed rest. Findings to date indicate that after prolonged bed rest there is a diminution in neural and baroreceptor function, which regulate cardiovascular activity.
- Initiated investigation of the use of pharmacologic countermeasures to the development of orthostatic hypotension.
- Demonstrated that the method of cardiovascular system identification may also be useful in the monitoring of neural damage in patients with diabetes.
- Measured alterations in electrical stability in context of short- and long-term bed rest studies. Preliminary data indicate that alterations in electrical stability may become manifest in as little as two weeks under conditions of bed rest. These changes, although not large enough to be of current clinical concern, suggest that there is a measurable effect. Extrapolation of these data to many months or years of exposure to microgravity might imply a risk. More data are required before conclusions can be drawn.
- Successfully commercialized the measurement of microvolt level T wave alternans, which was cleared by the FDA in April 1999 for the identification of individuals at increased risk of sudden cardiac death. This is the only test that the FDA recognizes for this purpose and the test is now clinically available.

(*G. Williams*) Using a human bed-rest model, we have found that:

- There is a suggestion that weightlessness induces an apparent dysregulation of the primary hormonal system, the renin-angiotensin-aldosterone system (RAAS), which regulates fluid balance in the body. Despite a constant fluid, sodium, and potassium intake investigators measured approximately a 16% decrease in plasma volume in response to microgravity simulation. One possible mechanism to effect this reduction in plasma volume would be a down-regulation of the RAAS, which would cause sodium and water loss in the urine. It is, however, not clear that this actually occurs. Rather than decreased renin levels, preliminary analysis of the data suggests that renin levels are increased during microgravity simulation. This suggests that some other mechanism might be responsible for reducing body fluid levels during weightlessness, and that the RAAS is actually reacting to and/or attempting to compensate for this effect.
- The end organ response to renin and angiotensin after bed rest was blunted. This diminished responsiveness of end organs to hormonal secretion also implies a major

dysregulation of the RAAS in individuals in space. During weightlessness these hormonal systems no longer have gravity as a reference point and, without these usual parameters, their ability to adapt to volume changes becomes somehow misaligned. That is, when a hormone (one part of the system) acts as if the body is volume depleted, and an organ (another part of the system) acts as if it is volume overloaded, the organ being acted upon by the hormone does not respond appropriately, and vice versa, suggesting a desynchronization of the hormonal system. A similar, although not identical, kind of system dysregulation occurs during heart failure, when the pump fails, and the body has no reference point that helps it adapt to the phenomenon.

- Determined that angiotensin levels need to be determined during simulated and actual weightlessness. If plasma renin activity is persistently elevated, and the downstream hormone, angiotensin is also chronically elevated, this may have harmful effects on the heart and vasculature, putting space crews on long duration missions at risk. Finding the agency of dysregulation in the hormonal system could be key to preventing this chronic up-regulation of upstream elements of the RAAS and ensuring the optimum cardiovascular health of space crews; it could also provide us with tools for treating heart disease here on Earth.

(*Shoukas*) Using a hind limb unweighted (HLU) rat model, we:

- Demonstrated impaired cardiac output (CO) responses to an orthostatic challenge in rats. After about 60 hours of recovery, CO responses to tilt approached pre-HLU values.
- Demonstrated both alpha-1-AR and non-alpha mediated responses in large arteries (aorta) of HLU animals.
- Demonstrated primarily impaired alpha-1 AR responses in the femoral arteries of HLU rats and demonstrated that the vascular phenomenon observed is reversible.
- Observed alpha-1AR specific abnormalities in mesenteric micro vessel responses.
- Observed a decrease in alpha-1AR specific radioligand binding in aortic vessels from HLU animals.

(*Kamm*) We have:

- Developed an operational model capable of simulating cardiovascular response to orthostatic stress. The model consists of a lumped parameter hemodynamic model and a complete neural reflex control system. The latter includes cardiopulmonary and carotid sinus reflex limbs and interactions between the two.
- Modeled the physiologic stress of tilt and lower body negative pressure procedures (LBNP). The model's predictions were verified by comparing them with experimental findings from literature.
- Established a standardized transfer of data from NSBRI bedrest studies to MIT. Data from the NSBRI bedrest studies are used to verify the model's predictions and to estimate input parameters for the model.
- Embarked on simulating specific theories of orthostatic intolerance by matching the simulations to stand test data collected from astronauts pre- and post-flight. A JAVA version of this simulator is being prepared for distribution to cardiovascular team members via the Internet. This simulation technology offers great possibilities for Earth applications, as well. It could provide a basis for interpreting real-time cardiovascular data in intensive care units or in situations where physiological data must be interpreted remotely. It could also provide a powerful environment for the teaching of normal and pathologic cardiovascular physiology.

(Schneider) Using a mouse model, we:

- Established a simpler and more cost-effective means for invasive hemodynamic monitoring in rodent models. Compared *in vivo* measurements using left ventricular (LV) catheterization versus utilization of high-fidelity micromanometer tip catheters. Found that in the *vivo* adult mouse, similar to the large rat, direct LV catheterization can be used for extremely accurate evaluation of LV performance.
- Demonstrated that *in vivo* echocardiography in the mouse can discriminate changes in LV mass and morphology and serial changes in LV performance indices in the aortic stenosis mice. This approach has major implications for non-invasive application in cardiovascular mouse experimentation in space.
- The pharmacological countermeasure, growth hormone, was shown to rescue cardiac function even under conditions where it does not augment cardiac mass. The improvement in heart contractile function, achieved after only short-term treatment with growth hormone, was associated with increased expression of SERCA-2 at the level of the myocyte. Now the project is seeking to determine if short-term growth hormone therapy will be an effective countermeasure to enhance cardiac performance in cardiac atrophy due to simulated microgravity.
- Established a novel method to directly clone genes that are regulated by mechanical load. Identified several dozen novel targets of the mechanical signaling cascade, including integrin-linked kinase. Integrin-linked kinase is an especially promising target for mechanical signal transduction.

Human Performance Research Team

(Czeisler) Using human subjects, we have:

- Determined that some individuals can maintain circadian synchronization to the 24-hr Earth day in a dim light environment whereas others cannot. These data demonstrate for the first time that the human circadian pacemaker in some individuals can be entrained to a scheduled 24 hr light-dark cycle of such a weak strength. The ability of the human circadian pacemaker to synchronize to the 24-hr Earth day appears to be dependent upon the strength of the light-dark cycle, the light intensity to which individuals are exposed, and to the intrinsic period of the individual's circadian pacemaker. The average intrinsic period of people tested in our laboratory is 24.18 hrs with a standard error of .03.
- Subjects' entrained circadian phases to a 24-hour dim light dark cycle appear to be dependent upon the underlying period of their circadian pacemakers.
- Preliminary results suggest that humans can not synchronize to the 24.6 hr day length of Mars in a dim light environment, such the lighting environment aboard the mid-deck of the space shuttle, because the Mars day length appears to be outside the range of entrainment for the human subjects tested. The apparent inability to synchronize to the Mars day may have negative consequences on sleep and human growth hormone regulation.

(Dinges) Using human subjects, we have:

- Found that splitting sleep hours between anchor sleep and a nap may be more effective than continuous sleep in preventing performance deficits when sleep is chronically shortened.
- Identified and introduced a new technology for blood sampling that markedly facilitates frequent, unobtrusive sampling on Earth or during space flight. This technology enables us to closely monitor hematological, immune, endocrine, and pharmacologi-

cal variables. This project is evaluating the effect of different sleep/wake schedules on growth hormone release.

- Found that individual vulnerability to performance impairment in the face of sleep loss may be a relatively stable trait on which individuals differ. If this preliminary finding proves to be accurate, it will help to target countermeasures more precisely to those astronauts who most need them.

(*Dijk*) Using human subjects, we have found that:

- The spectral composition of the EEG during wakefulness exhibits pronounced and predictable changes during a 24-h period of sustained wakefulness.
- The changes associated with sleep loss are most pronounced in EEGs derived from frontal areas of the brain, and particularly so in the delta and theta frequencies, both during wakefulness and during sleep.
- Changes in alertness and psychomotor vigilance correlate with changes in EEG power density in the delta and theta frequencies in frontal derivations.
- The incidence of slow eye movements during wakefulness increases during sleep loss and correlates with changes in alertness and psychomotor vigilance. This correlation is so tight that inter-individual differences in the time course of the incidence of slow eye movements closely resemble the inter-individual differences in the time course of neurobehavioral performance during a 24-h episode of sustained wakefulness.
- The circadian pacemaker modulates the incidence of slow eye movements as well as the spectral composition of the EEG during wakefulness.
- Light-induced changes in the amplitude of the circadian pacemaker and associated changes in the amplitude of the circadian modulation of alertness are associated with changes in the amplitude of the circadian modulation of the incidence of slow eye movements.
- Light-induced acute changes in alertness are associated with acute changes in the EEG and the incidence of slow eye movements during wakefulness.
- Posture modulates the apparent amplitude of the circadian rhythm of body temperature and heart rate such that this amplitude is reduced when subjects are in a supine posture during 40 hours of wakefulness.

(*Young*) Using humans, we:

- Conducted the first evaluation of a decision aid (Principal Investigator-in-a-Box) under controlled conditions in an effort to determine the applicability of expert systems in future space flight research and demonstrated that use of this decision aid improves experiment performance, compared to performance without the decision aid.

Immunology, Infection and Hematology Research Team

(*Shearer*) Using human subjects, we have:

- Established a linkage between the human immune response and the stress of sleep deprivation. In effect, linkages between the brain and hormones and the immune system become unregulated in sleep-deprived humans. Parallel studies of patients with nocturnal asthma are in progress to determine what effect sleep deprivation associated with asthma will have on the blood's chemical messengers. Nocturnal asthma affects at least 20 percent of the more than 15 million humans with asthma in the United States.

(Butel) Using human subjects, we have:

- Developed specimen collection and processing protocols and sensitive, specific polymerase chain reaction (PCR)-based assays to detect virus reactivation and shedding in human samples. The work has focused on human herpesviruses and polyomaviruses.
- Established normal baselines for virus shedding from a year long longitudinal study of healthy volunteers and determined that normal individuals over age 40 frequently shed the polyomavirus, JC virus (JCV).
- Obtained preliminary data from Antarctic isolation studies that suggest increased shedding of JCV by younger persons. These data suggest that the stress of isolation in Antarctica may change the host-pathogen balance and this is reflected in more viral shedding.
- Determined that herpesvirus EBV load in blood is elevated in immunosuppressed HIV-infected persons. This work, involving the use of HIV infection as a ground-based model, indicates that EBV genome loads can be used as a marker of immune competence.
- Determined, from the Antarctic isolation studies and HIV infection studies, that virus reactivation and shedding can be used as functional markers of changes in the host immune system.

Using antiorthostatic suspension of mice, we have:

- Observed a delay in rotavirus clearance following four days of suspension prior to primary rotavirus infection. This is most likely due to an alteration in cell-mediated immunity. Rotavirus is known to cause localized infection of the GI tract and is a good model for mucosal immunity.
- Determined that short-term anti-orthostatic suspension during primary infection did not alter the development of memory mucosal immune responses. Anti-orthostatically suspended mice re-infected with rotavirus six weeks after their first infection did not shed rotavirus; they were protected. However, the IgG subclass switch normally observed after a second exposure to virus (IgG2a to IgG1) did not occur.
- Obtained preliminary results that suggest that alterations in mucosal immune responses occur under simulated space flight conditions.
- Established that mice can tolerate suspension for longer periods of time than expected, with suspensions of 28 days now being carried out.

(Fox) Using *in vitro* techniques, we have:

- Discovered a non-toxic method of purifying DNA from RNA and vice versa. A patent application has been filed on the technique and a Nature Biotechnology article on the technique has generated a high level of inquiries from outside laboratories.
- Determined that molecular beacon technology provides a way to create a simple spacecraft borne test for bacterial detection. The beacon assay targets specific sequences in ribosomal RNA, which are, in essence, the fingerprint of the target bacterium. When developed, the test could be done by astronauts to screen for two to five critical classes of bacteria with one simple experiment, a technique that would be useful for routine daily monitoring.

Muscle Alterations and Atrophy Research Team

(Schwartz) Using a mouse model, we have:

- Determined that insulin-like growth factor I (IGF-I) increases muscle mass in transgenic mice. In the laboratory, the project was able to show that the mice had in-

- creased muscle mass (muscle hypertrophy) to the order of 20-30% in size. This discovery points to the role of IGF-I as a major muscle hypertrophic regulator.
- Determined that IGF-I could not sustain muscle hypertrophy under conditions of unweighting of the animal, probably related to calcium-induced degradation of a protein called IRS-I.
 - Developed a gene therapeutic vector that expresses a protein called growth hormone releasing hormone (GHRH). These studies were able to increase both animal weight and growth hormone secretion. It is the first demonstration expressing a hypothalamic factor, GHRH, in the blood system that has a direct effect on the anterior pituitary.
 - Developed synthetic muscle promoters that drive transcriptional activity greater than any known virus or muscle promoter. In gene therapy approaches, these types of muscle promoters will reduce the amount of DNA that has to be injected into muscle.

Using pigs, we have:

- Increased GHRH and IGF-I levels using synthetic muscle promoters and a novel protease resistant GHRH. By injecting young pigs with this modified and powerful vector, sustained expression doubled or tripled the animals' GHRH and IGF-I levels over a two-month period. The pigs grew approximately 40% faster than their control littermates.
- Developed a technique for gene delivery (electroporation technique) into muscle using needle injectors. This gene delivery technique increases gene activity up to about 5000-fold versus direct needle injection. The advantage to this technique is that it provides a uniform spread of DNA throughout the muscle fibers.
- Regulated expression of GHRH in muscle through use of a gene switch. Putting the GHRH gene under the control of a gene switch allows regulated expression of GHRH for muscle. The gene's on/off ability allows for gene utilization on an as needed basis.

(Hamilton) Using hindlimb-suspended mice, we found:

- An increase in resting calcium levels in muscle. This finding focused researchers on the pathways that are activated by increases in intracellular calcium, pathways that cause the activation of proteases and other calcium dependent enzymes leading to muscle atrophy.
- A decrease in the phosphatase, calcineurin. This was surprising since a calcium increase usually activates calcineurin.
- Evidence for the activation of pro-apoptotic pathways that lead to programmed cell death, pathways that may be contributing to muscle atrophy -- perhaps through the loss of myonuclei.

(Goldberg) We have found that:

- A specific pair of ubiquitination enzymes (termed the "N-end system," and consisting of the Ub-carrier protein, E2_{14k}, and the Ub-protein ligases, E3 α) are responsible for the majority of Ub conjugation in extracts of normal skeletal muscle and appear to be responsible for most of the enhanced Ub conjugation in atrophying muscles.

Using insulin-deficient rats, we found:

- In muscles, Ub conjugation by the N-end rule pathway is stimulated, similar to what we found in the muscle wasting seen in disuse, sepsis, cachexia, and hyperthyroidism. These findings support our working hypothesis that excessive proteolysis and muscle atrophy induced by diverse physiological or pathological stimuli occurs by a common cellular mechanism. The simplest interpretation of these findings is that small in-

- creases in E2_{14k} and E3 α lead to accelerated Ub conjugation and protein degradation in muscles of insulin-deficient (or insulin-resistant) animals (although additional adaptations may also contribute to the increased ubiquitination).
- Several critical new reagents have been developed to study this system (cDNAs cloned, antibodies prepared, and pure E3 α and E2_{14k} were isolated).
 - A dramatic influence of Ca²⁺ in retarding breakdown of calmodulin by the Ub-proteasome pathway.

(*Baldwin*) Using a rodent hindlimb suspension model, we found that:

- A single, isometric-type resistance training session performed daily during the initial stages of atrophy is not sufficient to counteract the imbalance of protein synthesis to protein degradation processes that occur during the acute stage (day 1-14) of the rapid atrophy process. The resistance-training program was not effective in significantly ameliorating atrophy occurring in either the fast-twitch or slow-twitch muscles.
- Using a model of chronic functional overload (created by surgical removal of muscle synergists), the augmentation of IGF-1 peptide expression at the muscle level is temporally linked to signaling processes associated with translational mechanisms to enhance protein accretion.

(*Epstein*) Using a mouse model, we:

- Identified new protein building blocks of muscle filaments. These new proteins are being called filagenins, or generators of filaments. Filagenins exist in addition to the well-known muscle protein myosin, which acts as sort of an engine or motor molecule for muscle contraction.
- Showed, by structural analysis, that the myosin filament is a tubule cross-linked by either filagenins (invertebrates) or myosin-binding proteins (vertebrates) rather than a rope-like model. The classic paradigm of protein assembly and organization has been the myosin thick filament with no crosslinks. This finding challenges that model and suggests a rigid tubular module of multiple smaller cylinders cross-linked at key distances. Both the myosin and the filagenins/myosin-binding proteins have a vital function in the muscle.
- Determined that additional enzyme-like molecules are necessary for proper myosin assembly. For myosin to form sub-filaments, the action of additional proteins on the molecule is needed. These proteins act as a scaffold, binding on one end the myosin molecule, and on the other end, a protein called the molecular chaperone. If the function of these additional proteins is mutated, the myosins assemble in a scrambled manner.
- Showed that, in the absence of myotonic dystrophy protein kinase (DMPK), there is an abnormal fiber-type switching and myosin-isoform switching upon unloading or suspension. This finding implicates DMPK in the process of muscle-fiber switching in space flight.
- Found potential mechanisms for the effects of DMPK:
 - (1) DMPK can affect the organization of the actin cytoskeleton and cell plasma membranes and may participate through these structures in apoptotic-like processes (cell death). Both the actin cytoskeleton and cell plasma membranes are necessary for normal development and remodeling of tissues.
 - (2) The DMPK molecule might be linked to two physiologically distinct signaling systems -- the signaling system from the adhesion of cells to other cells and surfaces and the signaling system to chemical messengers from outside the cells, such as hormones (including growth factor).

- (3) DMPK is important in regulating a transcription factor called serum response factor, which is necessary for muscle development.

(Mosier) Using tail-suspended mice, we:

- Stimulated single-fiber electromyography (S-SFEMG) technique developed and validated in mice. This is the first time this technique has been down-sized for mice.
- Observed abnormal functioning of the neuromuscular junction in muscle atrophy induced by hindlimb unloading. In some fibers, neuromuscular transmission was blocked and function was lost.
- Discovered that the atrophy response varies between different muscle groups in the pre-synaptic terminal of unweighted animals, i.e., the muscles atrophy differentially. The difference cannot be explained by mechanical loading or by a change in what the spinal cord motor neurons are telling the muscles to do.
- Found atrophy in the post-synaptic junctions of the soleus through examination of the neuromuscular junctions.
- Discovered that alterations in motor units that take place with unloading of muscle are not confined to the muscle site. There are clear changes that occur at the nerve muscle synapse and also pre-synaptically in the motor neuron. Abnormalities are seen on both sides of the synapse.

(Rosenthal) We found:

- Support for a model wherein different E proteins (a group of transcriptional regulatory proteins) are selectively expressed in muscle cells to determine fiber-restricted gene expression. These studies are a first step to define the molecular mechanisms responsible for the shifts in fiber type under conditions of microgravity, and to determine the potential importance of E proteins as upstream targets for the effects of weightlessness.
- That the expression of E Proteins is restricted to specific fiber types by post-transcriptional mechanisms. By far, the most prevalent mechanism of cellular control for achieving post-transcriptional regulation of gene expression is selective proteolysis through the ubiquitin – proteasome pathway.

Neurovestibular Adaptation Research Team

(Shelhamer) Using a monkey model, we:

- Discovered that gravity can function as a context cue during sensorimotor adaptation. Researchers have known for some time that humans can learn and retain two different sensorimotor adaptations simultaneously and switch between them based on a context cue, such as vertical eye position or viewing distance. This study demonstrates that gravity can also serve as a context cue for the adaptation of oculomotor (saccade) and vestibular (linear VOR) responses.
- Established an animal model for context-specific adaptation. Non-gravity-dependent contextual adaptation has also been demonstrated in the monkey. This model will enable future experiments investigating the effect of the cerebellum on such adaptation.
- Established equipment and verified procedures for the testing of adaptation paradigms during parabolic flight.

(*Oman*) Using human subjects, we:

- Found that even on Earth, subjective orientation can be determined by relative orientation of the visual scene rather than by gravity, and discovered that subjective orientation depends heavily on the perceived relation between vertical body alignment and visual cues. This finding has strong implications for extending the functionality of flight simulators.
- Detected higher susceptibility to visual reorientation illusions (VRIs) in older people. Data show that reliance on vision for static orientation perception seems to become more important as people age.
- Demonstrated that people eventually can learn to do difficult 3D spatial memory tasks. In tests conducted in both real and virtual environments, it was shown that people eventually learn to use strategies analogous to those used in 2D navigation when confronted with a 3D spatial memory task, and that their ability in the task correlates with conventional tests of mental rotation ability. These findings, which bring us closer to understanding the strategies people use to navigate in both real and virtual worlds, suggest new training strategies for astronauts and insights and even potential therapies for patients who have orientation and navigation difficulties.

Using laboratory rats, we have:

- Characterized head-direction cell discharge (from a population of neurons in the rat's brain that discharge as a function of the rat's head direction) under parabolic flight conditions of acute weightlessness. The data suggest that the rats maintained a normal allocentric frame of reference in 0-g and 1-g when on the floor or wall, but that when placed on the ceiling, the rats sometimes experienced a VRI, as evidenced by the reversal of the head-direction cell preferred direction across the cage axis of symmetry.

(*Wall*) Using human subjects, we:

- Have developed new methods for measuring and modeling head and trunk rotations during turning in order to elucidate the role of the balance system during linear and circular locomotion. One looks at the effects of the velocity of straight walking on trunk and head movements. Another, called head fixation distance, investigates the effects of viewing distance on compensatory vertical eye movements. A third investigates the role of head and eye movements during circular turning and locomotion. Out of these studies, we have developed new representational schemes for modeling and studying head and trunk rotations during turning.
- Have found that, for optimal walking speeds (1.4-1.8 m/s), the head fixation distance is fairly constant, at about 1 meter. Our hypothesis is that head fixation distance is an important parameter that should be controlled for maintaining stability of gait during straight walking following space flight, and ways to do this by maintaining the robustness of the vestibulo-ocular reflex during flight may be an appropriate counter-measure.

Radiation Effects Research Team

(*Dicello and Huso*) Using laboratory rats, we:

- Made many important early observations on long-term mammary carcinogenesis and chemoprevention following low-level exposure to accelerated iron ions and protons and are archiving tissue samples from all organs for potential additional future studies of other organ systems.
- Have preliminary evidence that sixty days of tamoxifen treatment has had a dramatic effect in reducing the incidence of mammary tumors.

(J. Williams) Using laboratory rats, we:

- Found significant differences, both quantitatively and qualitatively, between responses of different cell types to low-level exposure to accelerated iron ions and protons. However, there is an overall pattern that characterizes each type of radiation in most cell lines. Specifically, we observe significant resistance for induction of aberrations in rat mammary epithelial cells when they are irradiated *in vivo* and assayed *in vitro*.
- Observed some remarkable differences in susceptibility to certain radiation-induced aberrations in cells whose genome has been modulated for two cancer-relevant genes, TP53 (p53) and CDKN1A (p21). This data may represent the first evidence of gene-specific differences in cellular metabolism of damage induced by densely-ionizing radiation that confers substantial sensitivity to protons compared to photons.
- Demonstrated that dose-response patterns for induction of different types of aberrations is a complex function and varies in shape and intensity over different dose-ranges, with most variance between effects of Fe-ions compared to the effects of protons and photons. Our data suggest that it may be inappropriate to apply some models to predicting the relative biological efficiency (RBE) for Fe-ions, particularly at lower doses (< 0.5 Gy).
- Suggested that both Fe-ions and perhaps protons are more potent at inducing DNA double-strand breaks than photons; the effect of Fe-ions previously demonstrated by other methodology, but the effect of protons heretofore not demonstrated.

(Sinden) Using cell systems, we:

- Found that the rate of deletion of inverted DNA repeats in human cells is increased following exposure to heavy iron particles. This type of DNA mutation has been linked to many human diseases and to cancer and is similar to what is seen following excess x-ray exposure. Solar flares have heavy iron particles, and intergalactic cosmic radiation has many types of particles that can do damage to DNA. Exposure to heavy iron particles is a concern in space flight.

Technology Development Research Team

(Charles) We:

- Began construction of a working prototype of a compact, high precision, multiple projection dual energy X-ray absorptiometry (DEXA) scanner.
- Acquired a new, high quantum detection efficiency detector for the scanner, providing greatly increased quantum detection efficiency. This will lead to an improved signal-to-noise ratio in the images, which will in turn lead to greater precision in the geometry calculations. Dose to the patient will also be reduced.
- Initiated development of control and image processing software, which will enable measurement of patient parameters with significant improvements in scanner precision, accuracy and compaction.

(Maurer) We:

- Completed modeling of the neutron-silicon elastic scattering reaction begun in 1998. Since neutrons cannot be measured directly, they must first be converted to charged particles through several scattering processes. Modeling of the non-elastic reactions is in progress.

- Designed, modeled and tested a robust neutron spectrometer that measures the neutron spectrum from 10 KeV to 500 MeV. This dual detection system uses a highly efficient proportional counter Helium 3 tube in the low energy range and a 5 mm thick lithium drifted bulk silicon solid state detector in the high energy range.
- Designed and fabricated an aircraft flight package, which is presently in final calibration and qualification for system integration with NASA Dryden F-18 aircraft in preparation for upcoming environmental testing flights.

(Potember) We:

- Demonstrated mass capability resolution from under 100 to beyond 10,000 atomic mass units in a very small, low power, prototype time-of-flight mass spectrometer for biological analysis and designed an orthogonal extraction analyzer that will incorporate a dual matrix-assisted laser desorption/ionization and electron ionization source.
- Completed initial laboratory studies using the time-of-flight mass spectrometer with critical biomarkers identified by the Muscle Alterations and Atrophy Team and with biomarkers specific to the Bone Demineralization / Calcium Metabolism Team.
- Employed matrix-assisted laser desorption mass spectrometry as tool to quantitatively measure 3- methylhistidine in biological fluids.

(Cohen) We:

- Designed and developed the prototype of an automatic instrumentation system for non-invasive assessment of cardiovascular regulation that can be operated by the lay user. Produced a user-friendly prototype that automatically records signals while detecting and eliminating noise and artifacts.

Synergy Projects

(Cohen) We have:

- Evidence that, during and following a 17-week bed rest study, both autonomic nervous system dysfunction and changes in cardiac electrical stability occur.

(Mullington) We:

- Demonstrated that the effects of partial sleep deprivation on immune function appear to be consistent with those previously ascribed to acute total sleep deprivation. These preliminary data suggest that chronic sleep reduction to 50% of the normal daily diet alters the homeostasis of neuroendocrine and neuroimmune regulatory systems, possibly compromising the body's response to an immune challenge.

(Ramsdell) We:

- Demonstrated that static or moving visual stimuli can elicit transient autonomic responses in some subjects. New understandings of the links among the vision, inner ear and cardiovascular systems might be used in the future to enhance cardiovascular and/or vestibular coping mechanisms for long-duration space flight and provide valuable insight into the prevention and/or treatment of cardiovascular disease here on Earth.

3.2 Future Plans – Strengthening the NSBRI

During the initial year of operation of the Institute, it became very clear that the level of funding was inconsistent with the breadth of the mission of the NSBRI, as defined in NASA's original competitive announcement to develop the NSBRI. Institute management was faced with two choices: continue with the current programmatic approach involving reduced scope and depth, or seek additional funds to carry out the mission as it was originally described. In April 1998, at a brunch honoring the upcoming Neurolab (STS-90) mission and hosted by the NSBRI, Dr. DeBakey asked Mr. Goldin, the NASA Administrator, to provide the Institute with his vision for the future. Mr. Goldin did this in a letter to Dr. Alford, the Chairman of NSBRI's Board of Directors and NSBRI's Chief Executive Officer, dated July 9, 1998. That letter, a facsimile of which is included in Appendix H, provided the starting point for the development of the NSBRI's vision for strengthening the Institute's program.

In November 1998 (see Table 1), Mr. Goldin visited NSBRI Headquarters and discussed the Institute's ideas and plans. Following this meeting, on November 18, 1998, the NSBRI submitted an unsolicited proposal to NASA to strengthen the Institute's programs. NASA reviewed this proposal and, in March 1999, requested that the NSBRI prepare a Project Proposal regarding Tactical Planning and Integration. An Institute response was submitted in July 1999 and this, together with the unsolicited NSBRI proposal was used by NASA to assist them in planning for the development and augmentation of their overall biomedical program, enlarged and renamed the NASA Bioastronautics Program (see Appendix H for copies of these submissions). As a result of this planning, NASA has augmented the Institute's FY 2000 core budget by \$4 M in order for the Institute to develop the infrastructure needed to sustain an increased research base in FY 2001.

The Institute's growth plan involved several interacting components. First, to expand the NSBRI's consortium base, an open, competitive special announcement to institutions was released on May 10, 1999 (Appendix I). This announcement invited institutions to apply to become consortium members through a two-phase process. Thirty institutions responded to the announcement and submitted Phase I proposals (Table 2). A review panel representing the original NSBRI consortium, the external scientific community, and NASA was selected to review the applications (Table 3). Meeting in July, the panel identified eight institutions that were highly meritorious candidates for consortium membership and invited them to a reverse site visit panel meeting in Houston in early September (Table 4). Following this review, the panel developed recommendations to the Board of Directors and, at the end of September the Board selected five new institutions to add to the NSBRI consortium: Brookhaven National Laboratory, Mount Sinai School of Medicine, the University of Arkansas for Medical Sciences, the University of Pennsylvania Health System, and the University of Washington.

Second, the Institute's unsolicited proposal to NASA outlined four new research areas to be developed for the Institute: neurobehavioral and psychosocial factors; nutrition, physical fitness, and rehabilitation; smart medical systems; and, integrated human function. To implement this component of the proposal, four workshops were held over the course of the summer of 1999, on in each area. The panels that met and a summary of the workshop reports is contained in Appendix J. It is intended to develop and release a research announcement early in FY 00 soliciting projects for these four areas

Third, it is planned to hold workshops in the first quarter of FY 00 in each of the Institute's eight current areas of research in order to obtain community advice on the directions that future growth

of the Institute's programs should take. Then, a second research announcement would be prepared and released later in FY 00, enabling appropriate growth in program depth to occur at the beginning of FY 01.

<p align="center">Table 2. INSTITUTIONS SUBMITTING PROPOSALS TO BECOME CONSORTIUM MEMBERS</p>		
Brookhaven National Laboratory	Children's Hospital Medical Research Foundation	The Cleveland Clinic Foundation
Cornell University	Dartmouth Medical School and Creare, Inc.	Department of the Army U.S. Army Institute of Surgical Research
Kansas State University	Legacy Holladay Park Clinical Research and Technology Center	Loma Linda University Medical Center
Louisiana Tech	Mayo Clinic	Medical University of South Carolina
The Mount Sinai Medical School	Stanford University School of Medicine	Texas Tech University
University of Arizona	University of New Mexico Health Science Center	University of Texas System
Uniformed Services University of the Health Sciences	University of Arkansas for Medical Sciences	University of California at Davis
University of California, San Francisco	University of Houston System	University of Kansas Medical Center
University of Medicine & Dentistry of New Jersey	University of Minnesota	University of Pennsylvania Health System
University of Washington	Vanderbilt University Medical Center	Wisconsin Center for Space Automation and Robotics

**Table 3.
CONSORTIUM ENLARGEMENT REVIEW PANEL**

Bobby R. Alford, M.D. (Chairman) Baylor College of Medicine	J. V. Bonventre, M.D., Ph.D. (Phase I only) Harvard University-MIT Division of Health Sciences & Technology	Aaron Cohen Texas A&M University
M. J. Fettman, D.V.M., Ph.D. Colorado State University	E. Nigel Harris, M.D. (Phase I only) Morehouse School of Medicine	Richard J. Johns, M.D. Johns Hopkins Medical School
Jordan Konisky, Ph.D. (Phase II only) Rice University	J. David Litster, Ph.D. Massachusetts Institute of Technology	Peter R. MacLeish, Ph.D. (Phase II only) Morehouse School of Medicine
Larry McIntire, Ph.D. (Phase I only) Rice University	R. Y. Moore, M.D., Ph.D. University of Pittsburgh	James W. Patrick, Ph.D. Baylor College of Medicine
Danny A. Riley, Ph.D. Medical College of Wisconsin	John A. Rummel, Ph.D. NASA Johnson Space Center	Frank Sulzman, Ph.D. NASA Headquarters

**Table 4.
INSTITUTIONS INVITED TO SUBMIT PHASE II PROPOSALS**

Brookhaven National Laboratory	The Mount Sinai Medical School	Stanford University School of Medicine
University of Arkansas for Medical Sciences	University of Minnesota	University of Pennsylvania Health System
University of Texas System		University of Washington

4.0 KEY PERSONNEL

The senior Institute management team (Bobby R. Alford, M.D., Chairman of the Board and Chief Executive Officer, Laurence R. Young, Sc.D., Director, and Ronald J. White, Ph.D., Associate Director) has not changed since the beginnings of the Institute. During FY 99, all eight team leaders have continued to function as the research "program directors." Frank Booth, from the University of Texas Health Science Center at Houston, was appointed co-leader of the Muscle Alterations and Atrophy Team. He served in this position until his departure for the University of Missouri at the end of the year, and has been replaced as co-leader by Susan Hamilton of Baylor College of Medicine.

Two principal investigators were changed during FY 99. On the Radiation Effects Team, David Huso, Ph.D. replaced S. P. Howard, M.D. who moved to the University of Wisconsin and could not continue to lead the project entitled "Chemoprevention of Radiation-Induced Rat Mammary Neoplasms." Dr. Howard will continue as a co-investigator on the team. C. Ramsdell, Ph.D. replaced T. Mullen, M.D. as the principal investigator for the project "Visual- and Vestibular-Autonomic Influence on Short-term Cardiovascular Regulatory Mechanisms." Dr. Mullen assumed other duties that did not permit him to continue with this study.

One principal investigator, L. W. Schultheis, changed institutions, moving from Johns Hopkins University to the Washington Hospital Center. His project, "The effects of Partial Mechanical Loading and Ibandronate on Skeletal Tissues in the Adult Rat Hindquarter Suspension Model of Microgravity," will follow him in FY 00.

5.0 MANAGEMENT PLAN

During the Institute's second full year of operation, the Management Plan described in the original proposal to NASA has continued to serve the NSBRI's needs. Figure 1, adopted from the original proposal, shows the relationships among the NSBRI's management elements. NASA has not exercised its option to involve the Institute in the management of the non-Institute NASA biomedical research program, so that component of the program is still absent from Figure 1.

Current membership of the NSBRI *Board of Directors* is shown in Table 5. This Board met in Houston twice during FY 1999 (see Table 1). After the Spring meeting, Dr. Gary Smith resigned from the Directorship of Johns Hopkins' Applied Physics Laboratory and from the NSBRI Board. He was replaced by Dr. Steven Knapp, the Provost and Vice President for Academic Affairs at Johns Hopkins. Dr. Knapp attended the Fall meeting of the Board. At each meeting, the Board discussed the NSBRI's current program, and reviewed and approved, sometimes with modification, the Institute's program plan for the next six months

Current membership of the NSBRI *External Advisory Council* is shown in Table 6. Membership in the Council was stable in FY 99; rotation will take place in FY 00. The External Advisory Council also met twice during the year (see Table 1), the Spring meeting in Baltimore at the Applied Physics Laboratory and the Fall meeting in Houston. At each of the meetings, the status of the entire research program and the Institute outreach program was presented and discussed. In-depth presentations and corresponding discussions were initiated in February (Technology Development Team) and continued in September 1999 (Immunology, Infection and Hematology Team).

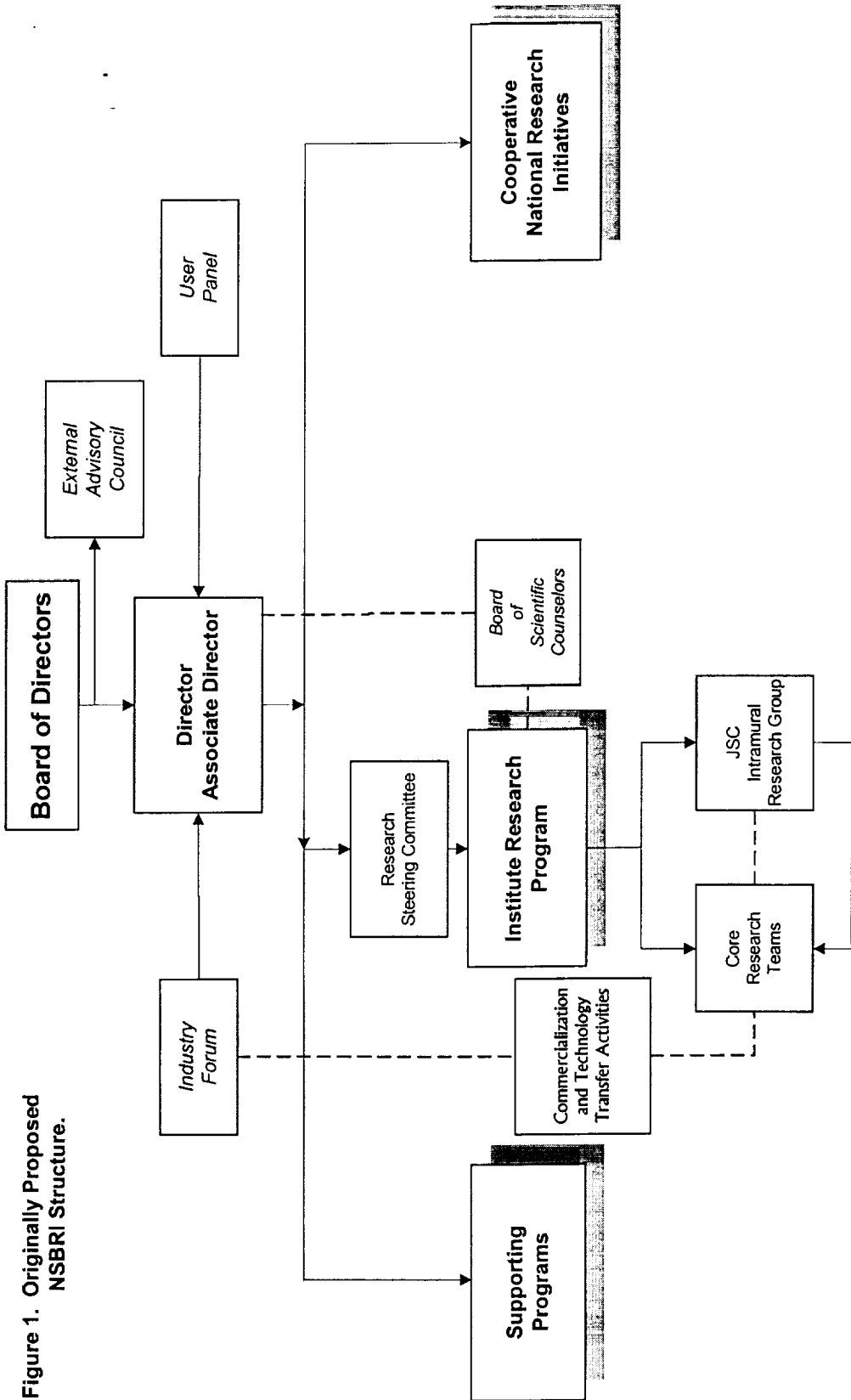


Figure 1. Originally Proposed NSBRI Structure.

Table 5. National Space Biomedical Research Institute **BOARD OF DIRECTORS.**

<p>Bobby R. Alford, M.D. (Chairman) Executive Vice President and Dean of Medicine Baylor College of Medicine</p>	<p>William L. Allen Editor National Geographic Magazine</p>	<p>Joseph V. Bonventre, M.D., Ph.D. Co-Director, Harvard-MIT Division of Health Sciences & Technology Harvard Medical School</p>
<p>James F. Buchli Space Station Program Manager United Space Alliance</p>	<p>Aaron Cohen Zachry Professor of Mechanical Engineering Texas A&M University</p>	<p>Bernard Cohen, M.D. (<i>ex officio</i>) Professor of Neurology Mount Sinai School of Medicine</p>
<p>Michael DeBakey, M.D. Chancellor Emeritus Baylor College of Medicine</p>	<p>E. Nigel Harris, M.D. Dean and Senior Vice President for Academic Affairs Morehouse School of Medicine</p>	<p>Richard J. Johns, M.D. Distinguished Service Professor of Biomedical Engineering Johns Hopkins University School of Medicine</p>
<p>Dennis Kasper, M.D. Executive Dean of Academic Programs Harvard Medical School</p>	<p>Robert A. Kennedy, Ph.D. Vice President for Research and Associate Provost for Graduate Studies Texas A&M University</p>	<p>Joseph P. Kerwin, M.D. Senior Vice President Wyle Laboratories</p>
<p>Steven Knapp, Ph.D. Provost and Vice President for Academic Affairs Johns Hopkins University</p>	<p>Jordan Konisky, Ph.D. Vice Provost for Research & Graduate Studies Rice University</p>	<p>J. David Litster, Ph.D. Vice President for Research & Dean of Graduate Education MIT</p>
<p>Larry McIntire, Ph.D. E.D. Butcher Professor of Chemical Engineering Rice University</p>	<p>Francis D. Moore, M.D. Moseley Professor of Surgery, Emeritus Harvard Medical School</p>	<p>James W. Patrick, Ph.D. Vice President and Dean of Research Baylor College of Medicine</p>
<p>Walter Sullivan, Ph.D. Vice President of Operations and Planning Morehouse School of Medicine</p>	<p>W. Dalton Tomlin (Secretary/Treasurer) Senior Vice President & General Counsel Baylor College of Medicine</p>	<p>Arnold N. Weinberg, M.D. Medical Director MIT</p>
<p>Torsten N. Wiesel, M.D. President Emeritus Rockefeller University</p>		<p>Laurence R. Young, Sc.D. (<i>ex officio</i>) Institute Director</p>

Table 6. National Space Biomedical Research Institute *EXTERNAL ADVISORY COUNCIL*.

<p>Bernard Cohen, M.D. (Chairman) Professor of Neurology Mount Sinai School of Medicine</p>	<p>Martin J. Fettman, D.V.M., Ph.D. Professor of Pathology Colorado State University</p>	<p>Antonio Gotto, M.D. Provost for Medical Affairs and Dean Weill Medical College of Cornell University</p>
<p>Michael N. Gould, Ph.D. Professor of Human Oncology University of Wisconsin</p>	<p>Michael F. Holick, M.D., Ph.D. Professor of Medicine, Physiology & Dermatology Boston University Medical Center</p>	<p>Ann R. Kennedy, D.Sc. Professor of Research Oncology University of Pennsylvania School of Medicine</p>
<p>Martin J. Kushmerick, M.D., Ph.D. Professor of Radiology University of Washington Medical Center</p>	<p>Donald J. Marsh, M.D. Dean of Medicine and Biological Sciences Brown University School of Medicine</p>	<p>Robert Y. Moore, M.D., Ph.D. Professor and Chairman of Neurology University of Pittsburgh</p>
<p>Danny A. Riley, Ph.D. Professor of Cell Biology and Anatomy Medical College of Wisconsin</p>	<p>Richard M. Satava, M.D. Professor of Surgery Yale University School of Medicine</p>	<p>M. Rhea Seddon, M.D. Assistant Chief Medical Officer Vanderbilt University Medical Center</p>
<p>Warren K. Sinclair, Ph.D. President Emeritus National Council on Radiation Protection & Measurement</p>	<p>Ronald J. White, Ph.D. (<i>ex officio</i>) Institute Associate Director</p>	<p>Victor J. Wilson, Ph.D. Professor of Neurophysiology Rockefeller University</p>
<p>Thomas J. Wronski, Ph.D. Professor of Physiological Sciences University of Florida</p>	<p>Bill J. Yates, Ph.D. Assistant Professor of Otolaryngology and Neuroscience University of Pittsburgh</p>	<p>Laurence R. Young, Sc.D. (<i>ex officio</i>) Institute Director</p>

Membership in the NSBRI *Board of Scientific Counselors (BSC)* is shown in Table 7. During FY 99, this Board began to function as a standing peer panel or study section for the NSBRI's intramural core research program. One new member was added to the Board, Joseph P. Allen, President of the National Technology Transfer Center in Wheeling, WV. Mr. Allen strengthened the Board's ability to review technological projects. This year, there were no new proposals for the Board to review, but they provided the investigators and team leaders with an annual assess-

ment of the quality of the ongoing program. Written progress reports were prepared for their review and they met in Washington, DC in June to discuss the individual projects and the research programs. Once again, they provided the NSBRI with a written critique of progress.

Table 7. National Space Biomedical Research Institute **BOARD OF SCIENTIFIC COUNSELORS.**

Hal E. Broxmeyer, Ph.D. (Chairman) Indiana University School of Medicine	H. Elliott Albers, Ph.D. Georgia State University	Joseph P. Allen National Technology Transfer Center
David J. Anderson, Ph.D. University of Michigan	James B. Bassingthwaite, Ph.D. University of Washington	Mary A. Carskadon, Ph.D. Emma P. Bradley Hospital East Providence, RI
Arthur A. Ciarkowski Food and Drug Administration	Priscilla M. Clarkson, Ph.D. School of Public Health and Health Sciences Amherst	Paul M. DeLuca, Jr., Ph.D. University of Wisconsin Madison
Paul A. DiZio, Ph.D. Brandeis University	William J. Evans, Ph.D., F.A.C.S.M. University of Arkansas for Medical Sciences	R. J. Michael Fry, M.D. Oak Ridge National Laboratory
Benjamin D. Levine, M.D. Presbyterian Hospital of Dallas	Peter Lipsky, M.D. University of Texas Southwestern Medical Center	Robert Marcus, M.D. Veterans Affairs Medical Center Palo Alto
	Connie Weaver, Ph.D. Purdue University	

Finally, membership in the NSBRI *User Panel* is shown in Table 8. The User Panel did not meet during FY 99 because no specific countermeasures have yet reached the stage that User Panel review is appropriate.

During the second year of operation of the Institute, Institute personnel continued to work in partnership with the biomedical research personnel at the Johnson Space Center on the **Critical Path Roadmap Project**. In particular, we revised the critical questions to be more fully consistent with the 1998 report of the National Research Council's Committee on Space Biology and Medicine (CSBM) entitled "A Strategy for Research in Space Biology and Medicine in the New Century." We discussed this plan with the CSBM in March 1999 (see Table 1), and they

Table 8. National Space Biomedical Research Institute *USER PANEL*.

<p>David C. Hilmers, M.D. (Chairman) Astronaut STS 51-J, STS 26, STS 36, STS 42</p>	<p>Joseph P. Allen, Ph.D. Astronaut STS 5, STS 51-A</p>	<p>Ellen S. Baker, M.D., M.P.H. Astronaut STS 34, STS 50, STS 71</p>
<p>Roger D. Billica, M.D. NASA Flight Physician</p>	<p>William Carpentier, M.D. Flight Physician 1965-1972</p>	<p>Laurel B. Clark, M.D. NASA Mission Specialist</p>
<p>John M. Fabian, Ph.D. Astronaut STS 7, STS 51-G</p>	<p>Owen K. Garriott, Ph.D. Astronaut Skylab 3, STS 9</p>	<p>Robert L. Gibson Astronaut STS 41-B, STS 61-C, STS 27, STS 47, STS 71</p>
<p>Joseph P. Kerwin, M.D. Astronaut Skylab 2</p>	<p>Byron K. Lichtenberg, Sc.D. Astronaut (Payload Specialist) STS 9, STS 45</p>	<p>Sam L. Pool, M.D. NASA Flight Physician</p>

enthusiastically endorsed this approach for developing a research plan based on risk.. The following short narrative best describes the critical path project and its products:

“Extended human exploration of space will require maintenance of crew health, fitness and performance throughout all phases of the mission: the long transit periods to and from the destination; working and exploring after arrival for an extended time; and returning to the Earth’s surface gravity environment with no unacceptable long term health effects. Some of the most critical risks are below:

Radiation Effects

- Damage to central nervous system
- Carcinoma due to cosmic ray particles and ionizing radiation

Muscle Alterations and Atrophy

- Loss of skeletal muscle mass, strength and/or endurance which would affect piloting, landing and egress, performance of critical and precise motor tasks

Bone Loss

- Acceleration of age-related osteoporosis
- Fracture and impaired fracture healing
- Renal stone formation

Cardiovascular Alterations

- Occurrence of serious cardiac dysrhythmias
- Impaired cardiovascular response to orthostatic stress
- Diminished cardiac function

Immunology, Infection and Hematology

- Increased risk of infections due to impaired immune response and build-up of environmental contaminants
- Increased risk of cancer (long-term) due to decreased immune system responsiveness
- Impaired wound healing and altered hemodynamics

Human Performance

- Human performance failure due to poor psychosocial adaptation leading to serious problems in interpersonal relationships and group dynamics.
- Human performance failure due to degradation in sleep and altered circadian rhythms leading to human error in critical operational activities, injury, accident or illness.

Neurovestibular Alterations

- Disturbances in vestibular sensorimotor performance which could interact with known deteriorations in muscle, bone and cardiovascular activity, leading to failures in posture, locomotion and performance of precise tasks.
- Irreversible changes in neurovestibular structure and function (permanent loss of balance)

Resolution of all of these risks will require implementation of a highly focused research and technology development program lasting a decade or more. However, successful missions can be accomplished even before all risks are ameliorated, by reducing the uncertainties associated with these risks to an acceptable level. Uncertainty is reduced by increasing our knowledge about the hazards and then developing risk mitigation approaches. A critical path roadmap has been developed to focus NASA's research and technology resources on the "deliverables" which will include knowledge about the risks and about their mitigation through understanding basic mechanisms or processes, development of methods, models, technologies, instruments, and other tools. These deliverables will permit risk assessment and quantification, countermeasures or other risk mitigations, and better diagnosis and treatment strategies. This information will then guide the allocation of resources required to accomplish these tasks."

Future growth and development of the NSBRI's programs will be strongly related to the critical path roadmap project. In particular, the Institute's research announcements will focus on an appropriate subset of the critical questions.

6.0 COMMERCIALIZATION, EDUCATION AND PUBLIC OUTREACH

During the second year of operation of the Institute, the *Industry Forum* (Table 9) increased in membership and began to contribute support directly to the NSBRI's activities. Thus, during FY 99, the original membership was expanded by the addition of Michigan Biotechnology International and the United Space Alliance, and the formal addition of Wyle Laboratories, whose Senior Vice President was an initial member of the NSBRI's Board of Directors. The purpose of the Forum remained the same: to advise the Director and the Board of Directors, to provide technological advice and support to the Institute and its investigators, and to assist in technology transfer.

The Industry Forum is just beginning to support the Institute tangibly. Veridian (along with NASA Ames Research Center) provided funds to partially sponsor a special NSBRI workshop on Biomathematical Models of Circadian Rhythmicity, Sleep Regulation and Neurobehavioral Function in Humans (see Appendix K). The workshop proceedings will be published as a special issue of the *Journal of Biological Rhythms*. Boeing has distributed NSBRI informational materials at their booth during several scientific meetings and has offered to share booth exhibit space with the NSBRI free of charge.

Table 9. Membership in the National Space Biomedical Research Institute **INDUSTRY FORUM**.

<p>Boeing Space and Communications Group</p> <p>The Charles Stark Draper Laboratory</p> <p>Information Dynamics, Inc.</p> <p>Lockheed Martin Engineering & Science Services</p> <p>Merck Research Laboratories</p> <p>Michigan Biotechnology International</p> <p>Payload Systems Inc.</p> <p>Raytheon Company</p> <p>Silicon Graphics Inc.</p> <p>Southwestern Bell</p> <p>United Space Alliance</p> <p>Veridian</p> <p>Wyle Laboratories</p>

National Space Biomedical Research Institute (NSBRI) **education and public outreach** activities directly support the Institute's mission by *ensuring open involvement in the Institute's activities by the scientific community, industry, and the public at large, and a robust exchange with NASA*. By targeting multiple and diverse populations, Institute outreach programs aim to:

- inform a large community about NSBRI activities;
- attract young people to related fields in science, engineering and medicine;
- provide opportunities for promoting excellence and innovation in America's science education system;
- promote scientific literacy among teachers, students and their families, and the general population; and
- engender public awareness and appreciation of the opportunities and benefits of space life sciences research.

This is being accomplished through an integrated array of programs that focuses on students and teachers at all levels, K–undergraduate, as well as the general public.

The educational programs created for the NSBRI respond to the needs of the full educational spectrum and focus on three primary areas: creation of supplementary educational materials for use by teachers and students in elementary and secondary schools; development of educational opportunities and courses for undergraduate students and teachers; and production of educational resources for school audiences and the general public using a variety of electronic media, such as computer-based multimedia (including the World Wide Web), radio and television.

Activities in these three areas are supported by the creation of a compendium of existing educational resources from NASA and NSBRI consortium institutions, and through the identification of relevant content areas described within the National Science Education Standards that can be taught by using space life sciences as unifying themes. Current outreach activities are being led by teams at three consortium institutions: Morehouse School of Medicine, Texas A&M University and Baylor College of Medicine. Project activities being conducted by each partner are described below.

Morehouse School of Medicine (MSM). The overall aim of MSM-National Space Biomedical Research Institute (NSBRI) Education and Outreach Program is the establishment and maintenance of partnerships to create multimedia educational materials that bring space biomedical sciences to America's schools and communicate the benefits of space exploration and NSBRI technology spin-offs to the nation's lay public.

Supplementary Educational Modules. MSM accomplished its FY 99 goal to produce two secondary case-based lessons. Case-based learning is a unique method for teaching basic concepts and principles through the study of a particular incident. The first case, *Cecilia's Story*, focuses on the vestibular system. The second case, *What's Up With José?*, focuses on sleep. The cases are designed to meet the needs of teachers and students through activities and teacher's guides to individual lessons. In addition, the Teacher's Guide includes a rationale for case-based learning, key neuroscience and space life sciences concepts, glossary and references, related websites and appendices. The lessons and activities allow students to use neuroscience and space concepts and encourage on-going reflection as the lessons and activities progress. The cases meet the National Council of Teachers of Mathematics Curriculum and Evaluation Standards.

A team comprised of educators and scientists from Harvard Graduate School of Education, Harvard Medical School and Boston public school teachers wrote the cases. Principal authors of the vestibular case are Gianluca Callini, S.M., Research Engineer, Man-Vehicle Laboratory, Massachusetts Institute of Technology, and Jeffrelyn Brown, Ed.M., Curriculum Development, Harvard Graduate School of Education. Principal authors of the sleep and circadian rhythm case are Kenneth P. Wright Jr., Ph.D., Research Fellow in Medicine, Circadian, Neuroendocrine and Sleep Disorder Section, Harvard Medical School/Brigham and Women's Hospital, and Jeffrelyn Brown, Ed.M.

The cases will be accompanied by videos created by MSM. Video treatments and scripts are being written by MSM. Filming is scheduled for fall 1999. The cases will be disseminated at professional meetings, used in scheduled teacher training activities, and will be made available to general audiences via the NSBRI website.

NASA- Neurolab Mission Spin-off. A color version of the NASA-approved Neurolab curriculum, *The Brain in Space*, was formatted and is now available on the NSBRI Website. The curriculum was adapted as a training module by the Massachusetts Partnership for Learning

Mathematics and Science program and the Atlanta Public Schools Systemic Initiative. A partnership grant has been earmarked for the production of two space-neuroscience problem-based cases with Atlanta Public School (APS) teachers.

Undergraduate Education. The goal of the MSM-NSBRI undergraduate education program is to attract young people to science and to provide training opportunities that introduce them to space biomedical research. Two projects – a college course and a summer research internship are designed to accomplish this goal.

College Course. A course entitled *The Human Body in Space*, was taught at Spelman College this semester. This was the third offering of the pilot course. Drawing from several disciplines, the course develops a framework for understanding the societal impact of man's historic journey to the moon, the unique environment of space, the biomedical challenges to be understood if humans are to effectively explore and develop space, and some of the cultural implications of long-term human space flight and habitation of the International Space Station for people on Earth. Six students took the course this semester. All lectures were filmed and are included in the MSM-NSBRI film archives.

This pilot course is the basis for designing a national curriculum on the human body in space. The curriculum will include modules and video accompaniments appropriate for students at the college level. Enrollees in this course also create a pipeline of students interested in graduate education in biomedical sciences and the MSM-NSBRI Summer Internship Program.

Summer Internship Program. The FY 99 MSM-NSBRI summer internship program enrolled four students selected from a competitive, regional applicant pool of twenty-five students. NSBRI interns are participating in a twelve-week intensive research summer program in the MSM Neuroscience Institute Summer Program and the MSM-NASA Space Medicine Life Sciences Research Center. Students are required to attend weekly guest lectures by outside speakers; undertake a well-defined research project with a scientist-mentor; and present their findings to a public audience at the end of the course. Their presentations will be filmed as archival footage for NSBRI.

The staff of the MSM-NSBRI Education and Outreach Program will provide a module on science writing and use of twenty-first century technology to communicate science. A longitudinal data base is being maintained to measure outcomes of this project.

Public Radio Series. During FY 99, MSM completed five parts of a six-part public radio documentary series on space life sciences. The series engages NSBRI and NASA scientists in discussions about human biology and behavior through space biomedical research, including the ways microgravity adversely affects the human body and how these symptoms mirror clinical problems experienced by people on Earth.

Parts one and two – *Space Aging* and *Getting Your Bearings* - aired in April 1999 to a national audience of over three million. Parts three, four, and five, *The Human Clock*, *The Enigma Force and Telemedicine: Part One*, aired May 28, 1999, June 4, 1999, and June 25, 1999 respectively. The entire series will be aired as part of a national radio series, *Exploring Space Science*, dedicated to understanding how space research has forever changed the ways we look at health, our environment, our understanding of planet Earth, and the universe that lies beyond it.

Promotional Video. MSM-AETC is producing a 10-15 minute promotional video intended for multiple audiences, including corporations and industry, government officials and the general public. The video's message will be to communicate NSBRI's mission, to give a brief overview of the science and to put a "human face" on the science so that lay audiences can understand the impact of this science on their daily lives. The video will contain brief explanations of the science being conducted by the eight teams; highlight the relationship between the experiments and NASA's goal of long-term space travel and will communicate the NSBRI Education and Outreach Program's vision.

NSBRI Archives. MSM established a state-of-the-art, AVID film-editing suite to support the creation of broadcast quality video products and to support the development of a comprehensive space life sciences archives. The film archives contain all footage associated with the MSM-Neurolab Education Program, including documentary footage of the Neurolab documentary; a five-day teacher-training workshop on the brain, complete text and film of the Human Body in Space course, footage of the summer interns presentations, interactive NSBRI Education and Outreach Web material, and footage from various NSBRI events including the First Annual Education and Outreach Retreat and the NSBRI Del Largo Retreat.

MSM-NSBRI Education and Outreach Program has augmented its compendium of educational resources from NASA and NSBRI consortium institutions to take advantage of existing curricular material in creating NSBRI products. The compendium was made web-ready during FY 99.

Web Page. NSBRI Education and Outreach Program completed a comprehensive web presentation of its programs and activities in FY 99. The MSM-NSBRI Web is linked to the NSBRI Headquarters web, to other related sites and has audio capability for accessing the NSBRI-SOUNDPRINT public radio series. Biographical sketches on all MSM-NSBRI Education and Outreach Program staff are being constructed for the Web.

New Partnerships. A new partnership, DTV Partnerships for Education, was created in 1999. Preliminary research and design has begun for production of two modules – Space and Time and Our Living Environments: Discovering Earth and Space. This partnership includes Georgia State University, IBM- Reinventing Education, the American Telephone and Telegraph (AT&T) the Atlanta Systemic Initiative and MSM:NSBRI Education and Outreach Program.

Texas A&M University (TAMU). TAMU's scope of work for this period involved two program thrusts: the teacher academy and the electronic resources – website development. Robert James directed the teacher academy program and George Jessup directed the electronic resources – website development effort. Jon Denton provided overall program management. The following activities were conducted within the stated time frames.

Teacher Academy. The goal of this project is to prepare in-service and pre-service teachers to lead their peers in implementing learning activities in K-12 science classrooms through electronic curricular resources, such that students (and hence citizens of the next century) will be able to gain an understanding of the medical and policy issues associated with sustained space flight to Mars. During FY 99, the Fellows that took part in the FY 98 Teacher Academy gave presentations in nine states to a collective audience of over 800 educators. In addition, TAMU project staff presented demonstrations of the electronic resources available at the NSBRI website to over 200 teachers.

Electronic Resources – Website Development. The goal of this project is to prepare electronic curricular materials for K-12 science classrooms such that students (and hence citizens of the next century) will be able to gain an understanding of the medical and policy issues associated with sustained space flight to Mars.

During FY 98, an electronic version of the high school text supplement, *Human Physiology in Space* by B. F. Lujan and R. J. White, was made available to the teacher community and in January 1999, a brochure was released that contains a description of the NSBRI and the electronic version of the supplementary text. Over 58,000 “hits” occurred on the text over the next four months.

During FY 99, electronic profiles of 26 NSBRI research scientists have been developed and added to the NSBRI website. Accomplishing this task required interviews and video recording of the scientists and their laboratory environment, transforming the video images from the video tapes to digital format for editing, editing and adding textual titles and then converting the data for RealVideo delivery over the web.

Baylor College of Medicine (BCM). Within the comprehensive NSBRI Education and Public Outreach Program, the BCM component has the following objectives: (a) foster the acquisition of inquiry skills and science content knowledge— particularly in the areas of physical, earth/space and life science related to the research areas of the NSBRI—by elementary and secondary school teachers and students; (b) generate public awareness and enthusiasm for space; and (c) generate public awareness and enthusiasm for space biomedical research, and promote understanding of the relevance of NSBRI research to the treatment of patients suffering from diverse ailments on Earth. These objectives are being fulfilled through the following activities:

1. Identify and elaborate relevant content areas described within the National Science Education Standards that can be taught by using space life sciences topics as unifying themes (completed FY 98).
2. Partner scientists and educators in the design, production, evaluation and dissemination of age-appropriate, supplemental curriculum modules based on space biomedical themes for students and teachers in grades K-8 (ongoing).

In addition, during FY 99, the following additional activities were added:

1. Update the traveling NSBRI exhibit for use at conventions.
2. Complete the production and printing of a new series of 12 color tri-fold brochures about the NSBRI and the individual research team activities.
3. Create, produce and disseminate an activity-based educational poster for K-6 students, teachers and parents, to be distributed free-of-charge to approximately 8,400 elementary and middle schools (representing 4,900,000 students) in home states of consortium institutions.

FY 99 activities are providing a framework for achieving overall education and public outreach goals, as well as generating products that are, or will be, available nationally.

Production, evaluation, and dissemination of supplementary educational modules. Drawing upon BCM’s experience in producing educational units that address issues not found in other science and health education series and texts, age appropriate, supplemental curriculum modules based on space biomedical themes are being produced. Considerable effort was made during FY 99 to refine the design, approach and science content that would be contained within the teacher guides to insure that the final products would be useful to teachers, and interesting and pertinent for stu-

dents. This involved conducting a second field test of the *Sleep and Daily Rhythms Activities Guide for Teachers*, revising and reformatting all of the student pages in the same Guide, and completely rewriting four of the seven activities.

Workshops for Educators. BCM outreach personnel provided workshops and presentations on Sleep and Circadian Rhythms for more than 130 teachers and other educators as listed below:

- Moreno, N. and B. Tharp. 1998, *Sleep and Daily Rhythms*. Council for the Advancement of Science Teaching Annual Meeting, Corpus Christi, TX, November 20.
- James, R., R. White, V. Heilman, D. Jensen, M. MacLeish, and N. Moreno, 1999. Preparing Science Teachers and Other Citizens for the Trip to Mars: NSBRI. Panel presentation at Association for the Education of Teachers in Science Annual International Meeting, Austin, Texas, January 16.
- Moreno, N. and B. Tharp, 1999, *Sleep and Daily Cycles*. Presentation at the National Science Teachers Association Annual Meeting, Boston, Massachusetts, March 26.
- Tharp, B. and N. Moreno, 1999, *Tackling the Tough-to-Teach Topics: Daily Cycles on Earth*. Workshop for Houston teachers sponsored by Exxon Chemical. Two sessions: January 19 & 21.

Radio HealthLine Series. HealthLine stories on NSBRI-related topics are being produced and disseminated bimonthly. The news format stories are distributed free-of-charge to over 2,800 stations and are made available in both English and Spanish. The stories also are available through BCM's Web homepage and at <http://www.bcm.tmc.edu/pa/radh/radh1.html>. Stories corresponding to FY 99 are listed in Table 10.

Table 10. FY 99 Radio HealthLine Stories		
Date	Title	Guest Speaker
October 1998	<i>Muscle Matters</i>	Robert Schwartz, Ph.D.
December 1998	<i>A Bone to Pick</i>	Bert O'Malley, M.D.
February 1999	<i>Space and the Immune System</i>	William Schearer, M.D., Ph.D.
April 1999	<i>Space Virus</i>	Janet Butel, Ph.D.
June 1999	<i>Balancing Act</i>	Helen Cohen, M.D.
August 1999	<i>Cardiac Atrophy</i>	Michael Schneider, M.D.

Support Activities for Public Outreach. BCM's outreach team has provided support for a number of activities designed to generate public awareness and support of NSBRI activities. Each of these activities is outlined briefly below.

- *Updating of traveling NSBRI exhibit for use at conventions.* During fall 1997, a "pop-up" exhibit describing the mission and research objectives of NSBRI was created by BCM's outreach team. The exhibit was updated with two new panels for use in November 1998.

- *Design and production of a new series of informational brochures about the NSBRI and individual research team activities.* During FY 98 and 99, a new series of twelve full-color pocket-size tri-fold brochures, aimed at the general public, was created to be used with the traveling exhibit described. A graphics icon and unique graphics design was created to identify each research area. In addition, a unified theme, featuring an artist's rendition of the Martian surface, was created and used for both the exhibit and brochures. These designs also are being incorporated into educational materials being created by BCM's outreach team.
- *Production and dissemination of activity-based educational poster for K-6 students, teachers and parents.* During spring 1999, an activity poster containing basic information about NSBRI research, as well as activities for students was created and printed (100,000 copies). Packets containing four copies of the poster and an introductory letter were sent to 8,702 elementary and middle schools (representing 4,900,000 students) in home states of consortium institutions (Georgia, Massachusetts, Maryland and Texas). The poster is based on an original water color painting of an astronaut, created for this project by nationally recognized artist and cartoonist, T. Lewis. Approximately 500 copies of the poster were sent to each research team leader for use in outreach to schools and communities. Posters are available free-of-charge through BCM's Center for Educational Outreach.

7.0 INSTITUTE DIVERSITY AND SCIENTIFIC COMMUNITY OUTREACH

The NSBRI's research program for FY 99 consists of 41 research projects focussed on eight research areas and on synergistic activities relating two or more areas, just as it did during FY 98. The total number of different principal and co-investigators involved in NSBRI research is 130 from 27 different institutions. Appendix A provides a list of investigators and their institutions. Note that Rice University, a member of the NSBRI consortium, does not currently participate in the research program, but it does play a major role in the Institute's data archiving project.

Thus, in year two, as in year one, the Institute's activities include a broad, diverse base of researchers from within and outside of the consortium. In FY 99, the Institute reached out to an even broader community by informing scientists in many disciplines of the NSBRI's research activities and programs (see Appendix G for a partial list of presentations made by NSBRI scientists). Initial funding of the Institute's joint program with the NIDCD (see Appendix C) added six new principal investigators, seven co-investigators and five new institutions to the Institute family. Workshops (see Table 1 and Appendices J, L, M and N) brought a significant number of outside scientists into contact with the Institute. Presentations by NSBRI at various advisory committee meetings provided yet another means of reaching out to the scientific community in the United States. Signing international agreements with the Italians and French, and discussing the NSBRI at international meetings enlarged the community's awareness of the NSBRI and its mission.

During the summer of 1999, the Institute developed a small, model **summer intern program** to determine the feasibility of bringing undergraduate and medical school students to Houston to participate in research projects at Johnson Space Center. The program involved four students (from Vanderbilt University, Kansas State University Medical School, the University of Pennsylvania, and the Johns Hopkins School of Medicine) working in four JSC laboratories (Balance Control, Cardiovascular Physiology, Nutrition, and Bone and Muscle). The program was clearly a success. All involved were enthusiastic about the multiple contributions that such a program

could make to training and scientific community outreach. A formal, nationally competitive summer intern program will be developed as part of the future growth of the Institute.

At the end of FY 99, the Institute began a joint project with the Harvard-MIT Division of Health Sciences and Technology to develop a new, graduate-level course in the space life sciences. This course will be part of a new graduate program under development by the Institute.

8.0 SPECIAL PROJECTS

During the second year of Institute operation, NASA and the NSBRI continued to make use of the *Cooperative Agreement Management Plan* provision to undertake special projects outside of the core funding envelope of the NSBRI. Seven new projects were initiated in FY 99, two previously defined projects were continued, and one previous project was completed. Project 97-2, *Transition Plan: Universities Space Research Association (USRA) Visiting Scientist Personnel*, described in last years annual report, was completed in October 1998 with the appointment of Philip Foster, M.D. as an Assistant Professor in the Department of Medicine at Baylor College of Medicine.

Project 97-3, *National Space Biomedical Research Institute Visiting Scientist/Research Associate Program*, continued to enable young and established university-based researchers an opportunity to work side-by-side with government employees in JSC laboratories. Table 11 provides a list of the participants in this program; all faculty positions are held at Baylor College of Medicine.

Project 98-1, another ongoing, long-term project, the *NSBRI Data Archive System*, was initiated in April 1998. The project is led by Lora Suther of The Johns Hopkins University Applied Physics Laboratory (APL). Team members include Jennifer Drummond and Ross Reedstrom of Rice University and Bruce Hamill and Helene Winters of APL. This project was established with the goal of maintaining an appropriate, accessible archive of the data collected through the NSBRI research projects. Data collected by these funded research projects requires efficient processes to properly catalogue, archive, and provide retrieval access. The project team is responsible for:

- Identifying the Institute data archiving needs and requirements;
- Carrying out a functional analysis of those requirements;
- Determining an architecture and design for the Institute archive that is compatible with the Life Sciences Data Archive (LSDA) at the Johnson Space Center;
- Establishing and maintaining the Institute data archive;
- Identifying the operating procedures;
- Identifying data rights and release procedures;
- Specifying the management and development process for Institute data archives;
- Implementing the IDAS archive architecture and system.

These responsibilities are being fulfilled by developing the following products: a data management plan, the data archive architecture, data characterization, an appropriate user interface, and an electronic proposal submission system designed to capture the data relative to experiment plans at an early stage.

The Data Management Plan is a document that defines the NSBRI data archive system, structure, and policies. It is intended to inform the community of what types of products are available and how access is provided. This plan is currently in draft form, and has been sent to the NSBRI research team leaders for their review.

Table 11. Participants in the Visiting Scientist/Research Associate Program for FY 99.

Name	Current Position	JSC Sponsor	Starting Date
Johnny Conkin, Ph.D.	Assistant Professor	John Stanford	6/1/98
Dominick D'Aunno, M.D.	Assistant Professor	Jan Yelle	11/1/97
Philip Foster, M.D.	Assistant Professor	John Stanford	10/19/98
Brian Hashemi, Ph.D.	Research Associate	Clarence Sams	11/24/97
Victor Hurst, Ph.D.	Research Associate	Jan Yelle	8/23/99
Chantal Rivera, Ph.D.	Research Associate	Lakshmi Putcha	5/6/99
Yael Vodovotz, Ph.D.	Assistant Professor	Jim Lewis (see Project 99-7)	8/31/99
Wendy Waters, Ph.D.	Assistant Professor	Jan Yelle	11/24/97
JoAnna Wood, Ph.D.	Assistant Professor	Deborah Harm	10/1/98
Scott Wood	Research Associate	William Paloski & Todd Schlegel	9/14/98

The computer systems, software, and data base schema that define how data are stored and retrieved are the Data Archive Architecture. Computer systems to support the data archive are currently installed and operational at the NSBRI offices at Baylor College of Medicine. Software packages have been selected to implement the required functions. The initial data base design has been defined and implemented. Basic information, relating to projects and teams, has been delivered to the LSDA for incorporation into their data base.

Data Characterization is a process used by the project team to determine the metadata that are pertinent to the data collected by a research project. The metadata are used within the catalog to provide common search parameters across NSBRI projects. The metadata are further defined as Phase 1 metadata, relating to basic information about a project, and Phase 2 metadata that defines the type of data accumulated by a research project. Most of the Phase 1 metadata for all current NSBRI projects have been entered into the Institute's data base and delivered to LSDA. Phase 2 metadata have been defined for five research projects selected from three research teams.

A User Interface is being developed to provide restricted access to the NSBRI data archive. It is compatible with the LSDA interface, with similar features. Currently, the main page and the pages to access the catalog of metadata are implemented. An overview is available with information on the research teams. A full text search capability has been implemented to search the online descriptions.

An Electronic Proposal Submission System is being developed that will streamline the proposal submission process. In addition, it will facilitate early on-line determination and collection of metadata that are available at proposal time. This proposal system will be tightly integrated with the Institute data archive system, using a common data base. After evaluation of existing electronic proposal systems, the project team has generated and reviewed the requirements, design, and test plan for this system.

In addition to the development of the above products, two members of the project team attended the IEEE Metadata'99 conference held in Bethesda, MD at the campus of the National Institutes of Health. This meeting focuses on the problems of describing data base contents, or metadata. One focus is standards that allow interoperation and widespread access to archival data bases. The project team presented a poster, entitled "The NSBRI Data Archive: Promises and Challenges." This poster described how the Institute data archive system can be structured to ease future interactions with both the LSDA and other data archiving efforts in the larger scientific community.

Project 99-1, *Humans in Space - Information Management System*, is a project enabling the NSBRI to assist NASA in the development of a strong plan to manage health-related information at JSC. This project entails carrying out an independent review of NASA's current plans to manage medical records, space data resulting from medical monitoring, experimental data from flight investigations, data from longitudinal studies of the astronauts, and data available from and provided by international partners. This project was completed; the report is provided in Appendix L.

Project 99-2, *In Situ, Real Time Analyses of Urinary Constituents in the ISS Measuring System*, is a collaborative, co-funded project between NASA-JSC and the Johns Hopkins Applied Physics Laboratory focused on developing instrumentation for the inflight monitoring of urine constituents. Urine sampling with accurate measurement of void volumes has been a key requirement for many Space Shuttle (SLS-1, SLS-2, LMS, Neurolab, STS-95) and Phase I NASA/Mir missions. NASA has built and flown a urine measuring system (UMS) designed to provide accurate and reproducible urine void volumes and the acquisition of urine samples for post-flight analyses. Samples collected by the UMS were frozen, stored at -20° C, and returned to Earth for biochemical assay. The Shuttle UMS required that the entire unit be returned to Earth and disassembled in order to retrieve the urine volume data. Currently, NASA is redesigning the Shuttle UMS for ISS with the goal of increasing the fidelity (accuracy and precision) of urine volume measurements. However, without real-time, inflight urine analytical capabilities on ISS, there will be delays of months for analyses, a requirement for significant long-term frozen sample stowage, and the inability to use urine analytical data as a basis for inflight medical interventions to assure continued crew health or to monitor countermeasures designed to attenuate the untoward medical consequences long-term exposure of humans to microgravity. A solution to this problem is to provide the ISS with the capability to perform real-time urine volume determinations and measurements of urine constituents from each urine void in a system that is nearly transparent to ISS crew members. Within this project, the Applied Physics Laboratory will be responsible for design and fabrication of a prototype urine analysis system that can interface directly with the NASA UMS and provide the real-time measurement of calcium (Ca^{2+} in mg/dl), lithium (Li^+ in mg/dl), and creatinine (in mg/dl) among other analytes. NASA-JSC, in turn, will be responsible for comparison of analytical results from this prototype system with those from the existing ground based biochemical assay methods.

- Development of a concept for a "Space Biomedical Research and Data Center" located at or near the Johnson Space Center; and
 - Expansion of the NSBRI education and outreach program, consistent with the projected growth of the Institute.
3. Restructuring of the Joint NASA/NSBRI Discipline Teams
 - Identify and initiate new teams (e.g., psychosocial health); and
 - Plan for NSBRI to assume leadership role in joint teams, where appropriate.
 4. Other Expansion of the NSBRI
 - Consortium and institutional membership growth;
 - Development of graduate and postdoctoral training programs utilizing the resources at the "Space Biomedical Research and Data Center;" and
 - Growth of the NSBRI core research program, leading to an expansion of the number of tasks per research area.

Although it was intended to complete these initial plans in FY 99, it soon became clear that these plans for the NSBRI were strongly connected with a reorganization of activities at NASA and that the two plans (NSBRI and NASA) should evolve together. Thus, the Institute submitted a partial plan in FY 99 (see Appendix O) and deferred completion of the plan until NASA had made more progress on its own internal plans.

Project 99-6, *Collaboration with Russia's Institute for Biomedical Problems (IBMP)*, is a special project to enable the NSBRI to develop collaborative activities with Russia's Institute for Biomedical Problems (IBMP) allowing the NSBRI investigators and the U.S. scientific community to benefit from the knowledge, expertise, and related facilities accumulated during Russia's extensive human space flight program. This project involves two activities, to be initiated in FY 99 and continued through FY 00. The first is a collaborative research project with the IBMP and the second is a special scientific review workshop relating directly to the Russian experience with countermeasures. The research project involves using two research protocols that complement and augment the current projects of the Immunology, Infection and Hematology Team. Both research projects would be accomplished within the Russian Simulation of Flight of International Crew on Space Station (SFINCSS) program, a research program focussed on a long-term chamber study in Moscow. The scientific review workshop will involve six IBMP experts who will present all of the Russian data available to them, review the Russian experience with countermeasure development, including their experience related to countermeasure candidates that have not been adopted, and provide a written review document that presents the Russian data in English text. The areas covered will include the neurosensory system, the cardiovascular system, muscles, bones, metabolism, and psycho-emotional factors. The week-long course will be video taped and made available to reserachers.

Project 99-7, *Food Scientist, Food Laboratory*, is a project designed to enable the NSBRI and NASA JSC to develop joint, applied activities related to space flight food development, menu definition, nutritional requirements implementation, and packaging development for all U.S. space flight crews and missions. By acquiring a capability in these space flight related areas, the NSBRI will gain expertise in and develop a more thorough understanding of the food science, nutritional requirements, and research and development areas that are a subset of biomedical performance, and thereby enhance its ability to develop more effective countermeasures. To fulfill the initial requirements of this project, the NSBRI hired Yael Vodovotz, Ph.D. (see Table 11). This is a long-term project.

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

Principal and Co-Investigator List FY 1999

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University of Houston: Fox, G. E., and Willson, R. C.

University of Maryland: O'Malley, B. W. Jr.

University of Pennsylvania: Dinges, D. F., Maislin, G., and Van Dongen, H. P.

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University of Texas M. D. Anderson Cancer Center: Reuben, J. M.

University of Washington: Ochs, H. D.

University of Wisconsin: Howard, S. P.

Wright State University: Shebilske, W. L.

York University: Howard, I. P.

**NATIONAL
SPACE BIOMEDICAL
RESEARCH INSTITUTE**

***CORE RESEARCH PROGRAM
YEARS 1 AND 2***

**October 1, 1997 – September 30, 1999
Updated July 31, 1999**

**National Space Biomedical Research Institute
Core Research Program – Years 1 and 2
October 1, 1997 – September 30, 1999
Updated July 31, 1999**

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**NSBRI RESEARCH PROGRAM
BONE LOSS**

Team Leader:	Shapiro, J. R.	Uniformed Services University of the Health Sciences (USUHS)/ Walter Reed Army Medical Center	
O'Malley, B. W.	PI Baylor	Novel Receptor-Based Countermeasures to Microgravity- Induced Bone Loss	B-7
Brown, E. M.	CO-I Harvard		
Smith, C. L.	CO-I Baylor		
Weigel, N. L.	CO-I Baylor		
Bloomfield, S. A.	PI Texas A&M	Bone Blood Flow During Simulated Microgravity: Physiological and Molecular Mechanisms	B-8
Delp, M. D.	CO-I Texas A&M		
Hogan, H.A.	CO-I Texas A&M		
Suva, L. J.	CO-I SmithKline Beecham		
Turner, R. T.	CO-I Mayo Clinic		
Schultheis, L. W.	PI Hopkins/SOM	The Effects of Partial Mechanical Loading and Ibandronate on Skeletal Tissues in the Adult Rat Hindquarter Suspension Model of Microgravity	B-10
Bloomfield, S. A.	CO-I Texas A&M		
Fedarko, N. S.	CO-I Hopkins/SOM		
Shapiro, J. R.	CO-I USUHS		
Thierry-Palmer, M.	CO-I Morehouse		
Ruff, C. B.	PI Hopkins/SOM	Skeletal Structural Consequences of Reduced Gravity Environments	B-12
Beck, T. J.	CO-I Hopkins/SOM		
Newman, D. J.	CO-I MIT		
Oden, Z. M.	CO-I Harvard		

BONE LOSS TEAM PROGRAM EXECUTIVE SUMMARY

Bone loss represents a critical problem for humans as they anticipate prolonged exposure to microgravity in the ongoing effort to expand the exploration of space. Consequences of bone loss are an increased risk of fracture and the development of renal calculi. Also of importance are associated soft injuries including those to intervertebral disc, joint cartilage and ligaments as may occur during extended spaceflight with habitation on another planet. The longer the exposure to microgravity, the greater the risk of damage to supporting skeletal and connective tissues with its attendant catastrophic effects on individual and crew performance.

The primary objective of the Bone Loss Team is the maintenance of normal bone mass during extended exposure to microgravity. These investigations focus on: a) assessment of amounts and patterns of bone loss (Dr. Ruff); b) the role of different receptor agonists in maintaining bone formation during microgravity (Dr. O'Malley); c) the response of bone to alterations in bone blood flow (Dr. Bloomfield); d) and the effects of altered mechanical loading and the administration of bisphosphonate in promoting the maintenance of bone mass during spaceflight-related microgravity (Dr. Schultheis). In terms of the development of specific countermeasures these projects will: a) provide structurally meaningful data on bone loss to facilitate more precise estimates of fracture risk, b) enable the design of effective receptor agonists that decrease bone resorption and enhance bone formation, c) define of the role of altered blood flow in promoting bone loss and definition of the vasoactive agent best suited to lessen this risk factor, d) quantitate the amount of mechanical loading required to maintain normal bone remodeling under reduced gravity conditions and the pharmacological agent best suited to increase the effect of added mechanical strain on bone.

A comprehensive review of existing data on amounts and patterns of flight-related bone loss, representing information derived from Skylab, Shuttle flights and Mir indicates marked variability in individual rates of loss as well as site-specific differences in the amounts of loss. There is little data available on occurrences of fracture, particularly stress-related fractures, during or after space flight. Dr. Ruff and Beck study 2-D structural patterns of bone loss by radiographic methods, based on DEXA (dual energy x-ray absorptiometry) scans using the femur shaft obtained from Mir cosmonauts and astronauts, as well as from individuals undergoing 17 week bedrest studies at Baylor College of Medicine. This includes 3-D finite element analysis to validate 2-D curved beam analytic methods and to construct models of fracture risk.

Structural analysis discloses differences between patterns of loss during bed rest and after spaceflight. Complete bed rest subjects experiencing bone loss showed a slight but significant increase in femoral neck periosteal diameter, an unexpected result but one similar to normal aging. The results of hip scans from 19 Mir cosmonauts indicate post flight loss of radiographic indices of bone strength as great as 58% during 6 month flight. No periosteal expansion was found, consistent with animal studies showing a cessation of periosteal bone formation during flight. In contrast to earlier data indicating slow return to baseline of bone mineral density following return to earth, section moduli suggest return to within 5-7% of base line strength within one year after flight. However, uncertainty exists because of the sometimes poor quality of conventional DEXA images from which estimates of bone strength are obtained. Nevertheless, analysis of data derived from both cosmonauts and bed rest subjects indicates that strength loss due to flight differs from that attributed to the normal aging process.

Dr. Ruff has conducted quantitative computer tomographic bone density measurements (pQCT) on the hindquarter suspended rat model in collaboration with Dr. Schultheis. These measurements have provided new data on the relationship of graded mechanical loading, initially at the 50% level, to bone density. Tail suspension has a negative effect on bone structural properties. Tail suspension appears to induce loss of both trabecular and cortical bone, more so in the trabecular compartment. Both the unweighted femur and the partially weighted forelimb are affected. pQCT measurements have demonstrated the protective effect of ibandronate on bone mass in the suspended animal. 3-D finite element analysis (Dr. Newman) applied to modeling fracture risk as might be encountered on Mars at 0.38 X g suggests that hip loading during locomotion or falls might be as great as earth-based activities due to the additional mass and inertia of the spacesuit and back pack.

Spaceflight in animals or humans has significant effects on calcitropic hormones. Hormone analyses before and after flight indicate: a 30% decrease in 25(OH) and 1,25(OH) vitamin D, decreased serum parathyroid hormone levels, decreased gastrointestinal calcium absorption and increased calcium loss in urine. Testosterone levels decrease in men. Estrogen levels may be maintained in women by the use of oral estrogen agents taken during flight. In males, the response of serum estrogen, now known to contribute to bone mass in men, is unknown. These data suggest that substantial alterations may occur in hormone receptor function during flight, and that correction of specific hormone deficiencies during flight may mitigate the profoundly negative effect of these deficiencies on bone mass. A variety of methods are used to evaluate the action of vitamin D receptor agonists (VDR), selective estrogen receptor agonists (SERMs) and agonists to the calcium sensing receptor (CaR) on osteoblastic and osteoclastic cell lineages. These methods include use of the cell bioreactor, tissue culture of osteoblastic and osteoclastic cells and their precursors and molecular biological techniques including improved methods for gene transfection and gene expression. In each case, the effects of hormonal agents on cell receptors is assessed with the objective of enhancing the function of cells to increase bone formation while diminishing the actions of cells that enhance bone resorption. Information gained about these processes will promote the development of newer and more effective agents to prevent bone loss during weightlessness. Both the separate and interactive actions of these three important bone cell receptors are under study.

The CaR has now been identified in several osteoblastic and osteoclastic models, including in osteoblastic precursor cells located in bone marrow. The presence of this receptor in bone-resorbing osteoclastic cell and/or osteoclast precursors suggests that agonists of this receptor may be employed to decrease osteoclastic function or the differentiation of osteoclast precursors thus limiting bone resorption. Additional studies involve the identification of the CaR in bone using immunocytochemical methods.

The estrogen-agonist activity of various SERMs has been assessed using transient transfection of ER to mediate the putative response to the SERM in the specific cell line MG-63. In addition, the cell line MC3T3-E1, which expresses sufficient ER levels to enable gene expression to be studied without the necessity of transfecting exogenous ER has also been examined. ER- β has been identified in these cells and the ER- α has been previously reported. Thus, these data indicate that bone cells express both ER receptors and are a suitable model for evaluation of SERMS. Idoxifene appears to be the most effective ER agonist studied to date. Studies also involve alternate pathways for SERM activity including the activation of various transcription factors.

In order to quantitate the cellular response to VDR agonists, assays for osteoblastic proteins have been established for MG 63 cells. The agonist EB1089 has been shown to be 10-100 fold more active than the native calcitriol. Rapid membrane effects of metabolites of vitamin D and calcitriol have been examined and applied to the study of VDR agonists. EB1089 is more potent in this system suggesting that it is an effective agonist for both membrane based and intracellular receptor based responses. Studies evaluating the functional relationship between the VDR and CaR are underway.

Results indicate that SERMS: 1) increase VDR expression levels in osteoblastic cells, 2) do not increase alkaline phosphatase activity, but, 3) may increase cell number in tissue culture in comparison to untreated cultures.

The STLV Bioreactor is used to study the effect of simulated microgravity on MG-63 and MC3T3-E1 cell function. Alkaline phosphatase, collagen $\alpha 1(I)$ mRNA and osteocalcin production are decreased with suspension in this system consistent with results derived from cells studied after spaceflight.

These cell based receptor agonist studies pave the way for an examination of the effects of gene-knockout on receptor action as well as opening the way for the study of receptor agonist in animals during hindquarter suspension in 5 month old rats, and eventually during spaceflight in humans. EB1089 will be the first receptor agonist studied in the rat.

Bone mineral loss during spaceflight occurs in the lumbar spine and lower extremities: the upper extremities do not lose bone mass. Decreased blood flow to the lower extremities is associated with a fall in bone mineral density. The measurement of unweighted extremity blood flow using the microsphere technique in hindlimb unloaded rats (Dr. Bloomfield) has demonstrated significant and consistent declines in blood flow to all four compartments of femoral bone and in 2 of 3 tibial bone compartments. Short duration studies after only 10 minutes of suspension also show a decline in blood flow that is maintained during 7 additional days of suspension. By contrast, the forelimb showed an increase in blood flow that was not statistically significant in a limited number of animals studied to-date. Histomorphometric analysis of bone during these short duration studies has not shown significant alteration, however, data collection is continuing to explore the relationship between blood flow and bone turnover.

Exercise has been the mainstay of efforts to prevent bone loss since the inception of the manned space program. Although various paradigms such as the Russian Exercise Program have maintained exercise tolerance, these have not been effective in preventing bone loss. In addition, and recognizing the Mir experience, we do not know how much mechanical strain (loading) will be required to maintain normal bone remodeling in the face of 6 month stays on the ISS or during the planned human flight to Mars. However, the widespread clinical use of third-generation bisphosphonates as anti-resorptive agents has suggested that these may be of value in diminishing the increased bone resorption characteristic of the human response to microgravity. L. Schultheis and co-workers have employed the adult 350 gm Sprague Dawley rat to study the effect of mechanical loading at different levels with and without administration of the bisphosphonate ibandronate on various parameters of bone. These include bone mineral density, bone histomorphometry, bone biomechanics and bone biochemistry. Animals are hindquarter suspended for 35 days in a novel servo-controlled system that permits the application of different levels of mechanical loading to the forepaws while the hindpaws are suspended and weightless. Treatment regimens include short periods of free roaming exercise for 2 hours per day, and the administration of ibandronate in different combinations. The results indicate that the high

frequency component of impact forces are potent inducers of mechanical strain on bone. Furthermore, results suggest that: 1) Mechanical unloading results in substantial bone loss in the weight-bearing humerus and unweighted femurs of 350 gm rats. 50% of normal weight bearing on the humerus decreases the amount of loss as does episodic exercise but the effect on bone mass is partial. Ibandronate added to mechanical loading significantly decreases the extent of loss. Bone strength measured as section modulus is also improved by ibandronate. Bone mass determined histomorphometrically also appears to increase after ibandronate. Biochemical analysis of bone indicates that 50% weightbearing and exercise increase bone matrix collagen. Treatment with ibandronate leads to bone collagen levels slightly higher than in free roaming controls. Furthermore, ibandronate appears to increase bone volume determined by histomorphometry.

The results of these investigations indicate that both pharmacological and mechanical means should be considered as potential countermeasures to microgravity-induced bone loss.

RESEARCH AREA:	Bone Loss
PRINCIPAL INVESTIGATOR:	Bert W. O'Malley, M.D.
ORGANIZATION:	Baylor College of Medicine
PROJECT TITLE:	Novel Receptor-Based Countermeasures to Microgravity-Induced Bone Loss
FUNDING:	\$281,000 (FY 1998); \$283,584 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The biological actions mediated by the estrogen receptor (ER), vitamin D receptor (VDR) and Ca^{2+} -sensing receptor (CaR) play key roles in the normal control of bone growth and skeletal turnover that is necessary for skeletal health. These receptors act by controlling the differentiation and/or function of osteoblasts and osteoclasts, and other cell types within the bone and bone marrow microenvironment. The appropriate use of selective ER modulators (SERMs) which target bone, vitamin D analogs that favor bone formation relative to resorption, and CaR agonists may both stimulate osteoblastogenesis and inhibit osteoclastogenesis and the function of mature osteoclasts, should make it possible to prevent the reduction in bone formation and increase in bone resorption that normally contribute to the bone loss induced by weightlessness. Indeed, there may be synergistic interactions among these receptors that enhance the actions of any one used alone. Therefore, we proposed to: 1) assess the *in vitro* ability of novel ER, VDR and CaR agonists, alone or in combination, to modulate osteoblastogenesis and mature osteoblast function under conditions of 1g and simulated microgravity; 2) assess the *in vitro* ability of novel ER, VDR and CaR agonists, alone or in combination, to modulate osteoclastogenesis and bone resorption under conditions of 1g and simulated microgravity; and 3) carry out baseline studies on the skeletal localization of the CaR in normal rat bone as well as the *in vivo* actions of our novel ER- and VDR-based therapeutics in the rat in preparation for their use, alone or in combination, in well-established ground-based models of microgravity and eventually in space flight.

RESEARCH AREA:	Bone Loss
PRINCIPAL INVESTIGATOR:	Susan A. Bloomfield, Ph.D.
ORGANIZATION:	Texas A&M University
PROJECT TITLE:	Bone Blood Flow During Simulated Microgravity: Physiological and Molecular Mechanisms
FUNDING:	\$212,000 (FY 1998); \$217,217 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Blood flow to bone has been shown to affect bone mass and presumably bone strength. Preliminary data indicate that blood flow to the rat femur decreases after 14 days of simulated microgravity, using hindlimb suspension (HLS). If adult rats subjected to HLS are given dobutamine, a synthetic catecholamine which can cause peripheral vasodilation and increased blood flow, the loss of cortical bone area usually observed is prevented. Further, mechanisms exist at the molecular level to link changes in bone blood flow to changes in bone cell activity, particularly for vasoactive agents like nitric oxide (NO). The decreases in fluid shear stress created by fluid flow associated with the shifts of plasma volume during microgravity may result in alterations in expression of vasoactive agents such as NO, producing important functional effects on bone cells. The primary aim of this project is to characterize changes in 1) bone blood flow, 2) indices of bone mass, geometry, and strength, and 3) changes in gene expression for modulators of nitric oxide activity (e.g., nitric oxide synthase) and other candidate genes involved in signal transduction of mechanical loading after 3, 7, 14, 21, and 28 days of HLS in the adult rat. Using a rat of at least 5 months of age avoids inadvertently studying effects of simulated microgravity on growing, rather than adult, bone.

Utilizing the results of these studies, we will then define how altered blood flow contributes to changes in bone with simulated microgravity by administering a vasodilatory agent (which increases blood flow to tissues) during hindlimb suspension. In all studies, responses in the unloaded hindlimb bones (tibial shaft, femoral neck) will be compared with those in the weightbearing humeral shaft and the non-weightbearing calvarium (skull) from the same animal. Bone volumetric mineral density and geometry will be quantified by peripheral quantitative CT; structural and material properties of the long bones will be determined by 3-point bending (tibia, humerus) or compression (femoral neck) testing to failure. A unique aspect of these studies will be defining the time course of changes in gene expression in bone cell populations with unloading, accomplished with Northern blots, *in situ* hybridization, and immunohistochemistry. These studies have high relevance for concurrent protocols being proposed by investigators on NSBRI Cardiovascular and Muscle teams, with blood flow data available on a number of tissues other than bone. Further, dobutamine and other β -agonists have been tested as countermeasures for altered muscle and cardiovascular function. Results of the intervention tested in our studies have potential relevance for a number of systemic changes seen with prolonged spaceflight.

Most project objectives for this stage of Year 2 (which ends September 30, 1999) have been met or exceeded. Work productivity in the PI's laboratory (Dr. Bloomfield) has been greatly enhanced by two factors: 1) the hiring of an experienced full-time lab technician, Ms. Jan Stafinsky, in August of 1998 and 2) the acquisition of a pQCT device in November, 1998, allowing a vast increase in "through-put" for determinations of bone density and geometry before bones are to be mechanically tested. A working visit to the laboratory of Dr. Tom Wronski (Univ. of Florida) in September 1998 afforded Ms. Stafinsky intensive training in embedding, sectioning and staining of undemineralized bone samples. Improvements have been made to the

microsphere counting procedure, automating the weighing of samples before counting and then the subsequent calculations of blood flow to each tissue measured. A total of 58 animal suspension experiments have been completed, 15 of which are dedicated to the blood flow determinations and the remaining 43 to the time course study documenting changes with hindlimb unloading in histomorphometric measures of bone formation, bone density and geometry, mechanical properties, and gene expression.

The most novel finding of this work is a substantial reduction in blood flow (up to 35% decline) to hindlimb bone in control rats (n=6) subjected to only 10 minutes of tail suspension. After a full week of hindlimb unloading by suspension, blood flow is halved to all portions of femoral bone (including marrow, measured separately) and to proximal and diaphyseal tibia. Although the control rat findings are not yet statistically significant, we are confident that with the completion of these studies (2-4 more experiments) the power of our statistical analyses will improve enough to render these comparisons significant. Interestingly, blood flow to the weighted humerus tended to increase (+48-99%, depending on bone site) with only 10 minutes of tail suspension in control rats (p values ranging from 0.07-0.20). However, after a full week of suspension humeral blood flow returned to control standing values, implying an adaptation to the increased hydrostatic pressure generated with the head-down/tail-up posture of tail suspension. Dr. Delp's laboratory has manuscripts in review supporting the hypothesis that blood vessel walls undergo structural remodeling in response to changes in hydrostatic pressure gradients associated with chronic tail suspension.

The time course study involving bone histomorphometry, pQCT studies, and mechanical testing reveal few changes after 3 or 7 days of tail suspension. This is not unexpected in mature male rats, although recently published work by Dehority et al. (*Am. J. Physiol.* 276:E62-E69, 1999) verifies that longer term suspension (up to 5 weeks) does produce significant decrements in bone formation and the utility of this age rat in studying bone loss with unloading simulating spaceflight effects. Preliminary gene expression analyses provide suggestive evidence that a number of proteins important in bone physiology are up-regulated after two weeks of tail suspension, including integrin avb3 and avb5, nitric oxide synthase, and prostaglandin synthase 1 and 2; BMP receptors may be down-regulated. Expression of several important bone matrix proteins (Type I collagen, osteocalcin, osteonectin) as well as IGF-I does not change after short-term (3-d) tail suspension. These expression studies will be replicated at other time points and confirmed with immunohistochemistry and *in situ* hybridization studies in the coming months.

One of our important objectives has been accomplished. Significant declines in blood flow to the unweighted hindlimb have been demonstrated to occur *before* significant changes can be detected in bone density, bone geometry, or histomorphometric indicators of bone formation activity. The major portion of this decline in blood flow appears to occur within minutes of the assumption of the tail suspension posture. We will confirm the maintenance of this decreased blood flow by next studying rats subjected to long-term (28-d) tail suspension. By the beginning of Year 3 of this project, we will be performing the definitive experiments testing the effectiveness of a pharmacological vasodilator agent in attenuating the bone changes typically observed with hindlimb unloading. Gene expression studies should help define molecular mechanisms linking altered blood flow to changes in bone cell activity with simulated microgravity. If we are successful in these aims, our data will provide a solid rationale for exploring various potential countermeasures for bone loss based on their effectiveness in maintaining adequate blood flow to lower limb bone during exposure to microgravity.

RESEARCH AREA:	Bone Loss
PRINCIPAL INVESTIGATOR:	Lester W. Schultheis, M.D. (Replacing J. R. Shapiro)
ORGANIZATION:	Johns Hopkins School of Medicine
PROJECT TITLE:	The Effects of Partial Mechanical Loading and Ibandronate on Skeletal Tissues in the Adult Rat Hindquarter Suspension Model for Microgravity
FUNDING:	\$279,000 (FY 1998); \$285,696 (FY 1999)

PROJECT EXECUTIVE SUMMARY

We report initial data from a suspended rat model that quantitatively relates chronic partial weightbearing to bone loss. Chronic partial weightbearing is our simulation of the effect of limited artificial gravity aboard spacecraft or reduced planetary gravity. Preliminary analysis of bone by pQCT, histomorphometry, mechanical testing and biochemistry suggest that chronic exposure to half of Earth gravity is insufficient to prevent severe bone loss. The effect of episodic full weightbearing activity (Earth Gravity) on rats otherwise at 50% weightbearing was also explored. This has similarity to treatment by an Earth G-rated centrifuge on a spacecraft that normally maintained artificial gravity at half of Earth G. Our preliminary evidence, using the above techniques to analyze bone, indicate that 2 hours daily of full weightbearing was insufficient to prevent the bone loss observed in 50% weightbearing animals. The effectiveness of partial weightbearing and episodic full weightbearing as potential countermeasures to bone loss in spaceflight was compared with treatment by ibandronate. Ibandronate, a long-acting potent bisphosphonate proved more effective in preventing bone loss and associated functionality based upon structure than our first efforts at mechanical countermeasures. The effectiveness of ibandronate was notable by each of the testing methods we used to study bone from gross structure and strength to tissue and biochemistry. These results appear to be independent of generalized systemic stress imposed by the suspension paradigm. Preliminary evidence does not suggest that blood levels of vitamin D were affected by our countermeasures. Despite the modest therapeutic benefit of mechanical countermeasures of partial weightbearing and episodic full weightbearing, we know that some appropriate mechanical signal maintains bone mass in Earth gravity. Moreover, the only mechanism that correctly assigns bone mass and strength to oppose regionally specific force applied to bone is mechanical, a process based upon bone strain. Substantial evidence indicates that the specifics of dynamic loading i.e. time-varying forces are critical. Bone strain history is a predictor of the effect that mechanical conditions have on bone structure mass and strength. Using servo-controlled force plates on suspended rats with implanted strain gauges we manipulated impact forces of ambulation in the frequency (Fourier) domain. Our results indicate that high frequency components of impact forces are particularly potent in producing bone strain independent of the magnitude of the peak force or peak energy applied to the leg. Because a servo-system responds to forces produced by the rat's own muscle activity during ambulation, the direction of ground-reaction loads act on bone through the rat's own musculature. This is in distinction to passive vibration of the floor where forces reach bone through the natural filters of soft tissue and joints. Passive vibration may also be effective, but it may or may not increase bone in the appropriate architectural pattern to oppose the forces of normal ambulatory activity. Effectiveness of high frequency mechanical stimulation in producing regional (muscle directed) bone response will be limited by 1. the sensitivity of bone to a particular range of frequencies and 2. the inertia of the muscles, limiting their response to external forces by increasing tension along insertions. We have begun mathematical modeling of

the rat forelimb as a transfer function between impact force and bone strain to predict optimal dynamic loading conditions for this system.

We plan additional studies of mechanical countermeasures that incorporate improved dynamic loading, features relevant to anticipated evaluation of artificial gravity, exercise regimens and exposure to Martian gravity. The combination of mechanical countermeasures with ibandronate will also be investigated for signs of synergy.

RESEARCH AREA:	Bone Loss
PRINCIPAL INVESTIGATOR:	Christopher B. Ruff, Ph.D.
ORGANIZATION:	Johns Hopkins University
PROJECT TITLE:	Skeletal Structural Consequences of Reduced Gravity Environments
FUNDING:	\$168,000 (FY 1998); \$172,031 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The overall goal of this project is to provide structurally meaningful data on bone loss after exposure to reduced gravity environments so that more precise estimates of fracture risk and the effectiveness of countermeasures in reducing fracture risk can be developed. The project has three major components: 1) measure structural changes in the limb bones of rats subjected to complete and partial nonweightbearing, with and without treatment with ibandronate and periodic full weightbearing; 2) measure structural changes in the limb bones of human bedrest subjects, with and without treatment with alendronate and resistive exercise, and Russian cosmonauts flying on the Mir Space Station; and 3) validate and extend the 2-dimensional structural analyses currently possible in the second project component (bedrest and Mir subjects) using 3-dimensional finite element modeling techniques, and determine actual fracture-producing loads on earth and in space.

1) Suspended Rat Study (primary responsibility: Ruff; collaborators: Schultheis, Shapiro)

The primary goal of this study is to determine the longitudinal changes in skeletal structure resulting from a 35-day period of full or partial weight-bearing in rats, with and without treatment with a bisphosphonate (ibandronate) or periodic full weight-bearing. Peripheral quantitative computed tomography (pQCT) was used to obtain skeletal structural parameters non-invasively before and after the treatment period. Treatments included tail-suspension, resulting in near zero-G loads on the hindlimbs and approximately .5 G loads on the forelimbs, and two potential countermeasures: administration of ibandronate, and 2 hours/day of full weight-bearing. Twenty-four 100-day-old Sprague-Dawley rats were assigned to one of five groups: 1) free-ranging (i.e., cage controls, full weightbearing), 2) tail-suspended, 3) tail-suspended + periodic full weight-bearing, 4) suspended + ibandronate, and 5) free-ranging + ibandronate.

Four skeletal locations were scanned using pQCT: the humeral shaft, the femoral shaft, the proximal humeral metaphysis, and the proximal femoral metaphysis. These sites were chosen because they can be reproducibly located in serial scans of the same animal, and encompass both the fore and hind limbs as well as primarily compact (shaft) and compact-trabecular (metaphyseal) bone tissue. The properties of most interest in the shaft locations are measures of cortical bone strength (section moduli), while the metaphyseal scans were used primarily to measure changes in trabecular bone density.

Results of analyses of variance and post-hoc pairwise comparisons between treatment groups indicate the following: 1) Tail-suspension has a negative effect on bone structural properties, particularly trabecular density. This is just as true for the .5 G loaded humerus as for the unloaded femur, i.e., partial loading (to half gravitational force) does not protect against bone loss. 2) Ibandronate is a very effective countermeasure to bone loss induced by a low gravity environment. This is particularly true for trabecular bone loss. In addition, free-ranging rats

treated with ibandronate had higher trabecular bone densities than free-ranging controls. 3) Periodic full weight-bearing had much smaller, if any, effect on bone loss and bone strength. A possible explanation for this is that during the full weight-bearing periods rats were relatively inactive, and thus not subjecting their bones to substantially increased mechanical loads. Future studies will incorporate more controlled increases in mechanical loads (strains) as a potential countermeasure.

2) Bedrest/Mir Study (primary responsibility: Beck; collaborators: LeBlanc, Shackelford, Schneider)

The primary goal of this study is to determine changes in hip structural parameters derived from DEXA (dual energy x-ray absorptiometric) scans of human subjects under two microgravitational conditions: bedrest and space flight aboard Mir. The work is based on knowledge that the strength-related changes in bone due to loss of mineral mass are manifested in its mechanical structure but are not readily apparent in conventional bone mineral density (BMD) measurements. For example, there is evidence that throughout most of adult life, age-related loss of bone mass is partially compensated by structural changes that tend to maintain strength in the presence of net loss of bone mass. Bone tends to be lost from the endosteal surface with aging but this is accompanied by an increase in the periosteal diameter of long bones. The stimulus for subperiosteal expansion is thought to be the mechanical strains within bone due to muscle-mediated loading forces. Under physiological loading, strains in long bones are greatest on the subperiosteal surface and are smaller on the endosteal surface and within the cancellous bone filling the bone ends. The aging process causes loss of bone predominantly from the endosteal surface, in the presence of normal mechanical load - this causes a transitory increase in subperiosteal strains stimulating new bone formation on the subperiosteal surface. Under microgravity conditions, normal astronaut activities involve mainly the upper extremity and upper body and except for specially designed exercise conditions, muscle forces on the lower extremity are nearly absent. Thus, it is not surprising that bone and muscle losses in spaceflight are greater in the trunk and lower extremity. A further implication is that if residual strains on the subperiosteum in the lower extremity skeleton remain low, net loss of bone from the endosteal surface will cause a greater degradation in mechanical strength than an equivalent loss in aging, since there will be no stimulus for compensatory subperiosteal expansion.

To investigate this hypothesis, in year 1 we studied hip DEXA scans on a group of 6 normal young adults subjected to 17 weeks of bedrest. We would expect that in the absence of mechanical stimulus, loss in bone mass would not be accompanied by subperiosteal expansion. We did however detect a slight but significant increase in subperiosteal expansion at the femoral neck, but not in the intertrochanteric or shaft regions. This may be an artifactual result or may mean that mechanical stimuli are not completely absent in the femoral neck of the bedrest subject.

In the second year of the project we studied pre-and post-flight hip scans on 19 Russian cosmonauts, averaging 178 days (126 to 312) on the Mir Space Station. In these cosmonauts we saw a greater loss of bone mass than in the bedrest subjects, and were also unable to detect subperiosteal expansion in any of the three hip locations analyzed. Declines in the section modulus, an index of bending and torsional strength, averaged about 8% in the femoral neck and about 4.5% in the femoral shaft. These data suggest that countermeasures used on Mir to maintain bone integrity are inadequate. The magnitudes of declines in section modulus were weakly but significantly associated with duration of space flight at both locations, accounting for 17% and 13% of the variability in these parameters in the neck and shaft, respectively. We also

examined the issue of recovery of bone strength upon return to normal earth gravity. Here we used follow-up DEXA data from 8 cosmonauts taken an average of 481 days after return to earth, and compared them to the pre-flight scans. We found that on average, neck and shaft BMD returned to within 3% and 2% of preflight levels, respectively. The more strength-relevant neck and shaft section moduli on average returned to within 2% and 1%, respectively, of pre-flight values.

3) Finite Element Modeling (primary responsibility: Newman, Schaffner, Oden)

The primary goal of this study is to validate and extend the 2-D curved beam analysis performed on DEXA images (second part of the study project, above) through use of 3-D finite element analysis (FEA) applied to the proximal human femur, and to determine the actual mechanical loads on the skeleton during spaceflight and habitation on Mars using dynamic modeling. An important development during year 2 of this research effort was the modification of the research plan to account for new information gained from NSBRI bone team investigations. In particular, it has been determined that one effect of exposure to microgravity may be an increase in endosteal diameter with insignificant change in periosteal diameter, leading to cortical thinning and reduced cross-sectional moments of inertia. This effect has been incorporated into the modified finite element modeling strategy so that the impact on femur strength may be assessed.

Significant progress was made on the dynamic modeling effort. Interestingly, it has been found that hip loading anticipated during Mars-gravity locomotion and falls may be as severe as earth-based activities due to the additional mass and inertia of a spacesuit, particularly the backpack life support system. Loads of 2 to 3 times body weight are experienced during locomotion, while impact loading of as much as 8 times body weight would occur during a fall.

The finite element modeling has also made significant progress. An additional inside surface is used to partition the femur model into cortical and trabecular/medullary regions so that the element meshing and material properties can be controlled independently in each region. This separation also facilitates modeling of the increase in endosteal diameter. At this stage the new model has progressed to the point of meshing, but failure analysis cannot proceed due to a bug in the meshing function of the finite element modeling software. We are in the process of obtaining an upgrade to the software, which should solve this problem.

**NSBRI RESEARCH PROGRAM
CARDIOVASCULAR ALTERATIONS**

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CARDIOVASCULAR ALTERATIONS TEAM PROGRAM EXECUTIVE SUMMARY

The cardiovascular system seems to function remarkably well during conditions of space flight. However, particularly during prolonged space flight, the process of cardiovascular deconditioning impairs the cardiovascular system's ability to readapt to a gravity environment. Upon reentry from space flight into the Earth's gravitational field, astronauts experience orthostatic hypotension and reduced exercise capacity, which limits their ability to function during reentry and after landing. For example, in many cases, the orthostatic hypotension is sufficiently severe that astronauts cannot stand erect for some time after landing, thus precluding emergency egress on Earth or another planetary surface. Despite years of research, the mechanisms leading to orthostatic intolerance following microgravity exposure remain poorly characterized and current countermeasures are not adequately effective.

One aspect of cardiovascular deconditioning is a reduction in cardiac mass, the mechanism of which is not known, nor are its functional correlates and reversibility known. In addition, there is strong anecdotal evidence that space flight is associated with decreased cardiac electrical stability which may pose a life threatening risk to astronauts. For example, one crew member during the Skylab missions had a five beat run of ventricular tachycardia during lower body negative pressure. More ominously, analysis of nine 24 hour Holter monitor recordings obtained during long term space flight on Mir revealed one 14 beat run of ventricular tachycardia. Possible mechanisms of arrhythmias and countermeasure strategies have barely been addressed. As long duration missions and older astronauts become more common, alterations in cardiovascular function resulting space flight are more likely to have an impact on mission success and astronaut safety. Thus, it becomes imperative to understand mechanisms of cardiovascular deconditioning and to develop appropriate countermeasures. The recent deaths of two experimental primates shortly after return from space, with cardiovascular mechanisms suspected as primary or contributing causes, lends urgency to these objectives.

The objective of this research program is to apply the most powerful technologies available to determine, in ground-based studies, the mechanisms by which space flight affects cardiovascular function, and then on the basis of an understanding of these mechanisms to develop and test rational and specific countermeasures.

The research effort is divided among seven projects:

- A. Human Studies Core — Gordon H. Williams, PI
This project involves a bed-rest study that examines the mechanisms by which bed-rest and disruption of circadian rhythms affect cardiovascular function and regulation. The subjects in this study are used in the specialized investigations in projects B, C and D.
- B. Alterations in Cardiovascular Regulation and Function During Simulated Microgravity — Richard J. Cohen, PI
This study involves the application of a number of powerful new non-invasive measurement technologies, including cardiovascular system identification (CSI) for the assessment of closed-loop cardiovascular regulation.

- C. Renal and Cardio-Endocrine Responses in Humans to Simulated Microgravity — Gordon H. Williams, PI
This project studies alterations in the responsiveness of the renin-angiotensin-aldosterone hormonal salt and fluid regulatory system in response to the head down tilt model of weightlessness, and to disruption of circadian rhythms.
- D. Non-Invasive Assessment of Susceptibility to Ventricular Arrhythmias During Simulated Microgravity — Richard J. Cohen, PI
This study involves measurement of microvolt level T wave alternans, and other non-invasive measures, as a sensitive measure of cardiac electrical stability to determine whether simulated space flight causes cardiac electrical instability.
- E. Cardiovascular Deconditioning in Rodents — Artin A. Shoukas, PI
Mechanisms of cardiovascular deconditioning are studied in the tail suspended rodent model while taking advantage of the more invasive measurements that can be made in the rodent model as compared to the human model. The rodent model may also serve as a platform to test potential countermeasures before they are evaluated in human studies.
- F. Computational Models of the Cardiovascular System — Roger Kamm, PI
In this project, a computer model that simulates the critical components and behaviors of the cardiovascular system is being developed. This model will be validated using the data collected in the rodent and human studies and used to test potential countermeasures.
- G. Cardiac Atrophy — Michael Schneider, PI
The objective of this project is to determine the cellular and genetic mechanisms by which cardiac mass is reduced during space flight and to develop appropriate countermeasures using a unique rodent model of cardiac unloading.

These studies address the major cardiovascular problems associated with space flight. The plan, in each case, is first to determine the basic mechanisms of the cardiovascular alterations and then, on the basis of the understanding of these mechanisms, to propose and test rational, specific countermeasures. For the current year these studies are mandated to involve only ground-based studies, but as described below, we plan to develop proposals for flight experiments as well.

RESEARCH AREA:	Cardiovascular Alterations
PRINCIPAL INVESTIGATOR:	Gordon Williams, M.D.
ORGANIZATION:	Brigham and Women's Hospital
PROJECT TITLE:	Cardiovascular Deconditioning in Humans: Human Studies Core
FUNDING:	\$420,000 (FY 1998); \$430,080 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Major cardiovascular problems, secondary to cardiovascular deconditioning, may occur on extended space missions. While it is generally assumed that the microgravity state is the primary cause of cardiovascular deconditioning, sleep deprivation and disruption of diurnal rhythms may also play an important role. Factors that could be modified by either or both of these perturbations include: autonomic function and short-term cardiovascular reflexes, vasoreactivity, circadian rhythm of cardiovascular hormones (specifically the renin-angiotensin system) and renal sodium handling and hormonal influences on that process, venous compliance, cardiac mass, and cardiac conduction processes. The purpose of the Human Studies Core is to provide the infrastructure to conduct human experiments which will allow for the assessment of the likely role of such factors in the space travel associated cardiovascular deconditioning process and to develop appropriate countermeasures. The Core takes advantage of a newly-created Intensive Physiologic Monitoring (IPM) Unit at the Brigham and Women's Hospital, Boston, MA, to perform these studies.

The Core includes two general experimental protocols. The first protocol involves a head down tilt bed-rest study to simulate microgravity. The second protocol includes the addition of a disruption of circadian rhythms to the simulated microgravity environment. Before and after each of these environmental manipulations, the subjects will undergo acute stressors simulating changes in volume and/or stress, which could occur in space and on return to Earth. The subjects are maintained in a rigidly controlled environment with fixed light/dark cycles, activity pattern, and dietary intake of nutrients, fluids, ions and calories.

Within the Core experimental protocol framework, investigators perform specific experiments, some based on the application of new non-invasive measurement techniques, to determine the effect of the environmental modifications on the status and responsiveness of the cardiovascular, endocrine, and renal homeostatic systems. In the project led by Professor Cohen, titled Alterations in Cardiovascular Regulation and Function during Simulated Microgravity, investigators apply cardiovascular system identification (CSI) techniques to characterize important cardiovascular regulatory responses including the heart rate and peripheral resistance baroreflexes. The application of CSI will involve the use of echocardiography for continuous beat to beat measurement of stroke volume. In the project led by Professor Williams, titled Renal and Cardio-Endocrine Responses in Humans to Simulated Microgravity, investigators characterize the renal and endocrine responses. Finally, in second project led by Professor Cohen, titled Non-Invasive Assessment of Susceptibility to Ventricular Arrhythmias during Simulated Microgravity, investigators apply novel techniques to quantify changes in the cardiac conduction processes and assess any increased tendency toward cardiac arrhythmias or cardiac electrical alterations. Together, these projects cover a broad spectrum of systems involved in maintaining cardiovascular homeostasis and promise to provide new insight regarding their

alterations in response to the major environmental changes of microgravity and disruption of circadian rhythms. The data from these studies, will be used to develop potential countermeasures so as to ensure the health, productivity, and safety of astronauts during and on return from extended missions (*e.g.*, those that will occur on the International Space Station).

RESEARCH AREA:	Cardiovascular Alterations
PRINCIPAL INVESTIGATOR:	Richard Cohen, M.D., Ph.D.
ORGANIZATION:	Massachusetts Institute of Technology
PROJECT TITLE:	Cardiovascular Deconditioning in Humans: Alteration in Cardiovascular Regulation and Function during Simulated Microgravity
FUNDING:	\$140,000 (FY 1998); \$130,860 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Alterations in cardiovascular regulation and function that occur during and after space flight have been reported. These alterations are manifested, for example, by reduced orthostatic tolerance upon reentry to the earth's gravity from space. However, the precise physiologic mechanisms responsible for these alterations remain to be fully elucidated. Perhaps, as a result, effective countermeasures have yet to be developed. In this project we apply a powerful, new method – cardiovascular system identification (CSI) – for the study of the effects of space flight on the cardiovascular system so that effective countermeasures can be developed.

CSI involves the mathematical analysis of second-to-second fluctuations in non-invasively measured heart rate, arterial blood pressure (ABP), and instantaneous lung volume (ILV – respiratory activity) in order to characterize quantitatively the physiologic mechanisms responsible for the couplings between these signals. Through the characterization of all the physiologic mechanisms coupling these signals, CSI provides a model of the closed-loop cardiovascular regulatory state in an individual subject. The model includes quantitative descriptions of the heart rate baroreflex, autonomic function, as well as other important physiologic mechanisms. We are in the process of incorporating beat-to-beat fluctuations of stroke volume into the CSI technique in order to quantify additional physiologic mechanisms such as those involved in control of peripheral vascular resistance and alterations in cardiac contractility.

We apply CSI in conjunction with the two general protocols of the Human Studies Core project. The first protocol involves ground-based, human head down tilt bed rest to simulate microgravity and acute stressors – upright tilt, standing and bicycle exercise – to provide orthostatic and exercise challenges. The second protocol is intended to be the same as the first but with the addition of sleep deprivation to determine whether this contributes to cardiovascular alterations. In these studies, we focus on the basic physiologic mechanisms responsible for the alterations in cardiovascular regulation and function during the simulated microgravity in order to formulate hypotheses regarding what countermeasures are likely to be most effective.

Compared to our original proposal, the protocol we are using has been slightly modified to lengthen the bed rest period to 16 days and streamline the data collection. These modifications provide us data on a longer bed rest period and have enabled us to increase our subject throughput.

Based on review of our preliminary data we have decided to test a countermeasure which is applied the very end of the bed rest period. We will use the same bed rest protocol to test this countermeasure. We anticipate completing the baseline data collection in our first protocol plus

testing of the countermeasure in an additional eight subjects by the end of the summer of 1999, at which time we plan to initiate the second protocol which includes sleep deprivation.

In future studies, we plan to apply CSI to test other potential countermeasures in conjunction with the same bed rest, sleep deprivation and acute stressor models. We also anticipate applying CSI for studying astronauts before and after space flight and ultimately, during space flight. The application of CSI is providing information relevant to the development and evaluation of effective countermeasures allowing humans to adapt appropriately upon re-exposure to a gravity field, and to live and work for longer periods of time in microgravity.

RESEARCH AREA:	Cardiovascular Alterations
PRINCIPAL INVESTIGATOR:	Gordon H. Williams, M.D.
ORGANIZATION:	Brigham and Women's Hospital
PROJECT TITLE:	Renal and Cardio-Endocrine Responses in Humans to Simulated Microgravity
FUNDING:	Included in Human Studies Core Funding

PROJECT EXECUTIVE SUMMARY

The volume regulating systems are integrated to produce an appropriate response to both acute and chronic volume changes. Their responses include changing the levels of the hormones and neural inputs of the involved systems and/or changing the responsiveness of their target tissues. Weightlessness during space travel produces a volume challenge that is unfamiliar to the organism. Thus, it is likely that these volume regulatory mechanisms may respond inappropriately, *e.g.*, a decrease in total body volume in space and abnormal responses to upright posture and stress on return to Earth. A similar "inappropriateness" also can occur in disease states, *e.g.*, congestive heart failure. While it is clear that weightlessness produces profound changes in sodium and volume homeostasis, the mechanisms responsible for these changes are incompletely understood. Confounding this analysis is sleep deprivation, common in space travel, which can also modify volume homeostatic mechanisms.

The purpose of this project is to provide the required understanding and then to design appropriate countermeasures to reduce or eliminate the adverse effects of microgravity. To accomplish this we are addressing five Specific Aims: 1) To test the hypothesis that microgravity modifies the acute responsiveness of the renin-angiotensin-aldosterone system (RAAS) and renal blood flow; 2) Does simulated microgravity change the circadian rhythm of the volume-regulating hormones?; 3) Does simulated microgravity change the target tissue responsiveness to angiotensin II (AngII)?; 4) Does chronic sleep deprivation modify the circadian rhythm of the RAAS and change the acute responsiveness of this system to posture beyond what a microgravity environment alone does? and 5) What effect does salt restriction have on the volume homeostatic and neurohumoral responses to a microgravity environment? Because the RAAS plays a pivotal role in blood pressure control and volume homeostasis, it likely is a major mediator of the adaptive cardio-renal responses observed during space missions and is a special focus of this project. Thus, the overall goal of this project is to assess the impact of microgravity and sleep deprivation in humans on volume-regulating systems. To achieve this overall objective, we are evaluating renal blood flow and the status and responsiveness of the volume-regulating systems (RAAS, atrial natriuretic peptide and vasopressin), and the adrenergic system (plasma and urine catecholamines) in both simulated microgravity and normal gravity with and without sleep deprivation. Furthermore, the responses of the volume homeostatic mechanisms to acute stimulation by upright tilt testing, standing and exercise are being evaluated before and after achieving equilibrium with these interventions.

We have observed sodium retention and potassium wasting during simulated weightlessness. These observations are consistent with increased plasma aldosterone levels. An augmented aldosterone response to the assumption of upright posture following bed-rest has been observed, which is also consistent with an increased gain of the renin-angiotensin-aldosterone hormonal axis in response to simulated weightlessness. We have measured an approximate 20% decrease in plasma volume in response to bed-rest (consistent with other previous bed-rest studies) despite

a constant fluid intake and urine output. Therefore this decrease in plasma volume may be due to a transudation of fluid into an extravascular fluid compartment (either intracellular or interstitial). Thus the body is responding "appropriately" to this decreased intravascular volume by activating the renin-angiotensin-aldosterone system in order to retain sodium and increase intravascular volume. This is very similar to the state of the cardiovascular system in congestive heart failure, and may underlie pathophysiological changes that contribute to both orthostatic intolerance and cardiac remodeling and arrhythmias. This hypothesis suggests angiotensin converting enzyme inhibitor drugs as a potential countermeasure to microgravity induced cardiovascular deconditioning.

One of the most interesting observations made in the preliminary analysis of the data from this project is a differential susceptibility to orthostatic intolerance prior to bed-rest that appears to correlate with differences in the basal tone of the renin-angiotensin-aldosterone axis. That is, those subjects who are avid sodium retainers during bed-rest tend to be less prone to orthostatic intolerance prior to bed-rest, whereas those subjects who were not avid sodium retainers during bed-rest tended to be more prone to orthostatic intolerance. Following bed-rest all control subjects were intolerant to orthostatic challenge, however there may be significant differences in hemodynamic parameters that correlate with the differences in sodium handling. Full analysis of these data is not yet complete. The difference in sodium handling between these groups may be due to polymorphisms of the angiotensin converting enzyme and angiotensinogen genes, which are known to play a role in the abnormalities in sodium homeostasis in essential hypertension. It is possible that manipulation of this enzyme system in certain subsets of people may beneficially modify the cardiovascular response to weightlessness.

The renin-angiotensin-aldosterone axis may also play an important role in the pathogenesis of the tendency toward increased ventricular dysrhythmias resulting from microgravity exposure. Pilot studies conducted in the Endocrine-Hypertension division of the Brigham and Women's Hospital on rats with genetic hyperaldosteronism have revealed a lymphocytic infiltration of the myocardium. This same finding was noted on a primate that died suddenly under anesthesia the day after returning to Earth from the Russian Bion 11 spacecraft. Aldosterone is known to be capable of inducing these morphologic changes in the myocardium. Thus chronically elevated aldosterone levels resulting from microgravity exposure in the presence of a normal or high salt intake may produce a state of "aldosterone toxicity" which can be at least partially responsible for the decreased cardiac electrical stability that appears to be associated with microgravity exposure.

This work has implications for the treatment and prevention of maladaptive hemodynamic responses experienced by astronauts in flight and on return to Earth. It will increase our understanding of the mechanisms by which weightlessness and sleep deprivation change plasma volume and sodium homeostasis, and possibly cardiac electrical stability, thereby, providing entrée to develop appropriate countermeasures.

RESEARCH AREA:	Cardiovascular Alterations
PRINCIPAL INVESTIGATOR:	Artin A. Shoukas, Ph.D.
ORGANIZATION:	Johns Hopkins University School of Medicine
PROJECT TITLE:	Rodent Studies of Cardiovascular Deconditioning
FUNDING:	\$175,000 (FY 1998); \$204,199 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Changes in blood pressure can occur for two reasons: 1) A decrease in cardiac output resulting from the altered contractility of the heart or through changes in venous filling pressure via the Frank Starling mechanism or; 2) A change in systemic vascular resistance. The observed changes in cardiac output and blood pressure after long term long term space flight cannot be entirely explained through changes in contractility or heart rate alone. Therefore, alterations in filling pressure mediated through changes in systemic venous capacitance and arterial resistance function may be important determinants of cardiac output and blood pressure after long term space flight. Our laboratory and previous studies have shown the importance of veno-constriction mediated by the carotid sinus baroreceptor reflex system on overall circulatory homeostasis and in the regulation of cardiac output.

Our proposed experiments test the overall hypothesis that alterations in venous capacitance function and arterial resistance by the carotid sinus baroreceptor reflex system are an important determinant of the cardiac output and blood pressure response seen in astronauts after returning to earth from long term exposure to microgravity. This hypothesis is important to our overall understanding of circulatory adjustments made during long term space flight. It also provides a framework for investigating counter measures to reduce the incidence of orthostatic hypotension caused by an attenuation of cardiac output. We continue to use hind limb unweighted (HLU) rat model to simulate the patho physiological effects as they relate to cardiovascular deconditioning in microgravity. We have used this model to address the hypothesis that microgravity induced cardiovascular deconditioning results in impaired vascular responses and that these impaired vascular responses result from abnormal alpha-1 AR signaling. The impaired vascular reactivity results in attenuated blood pressure and cardiac output responses to an orthostatic challenge.

We have used in vitro vascular reactivity assays to explore abnormalities in vascular responses in vessels from HLU animals and, cardiac output (CO), blood pressure (BP) and heart rate (HR) measurements to characterize changes in hemodynamics following HLU.

Our preliminary findings are summarized as follows:

- 1) We have demonstrated impaired CO responses to an orthostatic challenge in rats following HLU and recovery within ~60hrs;
- 2) impaired alpha-1-AR and non-alpha mediated responses in large arteries (aorta) of HLU animals;
- 3) primarily impaired alpha-1 AR responses in the femoral arteries of HLU rats;
- 4) reversibility of the vascular phenomenon observed;
- 5) alpha-1AR specific abnormalities in mesenteric microvessel responses;
- 6) a decrease in alpha-1AR specific radioligand binding in aortic vessels from HLU animals.

These data have allowed us to propose a working model:

That microgravity exposure is associated with a decrease in sympathetic neurotransmission (SN). This in turn is associated with a decrease in alpha-1 AR number and signaling as well as vessel smooth muscle mass (trophic effects of NE). Upon return to gravity, attenuated vascular contractility occurs secondary to end organ hyporesponsiveness, despite normal or accentuated sympathetic neurotransmission. Impaired venular and arteriolar responses to catecholamine stimulation results in impaired cardiac output and blood pressure responses.

This working model has allowed us to progress with our proposal as follows:

- 1) To further refine the integrated cardiovascular responses to orthostatic challenges in the HLU rats;
- 2) To further characterize the abnormalities in signaling pathways that result in attenuated vasoreactivity to alpha-1 AR and in some cases non-alpha1-AR agents;
- 3) To use our bioassays to test potential countermeasures that could attenuate or inhibit the development of the abnormal vasoreactivity and resultant CO and BP responses to HLU.
- 4) To begin to explore differences in gender in responses to HLU in parameters measured.
- 5) To integrate and incorporate our findings into understanding changes occurring in human bedrest models of microgravity, as well as astronauts.
- 6) To begin to explore mouse models of orthostatic intolerance and microgravity so that transgenic animals can be used to further understand mechanisms of orthostasis.

These aims will allow us to refine mechanisms, begin to test countermeasures, and bridge the gap between animal models and human subjects in our understanding of microgravity induced orthostatic intolerance.

RESEARCH AREA:	Cardiovascular Alterations
PRINCIPAL INVESTIGATOR:	Roger D. Kamm, Ph.D.
ORGANIZATION:	Massachusetts Institute of Technology
PROJECT TITLE:	Computational Models of the Cardiovascular System and its Response to Microgravity
FUNDING:	\$75,000 (FY 1998); \$76,800 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Computational models of the cardiovascular system are powerful adjuncts to ground-based and in-flight experiments. We will provide NSBRI with a model capable of simulating the short-term effects of gravity on cardiovascular function.

The model from this project will:

- provide a rational framework which quantitatively defines interactions among complex cardiovascular parameters and which supports the critical interpretation of experimental results and testing of hypotheses.
- permit predictions of the impact of specific countermeasures in the context of various hypothetical cardiovascular abnormalities induced by microgravity.

Major progress has been made during the first 18 months of the program:

- We have developed an operational first-order computer model capable of simulating the cardiovascular response to orthostatic stress. The model consists of a lumped parameter hemodynamic model and a complete reflex control system. The latter includes cardiopulmonary and carotid sinus reflex limbs and interactions between the two.
- We have modeled the physiologic stress of tilt table experiments and lower body negative pressure procedures (LBNP). We have verified our model's predictions by comparing them with experimental findings from the literature.
- We have established collaborative efforts with leading investigators interested in experimental studies of orthostatic intolerance, cardiovascular control, and physiologic responses to space flight.
- We have established a standardized method of transferring data to our laboratory from the ongoing NSBRI bedrest studies. We use this data to estimate input parameters to our model and compare our model predictions to actual data to further verify our model.
- We are in the process of systematically simulating current hypotheses concerning the mechanism underlying orthostatic intolerance by matching our simulations to stand test data from astronauts pre- and post-flight.
- We are in the process of developing a JAVA version of the simulator which will be distributed amongst the cardiovascular team members.

Future work on this project involves modifications of the model to represent a rodent (rat) model, further evaluation of the bedrest astronaut and animal data, and systematic investigation of specific countermeasures.

RESEARCH AREA:	Cardiovascular Alterations
PRINCIPAL INVESTIGATOR:	Michael D. Schneider, M.D.
ORGANIZATION:	Baylor College of Medicine
PROJECT TITLE:	Cardiac Atrophy
FUNDING:	\$140,000 (FY 1998); \$143,050 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The objective of this project is to determine the cellular and molecular mechanisms of cardiac atrophy caused by microgravity (already demonstrated in space-flown rats), determine the functional consequences on basal cardiac function and contractile reserve, and identify specific countermeasures. We will study a well-established rodent model of cardiac unloading that results in atrophy, heterotopic transplantation of the heart to the abdomen, as a test-bed for genes and gene products to protect against atrophy. The project will utilize measurements of cardiac genes which modulate growth, contractility, and calcium homeostasis. Cardiac muscle cell contractility and intracellular calcium will be assessed using fluorescence microscopy, and activity of key endogenous growth regulators will be monitored. We propose to address three Specific Aims: (1) Are ventricular myocyte intrinsic contractile function and intracellular calcium regulation impaired in cardiac atrophy, and are endogenous growth-regulators affected, such as the angiotensin converting enzyme (ACE)-angiotensin pathway, which augments growth and contractility, and nitric oxide formation, which inhibits growth and contractility? (2) Do hormonal countermeasures with direct trophic effects on cardiac cell growth (growth hormone) effectively blunt atrophy of the unloaded heart in vivo, or block the functional impairments? (3) Do genetic countermeasures that augment cardiac protein synthesis protect myocardium from cardiac atrophy?

Progress in Year 02 has focused on necessary refinements of the analytical procedures for assessment of cardiac phenotypes under altered loading conditions, which is indispensable for the more complex studies of countermeasures, to follow. Major progress included establishment of simpler and most cost-effective means for invasive hemodynamic monitoring in the rodent models, rigorous validation of the non-invasive echocardiographic monitoring in rodents, and implementation of automated, high-throughput means for quantitatively monitoring cardiac gene expression. The surgical model of unloading was successfully implemented, and the pharmacological countermeasure, growth hormone, was shown to rescue cardiac function even under conditions where it does not augment cardiac mass. In addition, we have established a novel method to directly clone genes that are regulated by mechanical load, and identified several dozen novel targets of the mechanical signaling cascade, including integrin-linked kinase, a especially promising target for mechanical signal transduction.

RESEARCH AREA:	Cardiovascular Alterations
PRINCIPAL INVESTIGATOR:	Richard J. Cohen, M.D., Ph.D.
ORGANIZATION:	Massachusetts Institute of Technology
PROJECT TITLE:	Non-Invasive Assessment of Susceptibility To Ventricular Arrhythmias During Simulated Microgravity
FUNDING:	\$10,800 (FY 1998); \$22,118 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The Cardiovascular Alterations Team is currently conducting studies to determine what alterations in hemodynamic regulation result from sixteen days of simulated microgravity exposure in normal human subjects. In this project we make additional measurements on these same study subjects in order to determine whether there is an increase in susceptibility to ventricular arrhythmias resulting from simulated microgravity exposure.

Numerous anecdotal and documented reports from the past 30 years suggest that the incidence of ventricular arrhythmias among astronauts is increased during space flight. For example, documented runs of ventricular tachycardia have been recorded from crew members of Skylab and Mir [Charles JB, Bungo MW, and Fortner GW, 1994, Fritsch-Yelle, et al., 1998], there was much attention given by the lay press to Mir Commander Vasily Tsibliyev's complaints of heart rhythm irregularities in July of 1997, and cardiovascular mechanisms may have been causal in the recent death of an experimental primate shortly after return from space [Richard Grindeland, Bion 11 Project Scientist, personal communication]. In 1986, a Mir cosmonaut, Alexander Laveikin, was brought home and replaced with an alternate cosmonaut as a result of cardiac dysrhythmias that began during extravehicular activity [Charles, 1998]. Furthermore, at a joint NASA/NSBRI workshop held in January 1998, cardiac arrhythmias were identified as the highest priority cardiovascular risk to a human Mars mission [Workshop to Develop Critical Path Roadmap, 1998]. Despite the evidence for the risk of a potentially lethal arrhythmia resulting from microgravity exposure, the effects of space flight and the associated physiologic stresses on cardiac conduction processes are not known, and an increase in cardiac susceptibility to arrhythmias has never been quantified.

In this project, we are determining whether simulated space flight increases the risk of developing life-threatening heart rhythm disturbances such as sustained ventricular tachycardia (defined as ventricular tachycardia lasting at least 30 seconds or resulting in hemodynamic collapse) and ventricular fibrillation. We are obtaining measures of cardiac susceptibility to ventricular arrhythmias in subjects exposed to simulated space flight in the Human Studies Core protocol being conducted by the Cardiovascular Alterations Team, which involves sixteen days of bed rest. In particular, we are applying a powerful new non-invasive technology, developed in Professor Cohen's laboratory at MIT for the quantitative assessment of the risk of life-threatening ventricular arrhythmias. This technology involves the measurement of microvolt levels of T wave alternans (TWA) during exercise stress, and was recently granted approval by the Food and Drug Administration to be used for the clinical evaluation of patients suspected to be at risk of ventricular arrhythmias. In addition, we are obtaining 24 hour Holter monitoring (to detect non-sustained ventricular tachycardia and to assess heart rate variability). We are also conducting protocols to obtain these same measures on a monthly basis for up to four months in subjects in the Bone Demineralization/Calcium Metabolism Team's long term bed rest study.

These protocols were submitted as an NSBRI Synergy Proposal in February 1998, and are currently in progress.

The preliminary information obtained in this study has already provided the first evidence that simulated space flight has a systematic and measurable effect on susceptibility to life threatening ventricular arrhythmias. In the short-term bed rest study, 2 of 6 subjects who did not have evidence of sustained TWA prior to bed rest developed TWA following bed rest. When tested two days later, TWA had disappeared in both of these subjects. In the long-term bed rest studies, only one subject has been tested at the end of the protocol, but this subject did develop TWA during the immediate post-bed rest phase, which was not present earlier. From these data we have concluded that bed rest induces sustained T wave alternans in normal subjects. This induction of TWA is reversible.

T wave alternans analysis is very sensitive, and does not require the presence of visually apparent arrhythmias to quantify an increased susceptibility to ventricular arrhythmias. Merely the presence of subtle alterations in T wave morphology on the electrocardiogram indicates an increased susceptibility to such arrhythmias. . It is clear from this study that bed rest alters the electrical stability of the myocardium, although by the criteria used in this study, no subject would have been considered clinically at increased risk for sudden death.

Based on our preliminary analysis of data in this study, we have increased our surveillance for changes in levels of urine and plasma anions and cations that may be responsible for mediating the change in myocardial electrical stability we have detected. If this yields a possible mechanism, we will devise animal studies in the future for clarification and preliminary testing of countermeasures.

**NSBRI RESEARCH PROGRAM
HUMAN PERFORMANCE FACTORS**

Team Leader:	Czeisler, C. A.		Harvard	
Czeisler, C. A.	PI	Harvard	Circadian Entrainment, Sleep-Wake Regulation and Neuro-behavioral Performance During Extended Duration Space Flight	B-33
Khalsa, S. B.	CO-I	Harvard		
Kronauer, R. E.	CO-I	Harvard		
Ronda, J. M.	CO-I	Harvard		
Wright, K. P.	CO-I	Harvard		
Dinges, D. F.	PI	Penn	Countermeasures to Neurobehavioral Deficits from Cumulative Partial Sleep Deprivation During Space Flight	B-35
Maislin, G.	CO-I	Penn		
Mullington, J.	CO-I	Harvard		
Van Dongen, H. P.	CO-I	Penn		
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Cajochen, C.	CO-I	Harvard		
Brown, E.	PI	Harvard	On-Line Analysis of Physiologic and Neurobehavioral Variables During Long-Duration Space Missions	B-40
Jewett, M. E.	CO-I	Harvard		
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Natapoff, A.	CO-I	MIT		
Szolovitz, P.	CO-I	MIT		

HUMAN PERFORMANCE FACTORS TEAM PROGRAM EXECUTIVE SUMMARY

Errors in human performance cause most accidents in technology-rich environments such as commercial aviation, where two-thirds of accidents are attributable to performance errors by cockpit crews. In space, the contribution of human performance factors to mission success is even greater, since a number of fundamental aspects of the space environment compromise physiologic systems critically involved in human performance. Human factors is a broad area that includes biological limits on performance [e.g., circadian rhythms, sleep need, microgravity, radiation, environmental factors (temperature)], operational demands on performance (e.g., skilled task demands, monitoring complex automation, mission requirements), psychosocial effects on performance (e.g., effects of isolation, crew selection, family contact, crew communication/coordination) and human ergonomics (e.g., habitability, equipment design, workload, training). Initially, the Human Performance Factors, Sleep and Chronobiology Team is focused on the biological limits of human performance, particularly those compromised by specific aspects of the space environment, including microgravity, an absence of geophysical 24-h cycles, limited sleep/rest opportunities, a high level of automation and a remote, inaccessible location. Such conditions will likely be ubiquitous among the astronauts and are known to affect physiologic, behavioral and cognitive processes critically involved in human performance. These aspects of the space environment result in or require: (a) disrupted circadian entrainment; (b) dyssomnia; (c) cumulative sleep loss; (d) execution of life science research remote from the Principal Investigator (PI).

The overall strategy of the Human Performance Factors, Sleep and Chronobiology Team is based on the recognition that optimizing human performance in space can best be achieved by: (1) understanding the basic mechanisms underlying the deterioration of human neurobehavioral function in space related to these factors; and (2) developing effective countermeasures based on those mechanisms to minimize human error and optimize human performance in the highly automated space environment. Currently, for example, astronauts' sleep duration, which is one of the most fundamental determinants of their waking neurobehavioral performance, averages only 6 hours per night, and may be as low as 3 to 4 hours per night. Ground-based studies indicate that within 2 weeks, the effects of such cumulative sleep deprivation are equivalent to the effects of 48-60 hours of total sleep deprivation. Recent work elsewhere indicates that as little as 24 hours of total sleep deprivation has been reported to degrade aspects of neurobehavioral performance to a level comparable to a blood alcohol level of 0.10 percent. To counteract their difficulty sleeping, astronauts and the flight surgeons responsible for their medical care currently rely during space flight on *ad lib* self-administration of hypnotic medications that were developed for the treatment of insomnia, with 50% of crew members in dual shift operations resorting to sleeping pill use during the missions.

This integrated research team is investigating a series of novel approaches to address such human performance factors, including: the mechanisms of circadian entrainment and sleep regulation; statistical algorithms for on-line analysis of physiologic variables monitored during long-duration space missions; and the development of expert systems for the remote execution of life science experiments. These approaches are integrated with the aim of developing countermeasures and testing their efficacy. The multi-disciplinary approach adopted for study of the affected physiologic, behavioral and cognitive processes in humans (i.e., including circadian entrainment, sleep homeostasis, and decision-making processes) incorporates five team projects and two inter-team synergy projects.

Integration will be achieved by thematic organization around the defining characteristics of the space environment that influence human performance. The research program of the Human Performance Factors, Sleep and Chronobiology Team is a goal-directed research program that will provide an integrated contribution to the overall NSBRI mission and will address the Institute's Aims and Objectives by: (1) Designing, implementing, and validating effective countermeasures to address the biological and environmental impediments to long-term human space flight; (2) Defining the whole-organism integrated-physiological and neurobehavioral responses that ultimately determine these impediments and designing novel countermeasures based on these responses; (3) Establishing support technologies to maximize human performance in space and to reduce the probability of human performance failure; (4) Transferring and disseminating the advances in knowledge and technology acquired to populations on earth in which performance is jeopardized; (5) Providing training of new scientists in the space life sciences by recruiting young scientists for active participation in the proposed ground-based research program and by mentoring these young scientists for the duration of these projects.

The proposed research is relevant for the round-the-clock work schedules (day, evening and night work) on the International Space Station, the altered sleep/wake schedule required on a Mars surface station, or any other situation in which the work-rest schedule is shifted or sleep loss is incurred. It also has relevance for ground personnel monitoring orbiting crew members who must do so around-the-clock. Through the efforts of this Program, the Human Performance, Sleep and Chronobiology Team plans to develop effective countermeasures to minimize human error and optimize human performance in the highly automated space environment. The research program of the Human Performance Factors, Sleep and Chronobiology Team is a goal-directed research program that will provide an integrated contribution to the overall NSBRI mission. The results of this team effort could have a profound effect on the health, safety and productivity of astronauts during extended duration missions, such as those planned for the International Space Station and for the manned mission to Mars.

RESEARCH AREA:	Human Performance Factors
PRINCIPAL INVESTIGATOR:	Charles A. Czeisler, M.D., Ph.D.
ORGANIZATION:	Harvard Medical School and Brigham and Women's Hospital
PROJECT TITLE:	Circadian Entrainment, Sleep-Wake Regulation and Neurobehavioral Performance during Extended Duration Space Flight
FUNDING:	\$390,577 (FY 1998); \$416,885 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Long-duration manned space flight requires crew members to maintain a high level of cognitive performance and vigilance while operating and monitoring sophisticated instrumentation. However, the reduction in the strength of environmental synchronizers in the space environment leads to misalignment of circadian phase among crew members, coupled with restricted time available to sleep, results in sleep deprivation and consequent deterioration of neurobehavioral function.

Crew members are provided, and presently use, long-acting benzodiazepine hypnotics on board the current, relatively brief space shuttle missions to counteract such sleep disruption, a situation that is only likely to worsen during extended duration missions. Given the known carry-over effects of such compounds on daytime performance, together with the reduction in emergency readiness associated with their use at night, NASA has recognized the need to develop effective but safe countermeasures to allow crew members to obtain an adequate amount of sleep. Over the past eight years, we have successfully implemented a new technology for shuttle crew members involving bright light exposure during the pre-launch period to facilitate adaptation of the circadian timing system to the inversions of the sleep-wake schedule often required during dual shift missions (Czeisler et al. 1991). However for long duration space station missions it will be necessary to develop effective and attainable countermeasures that can be used chronically to optimize circadian entrainment.

Our current research effort is to study the effects of light-dark cycles with reduced *zeitgeber* strength, such as are anticipated during long-duration space flight, on the entrainment of the endogenous circadian timing system and to study the effects of a countermeasure that consists of scheduled brief exposures to bright light on the human circadian timing system. The proposed studies are designed to address the following Specific Aims:

- 1) test the hypothesis that synchronization of the human circadian pacemaker will be disturbed in men and women by the reduction in LD cycle strength.
- 2) test the hypothesis that this disturbed circadian synchronization will result in the secretion of the sleep-promoting hormone melatonin during the waking day, disturbed sleep, reduced growth hormone secretion, and impaired performance and daytime alertness;
- 3) as a countermeasure, test the hypothesis that brief daily exposures to bright light (10,000 lux) will reestablish normal entrained circadian phase, resulting in improved sleep consolidation, normalized sleep structure and endogenous growth hormone secretion and enhanced daytime performance.

To date, we have carried out twelve experiments to address Hypotheses 1 and 2 and data analyses are in progress.

The results of the current research may have important implications for the treatment of circadian rhythm sleep disorders, such as delayed sleep phase syndrome and shift-work dyssomnia, which are anticipated to have a high incidence and prevalence during extended duration space flight such as planned for the International Space Station and manned missions to Mars.

RESEARCH AREA:	Human Performance Factors
PRINCIPAL INVESTIGATOR:	David F. Dinges, Ph.D.
ORGANIZATION:	University of Pennsylvania
PROJECT TITLE:	Countermeasures to Neurobehavioral Deficits from Cumulative Partial Sleep Deprivation During Space Flight
FUNDING:	\$297,700 (FY 1998); \$313,992 (FY 1999)

PROJECT EXECUTIVE SUMMARY

This project is concerned with identifying ways to prevent neurobehavioral and physical deterioration due to inadequate sleep in astronauts during long-duration manned space flight. The performance capability of astronauts during extended-duration space flight depends heavily on achieving recovery through adequate sleep. Even with appropriate circadian alignment, sleep loss can erode fundamental elements of human performance capability including vigilance, cognitive speed and accuracy, working memory, reaction time, and physiological alertness. Adequate sleep is essential during manned space flight not only to ensure high levels of safe and effective human performance, but also as a basic regulatory biology critical to healthy human functioning.

There is now extensive objective evidence that astronaut sleep is frequently restricted in space flight to averages between 4 hr and 6.5 hr/day. Chronic sleep restriction during manned space flight can occur in response to endogenous disturbances of sleep (motion sickness, stress, circadian rhythms), environmental disruptions of sleep (noise, temperature, light), and curtailment of sleep due to the work demands and other activities that accompany extended space flight operations. The mechanism through which this risk emerges is the development of cumulative homeostatic pressure for sleep across consecutive days of inadequate sleep. Research has shown that the physiological sleepiness and performance deficits engendered by sleep debt can progressively worsen (i.e., accumulate) over consecutive days of sleep restriction, and that sleep limited to levels commonly experienced by astronauts (i.e., 4 - 6hr per night) for as little as 1 week, can result in increased lapses of attention, degradation of response times, deficits in complex problem solving, reduced learning, mood disturbance, disruption of essential neuroendocrine, metabolic, and neuroimmune responses, and in some vulnerable persons, the emergence of uncontrolled sleep attacks.

The prevention of cumulative performance deficits and neuroendocrine disruption from sleep restriction during extended duration space flight involves finding the most effective ways to obtain sleep in order to maintain the high-level cognitive and physical performance functions required for manned space flight. There is currently a critical deficiency in knowledge of the effects of how variations in sleep duration and timing relate to the most efficient return of performance per unit time invested in sleep during long-duration missions, and how the nature of sleep physiology (i.e., sleep stages, sleep electroencephalographic [EEG] power spectral analyses) change as a function of sleep restriction and performance degradation. The primary aim of this project is to meet these critical deficiencies through utilization of a response surface experimental paradigm, testing in a dose-response manner, varying combinations of sleep duration and timing, for the purpose of establishing how to most effectively limit the cumulative adverse effects on human performance and physiology of chronic sleep restriction in space operations.

To develop a response surface model, 90 healthy men and women will undergo a 14-day ground-based laboratory protocol involving random assignment to one of 18 sleep-ration cells, each involving the same sleep ration for 10 consecutive days. The sleep-ration assignments involve 4 anchor sleep durations (4.2, 5.2, 6.2, 8.2 hr) and 6 nap sleep durations (0.4, 0.8, 1.2, 1.6, 2.0, 2.4 hr) crossed to yield a total of 4 anchor-sleep-only conditions, and 14 anchor + nap sleep conditions, and spanning a dynamic range of cumulative sleep debts (i.e., from 0 to 40 hr in a 10-day period). Subjects undergo a wide range of quasi-continuous neurobehavioral performance tests and continuous physiological monitoring of waking EEG, sleep PSG, behavioral motility, and core body temperature, while living in the laboratory for 14 consecutive days. The laboratory environment is designed to simulate the low light, tight quarters, and lack of social contact with the outside world that will characterize long-duration space flight.

To date, half of the data (from $n = 45$ subjects) required to develop the complete response surface map have been acquired in the project. As more data are obtained, the results of this experiment will be used in development of a biomathematical model of the effects of cumulative sleep loss (across days) relative to circadian dynamics (within days), in collaboration with other Team investigators at Harvard. In addition, in a recently awarded, complementary project, we will test the hypothesis that a probed performance algorithm, to be derived retrospectively from our data base of sleep-deprived subjects, can be used to prospectively predict individual vulnerability to cumulative sleep loss, thereby permitting more precise utilization of countermeasures for prevention of performance-impairing sleep loss during extended manned space flight.

Sleep duration and timing are being covaried in this project at two sleep-conducive circadian phases: (1) anchor sleep during sidereal night and (2) nap sleep during midday. Although scientific evidence strongly supports the view that the less sleep obtained, the greater the likelihood of waking deficits, both laboratory and field studies have demonstrated that a brief preplanned or preemptive nap (0.4 hr to 2.4 hr) may have the potential to sustain optimal performance capability when total sleep time is markedly curtailed. The basis for this disproportionate benefit from a relatively brief nap was recently discovered to be the result of a saturating exponential function, such that the first few hours of sleep net the greatest recovery. Thus, the disproportionate recovery potential of naps may be due to the exponential recovery of neurobehavioral performance functions in relation to sleep duration. This exponential process appears to parallel the time course of EEG slow wave activity (SWA obtained by power spectral analysis) during sleep, which is believed to manifest the physiological homeostatic drive for sleep. The data we have gathered to date on half of the subjects in this experiment support the conclusion that a dual sleep period with a nap longer than 1 hr results in normal to high levels of physiologically deep sleep and prevention of cumulative performance deficits, even when the total time being allocated for sleep in a day is restricted to just over 6 hr. This suggests that the implementation of a brief nap may be one way in which cumulative sleep loss and waking performance deficits could be reversed or prevented. Using a wide range of experimental conditions and a two-stage regression approach, we are establishing a response surface model (RSM) of the countermeasure effectiveness of multiple combinations and durations of anchor sleep and scheduled naps to test the hypothesis that such combinations can prevent the neurobehavioral performance deficits that accumulate within and across days of chronic sleep restriction. We are also systematically evaluating the relationship between sleep physiology and waking performance. Such data will help establish the extent to which homeostatic physiological processes during sleep respond to chronic sleep restriction.

Finally, this project has pioneered the use in the USA of a new non-thrombogenic catheter system to study the effects of chronic sleep restriction on human growth hormone secretion

(hGH), cortisol and plasma melatonin secretion, and in collaboration with the Dr. Janet Mullington, immune modulatory and growth factors. The focus on sleep loss and circadian effects on immune function have also extended to a project on the effects of severe acute sleep deprivation on soluble cytokines and cytokine receptors, in collaboration with Dr. William Shearer and the NSBRI Immunology Team. Working in collaboration with the NSBRI Technology team, we are also seeking to develop a fully portable, miniaturized, ambulatory blood acquisition system that will facilitate the ease of completion of ground-based and space flight experiments in which blood chemistry information is critical.

RESEARCH AREA:	Human Performance Factors
PRINCIPAL INVESTIGATOR:	Derk-Jan Dijk, Ph.D.
ORGANIZATION:	Harvard Medical School and Brigham and Women's Hospital
PROJECT TITLE:	Quantitative EEG Monitoring of Vigilance: Effects of Sleep Deprivation, Circadian Phase and Sympathetic Activation
FUNDING:	\$137,652 (FY 1998); \$121,497 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Shuttle astronauts typically sleep only 6 to 6.5 hours per day while in orbit. This sleep loss is related to recurrent sleep cycle shifting--due to mission-dependent orbital mechanics and mission duration requirements-- and associated circadian displacement of sleep, the operational demands of space flight, noise and space motion sickness. Such sleep schedules are known to produce poor subjective sleep quality, daytime sleepiness, reduced attention, negative mood, slower reaction times, and impaired daytime alertness. Countermeasures to allow crew members to obtain an adequate amount of sleep and maintain adequate levels of neurobehavioral performance are being developed and investigated. However, it is necessary to develop methods that allow effective and attainable in-flight monitoring of vigilance to evaluate the effectiveness of these countermeasures and to detect and predict online critical decrements in alertness/performance. There is growing evidence to indicate that sleep loss and associated decrements in neurobehavioral function are reflected in the spectral composition of the electroencephalogram (EEG) during wakefulness as well as in the incidence of slow eye movements recorded by the electro-oculogram (EOG). Furthermore, our preliminary data indicated that these changes in the EEG during wakefulness are more pronounced when subjects are in a supine posture, which mimics some of the physiologic effects of microgravity. Therefore, we evaluate the following hypotheses: (1) that during a 40-h period of wakefulness (i.e., one night of total sleep deprivation) neurobehavioral function deteriorates, the incidence of slow eye-movements and EEG power density in the theta frequencies increases especially in frontal areas of the brain; (2) that the sleep deprivation induced deterioration of neurobehavioral function and changes in the incidence of slow eye movements and the spectral composition of the EEG are more pronounced when subjects are in a supine position; and (3) that based on assessment of slow-eye movements and quantitative on-line topographical analyses of EEG during wakefulness an EEG and or EOG parameter can be derived/constructed which accurately predicts changes in neurobehavioral function.

In a series of experiments and data analysis projects conducted during the first two years of this project we have established that:

1. The spectral composition of the EEG during wakefulness exhibits pronounced and predictable changes during a 24-h period of sustained wakefulness.
2. The changes associated with sleep loss are most pronounced in EEGs derived from frontal areas of the brain, and in particular so in the delta and theta frequencies, both during wakefulness and during sleep.
3. Changes in alertness and psychomotor vigilance correlate with changes in EEG power density in the delta and theta frequencies in frontal derivations.
4. The incidence of slow eye movements during wakefulness increases during sleep loss and correlates with changes in alertness and psychomotor vigilance. This correlation is so tight that inter-individual differences in the time course of the incidence of slow eye movements

closely resemble the inter-individual differences in the time course of neurobehavioral performance during a 24-h episode of sustained wakefulness.

5. The circadian pacemaker modulates the incidence of slow eye movements as well as the spectral composition of the EEG during wakefulness.
6. Light-induced changes in the amplitude of the circadian pacemaker and associated changes in the amplitude of the circadian modulation of alertness are associated with changes in the amplitude of the circadian modulation of the incidence of slow eye movements.
7. Light-induced acute changes in alertness are associated with acute changes in the EEG and the incidence of slow eye movements during wakefulness.
8. Posture modulates the apparent amplitude of the circadian rhythm of body temperature and heart rate such that this amplitude is reduced when subjects are in a supine posture during 40-h of wakefulness.

These new findings establish a close and robust association of frontal EEG and EOG parameters with changes in neurobehavioral performance in a variety of protocols in which sleep homeostasis and circadian rhythmicity are manipulated. These data indicate that EEG/EOG based on-line monitoring of alertness/performance can serve as a practical and attainable tool to predict and prevent critical decrements in performance and alertness, without the need to conduct time consuming tests of neurobehavioral performance. Further understanding of the relationship between EEG/EOG and neurobehavioral function could thus have a profound effect on the health, productivity and safety of astronauts during space missions. The proposed research is relevant for the round-the-clock work schedules (day, evening and night work) on the International Space Station, the altered sleep/wake schedule on a Mars surface station, or any other situation where the work-rest schedule is shifted and sleep loss is incurred. It also has relevance for ground personnel monitoring orbiting crew members who must do so working round-the-clock schedules.

RESEARCH AREA:	Human Performance Factors
PRINCIPAL INVESTIGATOR:	Emery N. Brown, M.D., Ph.D.
ORGANIZATION:	Harvard Medical School and Massachusetts General Hospital
PROJECT TITLE:	On-Line Analysis of Physiologic and Neurobehavioral Variables During Long-Duration Space Missions
FUNDING:	\$104,027 (FY 1998); \$99,953 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The goal of this project is to develop reliable statistical algorithms for on-line analysis of physiologic and neurobehavioral variables monitored during long-duration space missions. Maintenance of physiologic and neurobehavioral homeostasis during long-duration space missions is crucial for ensuring optimal crew performance. If countermeasures are not applied, alterations in homeostasis will occur in nearly all-physiologic systems. During such missions data from most of these systems will be either continually and/or continuously monitored. Therefore, if these data can be analyzed as they are acquired and the status of these systems can be continually assessed, then once alterations are detected, appropriate countermeasures can be applied to correct them.

One of the most important physiologic systems in which to maintain homeostasis during long-duration missions is the circadian system. To detect and treat alterations in circadian physiology during long duration space missions requires development of: 1) a ground-based protocol to assess the status of the circadian system under the light-dark environment in which crews in space will typically work; and 2) appropriate statistical methods to make this assessment. The protocol in Project 1, Circadian Entrainment, Sleep-Wake Regulation and Neurobehavioral will study human volunteers under the simulated light-dark environment of long-duration space missions. Therefore, we propose to develop statistical models to characterize in near real time circadian and neurobehavioral physiology under these conditions.

The specific aims of this project are to test the hypotheses that: 1) Dynamic statistical methods based on the Kronauer model of the human circadian system can be developed to estimate circadian phase, period, amplitude from core-temperature data collected under simulated light-dark conditions of long-duration space missions. 2) Analytic formulae and numerical algorithms can be developed to compute the error in the estimates of circadian phase, period and amplitude determined from the data in Specific Aim 1. 3) Statistical models can detect reliably in near real-time (daily) significant alternations in the circadian physiology of individual subjects by analyzing the circadian and neurobehavioral data collected in Project 1. 4) Criteria can be developed using the Kronauer model and the recently developed Jewett model of cognitive performance and subjective alertness to define altered circadian and neurobehavioral physiology and to set conditions for immediate administration of countermeasures.

At the outset of Year 2 we made three changes in the research plan as a consequence of the research findings in Year 1 and the recommendations of the review committee.

Change 1: Dynamic Assessments of Circadian Phase from Forced Desynchrony Studies. In our Year 1 research plan, our original goal was to use the data collected during the 25 24 hour days of core-temperature data collected from Project 1 to develop a technique for making dynamic assessments of circadian phase. These estimates would provide the circadian input to

the performance and subjective alertness model prediction developed by Dr. Jewett. Our original hypothesis was that under low light conditions these subjects would free run and therefore these data would provide an excellent framework for making dynamic assessments of circadian phase. All of the 3 subjects analyzed by the end of Year 1 were entrained during the 25 24 hour day. Our analysis and the independent constant routine assessments confirmed this. Therefore to test the ability of our analytic framework to make dynamic assessments of circadian phase we use the temperature data from the forced desynchrony part of the protocol. During this phase of the protocol the subject is desynchronized from the 28-hour day.

Change 2: Average Prediction of Performance and Subjective Alertness. In our Year 1 research plan our original goal was to develop straight away an algorithm for making time specific individual predictions of performance and subjective alertness using the models developed by Dr. Jewett. We realized that moving directly to individual predictions was too large an initial step. Therefore we will use the performance, alertness and circadian phase data to first adapt the Jewett model to predict average performance, since this is what it was initially developed to predict. Once the model shows good predictions with average performance and subjective alertness, we will then return the problem of individual predictions.

Change 3: Using the Expertise of a Neurobehavioralist on the Project 4. Our scientific review committee recommended that we include a neurobehavioralist on our team in order to better focus the work on performance and subjective alertness. In response to this suggestion, we have Dr. Megan Jewett working on this component of the modeling for the project. She developed the performance and subjective alertness models for her Ph.D. dissertation and has been working with us to adapt them to the study of the subjects on the simulated long-duration space missions.

Core-Temperature Analysis. To date seven control subjects have completed the twenty-four 25 hour day and forced desynchrony protocols. Of those 7 subjects we have carried out dynamic phase and amplitude assessments on 6 of them using the forced desynchrony segment of the protocol for the reasons described above. For 5 of the 6 subjects we have been able to use the differential equation model to decompose each core-temperature series into its circadian, forced desynchrony and thermoregulatory components. Model fitting for the 6th subject has proved difficult because of numerical instability problems. Two of the subjects were studied at light levels of 15 lux whereas the other 3 were studied at less than 5 lux. At present we are able to make reliable dynamic assessments of circadian phase 10 days after the start of the forced desynchrony. We have successfully used our methods to analyze core-temperature data on the forced desynchrony protocol and demonstrate that the period of the human circadian pacemaker is closer to 24 instead of 25 hours. These findings will appear in Science in June or July of 1999.

Genetic Algorithm. All the models are fit to the core-temperature data using maximum likelihood based on a Kalman filter and Runge-Kutta algorithms imbedded in a Newton's procedure. The Newton's method may not always perform well because the parameter space has many local minima and flat regions. In these cases, the algorithm can fail to find the optimal parameter estimates because of poorly defined second derivatives. Therefore, Dr. Harry Luithardt has developed and implemented an algorithm for using a Monte Carlo method to find the best parameter estimates for the model based on a genetic algorithm. The genetic algorithm is based on a "survival of the fittest principle" in which the parameters that are retained, are the ones which make the likelihood the largest. An advantage of this procedure is that it works on the actual value of the likelihood rather than its first or second derivative. Because the genetic algorithm checks the actual function values, it can help identify regions where the likelihood may be flat. Flat regions of the likelihood suggest indeterminate parameter values. The genetic

algorithm has been successfully used to fit our differential equation model on evenly spaced simulated and actual core-temperature data, with serial correlation and forced desynchrony evoked effects. The simulations help us understand where the traditional Newton's procedure fails and also where change in the model formulation may be necessary.

Analysis of Performance and Subjective Alertness. With the collaboration of Dr. Jewett, we have been able to make dynamic assessments of circadian phase with sleep-wake history over a 16 to 23 day period and use them to predict subject's average performance and subjective alertness. The model had been developed from constant routine data as part of Dr. Jewett's thesis. It showed a very strong relation between average predicted performance and that of actual performance measured by cognitive throughput tests. Similarly, the model analysis showed a strong relation between average predicted subjective alertness and that measured by self-reporting. This work convincingly suggests that the performance and subjective alertness models can predict may be quite useful for predicting average performance and alertness in individual subjects. The analysis was presented at the NASA research conference in Houston in January 1999.

Growth Hormone Model. Because of the growing interest in the use of growth hormone as a marker rhythm for the human circadian and sleep wake systems, we have developed a linear two dimensional differential equation model of growth hormone plasma levels for subjects on scheduled days and the constant routine. The model is fit to experimental data by maximum likelihood and has been successfully used to analyze growth hormone data from normal women and ones with fibromyalgia as part of a collaboration with Dr. Gail Adler at the Brigham and Women's Hospital. These methods will help us improve our methods for melatonin analysis.

Core-Temperature Analysis. The methods developed for dynamic assessment of circadian phase will be applied in Year 3 to the two groups receiving the two different light pulse regimens in Project 1. We will compare the phase shifting effects of the two regimens using our analysis framework.

Genetic Algorithm. We plan to make the genetic algorithm a standard part of our analysis framework. Therefore, we will implement it with a continuous-time Kalman filter algorithm in order to fit unevenly spaced core-temperature data.

New Model for Core-Temperature. The new core-temperature model holds promise for giving a better description of the dynamics of the human circadian pacemaker. This description can be further enhanced if realistic models of the thermoregulatory and activity interactions with the circadian pacemaker can be characterized. We will work on developing these model components.

Analysis of Performance and Subjective Alertness. We will complete analysis of subjective alertness and performance for all of the subjects in each of the three groups in Project 1.

Growth Hormone Model. We will use the algorithm developed to analyze the growth hormone model to develop accurate means of assessing period from the long melatonin series collected under the forced desynchrony protocol and the twenty-four 25 hour day protocol.

RESEARCH AREA:	Human Performance Factors
PRINCIPAL INVESTIGATOR:	Laurence R. Young, Sc.D.
ORGANIZATION:	Massachusetts Institute of Technology
PROJECT TITLE:	Principal Investigator-in-a-Box
FUNDING:	\$30,000 (FY 1998); \$61,433 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Human performance in orbit is currently limited by several factors beyond the intrinsic awkwardness of motor control in weightlessness. Cognitive functioning can be affected by such factors as cumulative sleep loss, stress and the psychological effects of long-duration small-group isolation. When an astronaut operates a scientific experiment, the performance decrement associated with such factors can lead to lost or poor quality data and even the total loss of a scientific objective, at great cost to the sponsors and to the dismay of the Principal Investigator. In long-duration flights, as anticipated on the International Space Station and on any planetary exploration, the experimental model is further complicated by long delays between training and experiment, and the large number of experiments each crew member must perform. Although no documented studies have been published on the subject, astronauts report that an unusually large number of simple errors are made in space. Whether a result of the effects of microgravity, accumulated fatigue, stress or other factors, this pattern of increased error supports the need for a computerized decision-making aid for astronauts performing experiments.

Artificial intelligence and expert systems might serve as powerful tools for assisting experiments in space. Those conducting space experiments typically need assistance exactly when the planned checklist does not apply. Expert systems, which use bits of human knowledge and human methods to respond appropriately to unusual situations, have a flexibility that is highly desirable in circumstances where an invariably predictable course of action/response does not exist. Frequently the human expert on the ground is unavailable, lacking the latest information, or not consulted by the astronaut conducting the experiment.

In response to these issues, we have developed "Principal Investigator-in-a-Box," or [PI], to capture the reasoning process of the real expert, the Principal Investigator, and combine that with real-time data available in space in order to advise the astronaut about how to proceed in real time. [PI] advises the astronaut during the progress of an experiment in much the same way a real Principal Investigator might do while looking over the astronaut's shoulder. In its original application, [PI] mimicked several of the tasks of the Principal Investigator, including data quality monitoring, troubleshooting, prescheduling, protocol management and "interesting data" detection. The proposed research focuses on the efficacy of this technique as applied to the data quality monitoring and troubleshooting aspects of [PI].

This project completes Phase One of the 3-year NSBRI-funded ground based evaluation of Principal Investigator-in-a-Box. The experiment tests the efficacy of [PI] for assisting "astronaut surrogates" in detecting realistic experiment artifacts in the context of a space life sciences experiment that monitors sleep. It is the first evaluation of such a decision aid under controlled conditions, and should help determine the applicability of expert systems in future space flight research.

For this initial phase of the study, matched groups of subjects, receiving identical training on sleep monitoring, were tested. The time for test subjects to detect and identify the nature of a

signal abnormality was measured. Pre-recorded electrophysiological signals were played back for the subjects through a PC laptop computer, which either enabled or disabled the [PI] diagnostic routines. The subjects, none of whom had previously been exposed to human sleep research or [PI], began with 90 minutes of training before attempting to monitor electrophysiological sleep parameters. Half of the subjects received [PI] assistance in their first, and half in their second exposure to the tests. The laptop recorded test subject inputs for detection and diagnosis of signal failures, and made the time and accuracy data available for later analysis.

This project is representative of a large class of real-time decision aids; correspondingly, our findings concerning efficacy and the human-computer interface should generalize to many applications.

**NSBRI RESEARCH PROGRAM
IMMUNOLOGY, INFECTION AND HEMATOLOGY**

Team Leader:	Shearer, W.	Baylor		
Shearer, W. T.	PI	Baylor	Space Flight Immunodeficiency	B-51
Dinges, D. F.	CO-I	Penn		
Kanwar, S.	CO-I	Baylor		
Lugg, D. J.	CO-I	Australia		
Mullington, J. L.	CO-I	Harvard		
Ochs, H. D.	CO-I	Washington		
Pierson, D. L.	CO-I	NASA JSC		
Reuben, J. M.	CO-I	M. D. Anderson		
Rosenblatt, H. M.	CO-I	Baylor		
Sams, C.	CO-I	NASA JSC		
Smith, C. W.	CO-I	Baylor		
Smith, E. O.	CO-I	Baylor		
Smolen, J. E.	CO-I	Baylor		
Butel, J. S.	PI	Baylor	Immune Function and Reactivation of Latent Viruses	B-54
Conner, M. E.	CO-I	Baylor		
Lednicky, J. A.	CO-I	Baylor		
Ling, P. D.	CO-I	Baylor		
Pierson, D. L.	CO-I	NASA JSC		
Fox, G. E.	PI	U of Houston	DNA Probe Design for Preflight and Inflight Microbial Monitoring	B-57
Wilson, R. C.	CO-I	U of Houston		
Alfrey, C. P.	PI	Baylor	Neocytolysis: Mechanisms and Limitations	B-60
Byrne, B. J.	CO-I	University of Florida		
Kessler, P.	CO-I	Hopkins/SOM		
Rice, L.	CO-I	Baylor		
Trial, J.	CO-I	Baylor		

IMMUNOLOGY, INFECTION AND HEMATOLOGY TEAM PROGRAM EXECUTIVE SUMMARY

The four individual research projects and principal investigators that make up the Immunology, Infection, and Hematology Team are:

- Space Flight Immunodeficiency, William T. Shearer, M.D., Ph.D.
- Immune Function and Reactivation of Latent Viruses, Janet S. Butel, Ph.D.
- DNA Probe Design for Pre-Flight and In-Flight Microbial Monitoring, George E. Fox, Ph.D.
- Neocytolysis: Mechanisms and Limitations, Clarence P. Alfrey, Jr., M.D., Ph.D.

These four projects have been grouped together, because they come to the common focus of host protection afforded by the primordial bone marrow stem cell against the potentially harmful effects of space travel. The first three projects involve the white blood cell derivatives of the stem cell, lymphocytes and phagocytes, and the fourth project involves the red blood cells, erythrocytes. Each of the projects is unique in design and implementation, yet their common purpose is to explore the possibility that astronauts on long space voyages would be exposed and suffer damage to these crucial cellular components of the immune and hematologic systems. Because the study of astronauts on space missions is impractical and inconclusive due to limited numbers of subjects, it has been necessary to revert to earth-bound, space-equivalent models in most of the Team's research. Although these surrogate models present problems in extrapolation of the results and conclusions of experiments to humans in space, they provide a more than adequate mechanism with which to approach the scientific study of the likelihood that astronauts on long space trips, such as the projected two-year journey to Mars, would experience weakening of host immune surveillance systems, leading to acute and chronic infection by reactivated viral infections and pre-malignant conditions. The progress of the last year's research for each project is capsule-summarized below:

Space Flight Immunodeficiency

Sleep Deprivation and Cytokines

A possible linkage between the effects of space travel and alteration in human immune function has been made by the study of the effects of sleep deprivation upon plasma cytokines and their receptors. In this new synergy project begun with NSBRI investigators Dr. David F. Dinges, Chief of the Division of Sleep and Chronobiology and Director of the Unit for Experimental Psychiatry at the University of Pennsylvania School of Medicine in Philadelphia, and Dr. Janet Mullington, Director of the Sleep Laboratory at Harvard Medical School in Boston, we have measured key cytokine and soluble cytokine receptors in the earth-bound space flight-equivalent model, sleep deprivation. Subjects deprived of sleep for 88 hours experienced statistically significant alterations in plasma soluble tumor necrosis factor alpha receptor 1 (sTNF- α R1), sTNF- α R2, and interleukin-6 (IL-6). Partial sleep deprivation and caffeine treatment also exerted significant alterations in the plasma concentrations of these molecules.

Total sleep deprivation significantly increased the plasma concentration of sTNF α -R1 ($P < 0.02$), and caffeine treatment significantly lowered this increased concentration ($P < 0.01$). This finding may be explained by the effect of sleep deprivation increasing the level of TNF- α , which in turn upregulates the cell expression of its high-affinity receptor and release in soluble form (sTNF- α R1). Caffeine may block the adenosine A2 receptor, thus elevating extracellular adenosine

concentration which down regulates the TNF- α R1 expression, thus sustaining elevated plasma TNF- α concentrations. Although caffeine treatment lowered the plasma concentration of the low-affinity receptor, sleep deprivation (total or partial) did not alter the plasma concentration of TNF- α R2. Caffeine greatly elevated the plasma concentration of IL-6 in total sleep-deprived subjects ($P < 0.01$), but not in partial sleep-deprived subjects ($P < 0.01$). It is possible that total sleep deprivation increased plasma IL-6 concentration in caffeine-treated subjects by stimulating its production through the adenosine A2b receptor.

These observations prompt an immediate effort to more fully explore the impact of sleep deprivation on the important regulatory cytokines (and their receptors) of the immune system. These studies have obvious and major importance for astronauts in space travel because of the disturbances in sleep patterns that they experience.

Anti-Orthostatic Suspension and Hypersensitivity

We have shown that the anti-orthostatic murine model accentuates the antigen (oxazalone)-specific delayed type T-cell mediated hypersensitivity (DTH) reaction in mice. Since DTH reactions represent one of the classes of hypersensitivity reactions in humans, the discovery that the anti-orthostatic hind-limb suspension model produces a significant increase is an extremely important finding. Since this model is accepted as one of space travel, these findings may suggest that astronauts will suffer from accentuated hypersensitivity reactions, which would contribute to a state of immune T-cell imbalance. Moreover, using the spleens of these same mice, we have been able to document a significant increase in the proliferation of cells and the secretion of IL-2, the most powerful T-cell stimulatory cytokine.

The implication of these findings is that astronauts would suffer from exaggerated hypersensitivity reactions to antigens in their environment or even autoimmune diseases. Since human immune diseases can be traced to under-reactive conditions (immunodeficiency) and hyperreactive conditions (allergy, autoimmunity), these findings hold importance for humans in space flight, particularly long-term space flight where repetitive exposure to the same antigens might trigger manifestations of hypersensitivity diseases. It is well known that immunodeficiency and autoimmunity coexist in humans, such as patients with common variable immunodeficiency, hyper IgM syndrome, rheumatoid arthritis, systemic lupus erythematosus, and numerous autoimmune endocrinopathies.

Antarctic Research

We have collaborated with Dr. Desmond Lugg, Head of Polar Medicine for the Australian Antarctic Division and Program Leader for the Human Biology and Medicine component of the Australian National Antarctic Research Expedition (ANARE), and Dr. Hans Ochs, Professor and Head of the Immunology Research Laboratory at the University of Washington, in preparing and shipping the neoantigen, ϕ X-174 bacteriophage to the ANARE stations in the Antarctic, where the neoantigen will be administered to volunteer subjects after 4 months of isolation and post-immunization blood specimens obtained out to 9 months of isolation. Peripheral blood mononuclear cells (PBMC) have already been obtained on a monthly basis for study of specific T-cell responses to antigens (especially to latent viruses), cell surface phenotyping, and cytokine secretion. The latent viruses to be studied are: Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV). Dr. Janet Butel, Infection Project Leader, is already collecting monthly blood, saliva, and urine specimens for quantitative measurement of EBV, CMV, and HSV. We will correlate the lymphoproliferation responses of these Antarctic

subjects, particularly in those subjects who experience reactivation of these latent virus infections. Thus, we will assess the strengths of specific T-cell proliferation of subjects with reactivation of latent virus infection due to the isolation, stress, and microbial contamination in the 9-month winter-over in the Antarctic. We will also measure the important T-cell subsets that govern immune responses to infections and cancer cells: naive and memory T-cells (CD45RA+ and RO+), cytotoxic T-cells (CD8+CD28+), and activated T-cells (CD8+CD38+). Comparison of these T-cell subset markers in those subjects experiencing reactivation of latent viruses will help to explain the pathogenesis of latent virus infections, since CD45RA+ and CD8+CD28+ T-cells are lost while CD8+CD38+ T-cells increase in other immunosuppressive viral infections, such as HIV infection. In addition, we will follow the TH1 (IL-2, IFN- γ) and TH2 (IL-4, IL-6, IL-10, TNF- α) cytokine secretion patterns in stimulated PBMC in Antarctic subjects, again particularly those experiencing latent virus reactivation. Since the TH1 cytokine production decreases in individuals losing cytotoxic T-cell control of virus infection, and TH2 cytokines increase in individuals experiencing rapidly progressing viral infections, it will be important to determine whether these changes occur in those study subjects experiencing reactivation of latent virus infections, or worse, development of malignancy.

Immune Function and Reactivation of Latent Viruses Viral Reactivation

During Year 2 of this grant award, a one-year longitudinal study of 30 normal healthy volunteers was initiated. Blood, urine, and saliva samples are being collected at 2-month intervals and analyzed by PCR techniques for viral DNAs. This will provide the first year-long study of reactivation and shedding patterns of herpesviruses and polyomaviruses in normal individuals. Results of virus reactivation studies in ground-based analogs of space flights can then be meaningfully interpreted in the context of "normal" reactivation patterns. The first three collection points have been analyzed for detection of polyomaviruses. JC virus (JCV) excretion has been detected in urine samples from 13 test subjects. Viral shedding was most consistently observed in subjects over 40 years of age (10/13 positive subjects). DNA sequence analyses showed that JCV isolates could be distinguished genetically, information that could be used to track viruses in transmission studies. Only sporadic urine samples contained detectable amounts of BK virus (BKV) DNA. None of the blood samples from the first three collection time points contained polyomavirus DNAs.

A QC-PCR assay for herpesvirus EBV has been perfected. This assay is being utilized in a collaborative study to measure EBV genome loads in HIV-infected persons before and after treatment with highly active antiretroviral therapy (HAART). The study is not yet complete, but preliminary indications are that different people show different patterns of latent virus reactivation during changes in immune status, emphasizing the importance of establishing baseline patterns of viral reactivation for several latent viruses in normal hosts.

A synergy project in collaboration with Dr. Janet Mullington of the Human Performance Team is currently being analyzed under code. Our role in the project is to test whether short-term partial sleep deprivation has a measurable effect on reactivation of latent viruses.

Mucosal Immunity

An animal experiment was completed, testing the effects of anti-orthostatic suspension on clearance of a primary rotavirus infection and protection from virus challenge in outbred CD-1 mice. The experiment led to the following conclusions: (1) clearance of a primary rotavirus

infection was delayed by short-term anti-orthostatic suspension (4 days prior to inoculation), (2) the delay in clearance did not appear to be due to a delay in development of intestinal antibodies, (3) short-term anti-orthostatic suspension during primary infection did not alter the induction or development of memory mucosal immune responses, and (4) once memory mucosal immune responses were established under normal conditions, short-term anti-orthostatic suspension at the time of challenge did not alter the ability of the mucosal memory immune response to protect mice from reinfection with rotavirus. These results suggest that alterations in mucosal immune responses do occur under short-term simulated space flight conditions.

Data obtained from these studies will allow us to evaluate whether conditions that simulate certain aspects of space flight have serious enough effects on viral infections and mucosal immunity that they may jeopardize the success of long-term space flight missions. If so, appropriate countermeasures will be designed and tested. These studies will also provide a foundation from which rational experiments can be designed to monitor viral reactivation and shedding and immune changes in crew members participating in actual space flight missions.

DNA Probe Design for Pre-Flight and In-Flight Microbial Monitoring Capture Probes

During the first project year, we demonstrated the feasibility of a DNA chip-based assay for the monitoring of water quality using probes that target 16S rRNA. It was at the same time clear that three major difficulties needed to be overcome to make the approach useful. These are the: (1) development of an appropriate set of hybridization probes with minimal cross-reactivity, (2) development of spacecraft compatible procedures for extracting and purifying the target nucleic acids, and (3) increase in the sensitivity and ease of execution of the assay. The work undertaken in Year 2 focused on these issues, and considerable progress was made toward resolving them.

The prototype assay system for rapid examination of water quality from a microbial perspective will contain probes for: (1) total bacteria, (2) enteric organisms as a group (i.e., as a measure of fecal contamination), (3) specific detection of *E. coli*, (4) detection of the genera *Enterococcus* and *Burkholderia*, and (5) detection of the presence of *Pseudomonas aeruginosa* and closely related organisms. Capture probes were initially synthesized with a 5' amino linker, to allow chemical coupling to surfaces such as glass slides or microtiter plates. In collaboration with Genosys Inc., we tested these probes in a hybridization array format. The results suggested that this approach had great promise. However, these initial studies showed that most of the initial probes exhibited either too little specificity or too much cross reactivity for our purposes. Therefore, we have implemented two assays during the past year. The first is a dot-blot assay that utilizes biotinylated detector probes. The second is a traditional radioactive assay using alpha P³² ATP to end-label the DNAs. We first tested the initial set of oligonucleotide detector probes. The results showed that there is a considerable amount of non-specific binding evident at room temperature. Experiments with capture probes revealed that several were not as specific as hoped, and those which are problematic are now undergoing redesign.

Molecular Beam Technology

In order to increase the sensitivity and the usability of the assay, we are exploring molecular beacon technology. This approach would eliminate the need for washing steps. Such steps are required to remove unbound detector probes that would otherwise emit a false positive signal. Moreover, the beacon technology eliminates the need for the addition of reagents during hybridization. This technology is therefore very attractive for use in the space-based assay.

During the past year, experiments to evaluate the molecular beacon technology were undertaken. The experiments focused on a unique sequence in *Vibrio proteolyticus* 5S rRNA. This target sequence allows quantitative detection of this RNA in the presence of other 5S rRNAs, e.g. *E. coli*. However, only 25% of the expected signal was seen. This likely is due to quenching by the RNA structure and is a problem that needs to be overcome. We have repeated the experiment using chaperon probes in analogy to the planned sandwich assay. This increased the signal somewhat. Further experiments in this area are contemplated in the coming year.

RESEARCH AREA:	Immunology, Infection and Hematology
PRINCIPAL INVESTIGATOR:	William T. Shearer, M.D., Ph.D.
ORGANIZATION:	Baylor College of Medicine
PROJECT TITLE:	Space Flight Immunodeficiency
FUNDING:	\$165,001 (FY 1998); \$365,222 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The National Aeronautics and Space Administration (NASA) has had sufficient concern for the well-being of astronauts traveling in space to create the National Space Biomedical Research Institute (NSBRI), which is investigating several areas of biomedical research including those of immunology. As part of the Immunology, Infection, and Hematology Team, the co-investigators of the Space Flight Immunodeficiency Project began their research projects on April 1, 1998 and are now just into the second year of work. Two areas of research have been targeted: 1) specific immune (especially antibody) responses and 2) non-specific inflammation and adhesion. More precise knowledge of these two areas of research will help elucidate the potential harmful effects of space travel on the immune system, possibly sufficient to create a secondary state of immunodeficiency in astronauts. The results of these experiments are likely to lead to the delineation of functional alterations in antigen presentation, specific immune memory, cytokine regulation of immune responses, cell to cell interactions, and cell to endothelium interactions.

During the first year of operation, we have collaborated with Dr. Desmond Lugg, Head of Polar Medicine for the Australian Antarctic Division and Program Leader for the Human Biology and Medicine component of the Australian National Antarctic Research Expedition (ANARE), and Dr. Hans Ochs, Professor and Head of the Immunology Research Laboratory at the University of Washington, in preparing and shipping the neoantigen, ϕ X-174 bacteriophage to the ANARE stations in the Antarctic, where the neoantigen will be administered to volunteer subjects after 4 months of isolation and post-immunization blood specimens obtained out to 9 months of isolation. Peripheral blood mononuclear cells (PBMC) have already been obtained on a monthly basis for study of specific T-cell responses to antigens (especially to latent viruses), cell surface phenotyping, and cytokine secretion. The latent viruses to be studied are: Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV). Dr. Janet Butel, Infection Project Leader, is already collecting monthly blood, saliva, and urine specimens for quantitative measurement of EBV, CMV, and HSV. We will correlate the lymphoproliferation responses of these Antarctic subjects, particularly in those subjects who experience reactivation of these latent virus infections. Thus, we will assess the strengths of specific T-cell proliferation of subjects with reactivation of latent virus infection due to the isolation, stress, and microbial contamination in the 9-month winter-over in the Antarctic. We will also measure the important T-cell subsets that govern immune responses to infections and cancer cells: naive and memory T-cells (CD45RA+ and RO+), cytotoxic T-cells (CD8+CD28+), and activated T-cells (CD8+CD38+). Comparison of these T-cell subset markers in those subjects experiencing reactivation of latent viruses will help to explain the pathogenesis of latent virus infections, since CD45RA+ and CD8+CD28+ T-cells are lost while CD8+CD38+ T-cells increase in other immunosuppressive viral infections, such as HIV infection. In addition, we will follow the TH1 (IL-2, IFN- γ) and TH2 (IL-4, IL-6, IL-10, TNF- α) cytokine secretion patterns in stimulated PBMC in Antarctic subjects, again particularly those experiencing latent virus reactivation. Since the TH1 cytokine production decreases in individuals losing cytotoxic T-cell control of virus infection, and TH2

cytokines increase in individuals experiencing rapidly progressing viral infections, it will be important to determine whether these changes occur in those study subjects experiencing reactivation of latent virus infections, or worse, development of malignancy.

In a new synergy project begun with NSBRI investigators Dr. David F. Dinges, Chief of the Division of Sleep and Chronobiology and Director of the Unit for Experimental Psychiatry at the University of Pennsylvania School of Medicine in Philadelphia, and Dr. Janet L. Mullington, Director of the Sleep Laboratory at Harvard Medical School in Boston, we have measured key cytokine and soluble cytokine (s) receptors in another earth-bound space flight-equivalent model, sleep deprivation. Subjects deprived of sleep for 88 hours experienced statistically significant alterations in plasma sTNF- α R1, sTNF- α R2, and IL-6. Partial sleep deprivation and caffeine treatment also exerted significant alterations in the plasma concentrations of these molecules.

Total sleep deprivation significantly increased the plasma levels of sTNF α -R1 ($P < 0.02$), and caffeine treatment significantly lowered the levels in both groups ($P < 0.01$). This finding may be explained by the effect of sleep deprivation increasing the level of TNF- α , which in turn upregulates the cell expression of its high-affinity receptor and release in soluble form (sTNF- α R1). Caffeine may block the adenosine A2 receptor, thus elevating extracellular adenosine concentration which down regulates the TNF- α R1 expression, thus sustaining elevated plasma TNF- α concentrations. Although caffeine treatment lowered the plasma concentration of the low-affinity receptor, sleep deprivation, total or partial, did not alter the plasma concentration of TNF- α R2. Caffeine greatly elevated the plasma concentration of IL-6 in total sleep-deprived subjects ($P < 0.01$), and partial sleep reduced these levels ($P < 0.01$). It is possible that sleep deprivation increased plasma IL-6 concentration by stimulating its production through the adenosine A2b receptor.

All of these observations make an important discovery in sleep deprivation studies and prompt an immediate and major effort to more fully explore the impact of sleep deprivation on the important regulatory cytokines (and their receptors) of the immune system. These studies have obvious and major importance for astronauts in space travel because of the disturbances in sleep patterns that they experience. This discovery suggests the linkage between the effects of space travel and alteration in human immune function.

We have also made substantial progress in the pursuit of Specific Aim 2. For example, we have shown that the anti-orthostatic murine model accentuates the antigen (oxazolone)-specific delayed type T-cell mediated hypersensitivity (DTH) reaction in mice. Since DTH reactions represent one of the classes of hypersensitivity reactions in humans, the discovery that the anti-orthostatic hind-limb suspension model produces a significant increase is an extremely important finding. Since this model is accepted as one of space travel, these findings may suggest that astronauts will suffer from accentuated hypersensitivity reactions, which would contribute to a state of immune T-cell imbalance. Moreover, using the spleens of these same mice, we have been able to document a significant increase in the proliferation of cells and the secretion of IL-2, the most powerful T-cell stimulatory cytokine. Together, these recent observations suggest that space travelers will experience additional alterations in immune responses, possibly leading in the aggregate to a state of immunodeficiency.

We are greatly encouraged by the results of these preliminary experiments in human and animal earth-bound models of space flight. We have responded to the concerns of the Board of Scientific Counselors who last year, just 2 months after initiation of our project, recommended

that we obtain as much information as soon as possible in order to produce more specific hypotheses. Statistical input has been provided by Dr. E. O'Brian Smith, one of our co-investigators, and our preliminary data survive statistical scrutiny. We believe that we are launched upon an accelerating path and that new discoveries will continue to be made and new hypotheses generated.

RESEARCH AREA:	Immunology, Infection and Hematology
PRINCIPAL INVESTIGATOR:	Janet S. Butel, Ph.D.
ORGANIZATION:	Baylor College of Medicine
PROJECT TITLE:	Immune Function and Reactivation of Latent Viruses
FUNDING:	\$277,000 (FY 1998); \$283,648 (FY 1999)

PROJECT EXECUTIVE SUMMARY

A major concern associated with long-duration space flight is the possibility of infectious diseases posing an unacceptable medical risk to crew members. One major hypothesis addressed in this project is that space flight will cause alterations in the immune system that will allow latent viruses that are endogenous in the human population to reactivate and shed to higher levels than normal, which may affect the health of crew members. The second major hypothesis being examined is that the effects of space flight will alter the mucosal immune system, the first line of defense against many microbial infections, including herpesviruses, polyomaviruses, and gastroenteritis viruses, rendering crew members more susceptible to virus infections across the mucosa.

We are focusing the virus studies on the human herpesviruses and polyomaviruses, important pathogens known to establish latent infections in most of the human population. Both primary infection and reactivation from latent infection with these groups of viruses (especially certain herpesviruses) can cause a variety of illnesses that result in morbidity and, occasionally, mortality. Both herpesviruses and polyomaviruses have been associated with human cancer, as well. Effective vaccines exist for only one of the eight known human herpesviruses and available antivirals are of limited use. Whereas normal individuals display minimal consequences from latent viral infections, events which alter immune function (such as immunosuppressive therapy following solid organ transplantation) are known to increase the risk of complications as a result of viral reactivations.

The strategy of this project is to measure both the frequency and magnitude of viral shedding from humans participating in activities that serve as ground-based models of space flight conditions. We are developing sensitive quantitative competitive-polymerase chain reaction (QC-PCR)-based assays for herpesviruses and for polyomaviruses. Using these assays we are establishing baseline patterns of virus reactivation and shedding in normal volunteers over time. As a comparison, we will also measure patterns of reactivation and shedding from individuals who are severely immunosuppressed, in whom reactivation or primary infection with a herpesvirus or polyomavirus is known to be able to cause medical complications. In addition, we will test ground-based analogs in collaboration with Dr. Duane Pierson (NASA/Johnson Space Center). This will include measuring samples obtained from individuals living and working in the extreme environment of the ANARE Outpost in Antarctica and from individuals undergoing chamber isolation studies. Other ground-based models, such as stress associated with sleep deprivation, will be pursued in collaboration with other NSBRI Teams. These studies will be integrated with those of the "Space Flight Immunodeficiency" project, headed by Dr. W.T. Shearer, which will determine the immune competence of some of the same individuals.

We are addressing the mucosal immune system questions by using a ground-based mouse model (the anti-orthostatic suspension of mice) and rotavirus (a gastroenteritis virus known to be a mucosal immunogen and to cause human disease). This model system does not simulate all aspects of space flight, but it is accepted as a model for studies on alterations of the immune

system. The mucosal immunity study will determine whether immune clearance of primary rotavirus infection or establishment of a primary immune response is altered, whether induction of a memory immune response or resistance to a secondary infection is altered, and whether changes in the individual components of the mucosal immune system occur due to the anti-orthostatic suspension of mice. Finally, the ability of a subunit mucosal vaccine countermeasure to induce an immune response and protective efficacy will be determined using the ground-based mouse model.

Initial progress on this project included development of facilities, training of personnel, establishment of collaborations, and development of assays. A dedicated laboratory was designed and renovations are in progress; it will contain a sample processing room and a clean room for PCR assay set-up designed to avoid the possibility of contamination of human samples collected for this project. A QC-PCR assay for herpesvirus EBV was established, and standard PCR assays developed for several polyomaviruses. Cages were tested, design modified, and then fabricated for the mouse mucosal immunity studies.

Progress was made during Year 2 on both the viral reactivation and mucosal immunity arms of the project. A one-year-long longitudinal study of 30 normal healthy volunteers was initiated. Blood, urine, and saliva samples are being collected at 2-month intervals and analyzed by PCR techniques for viral DNAs. This will provide the first year-long study of reactivation and shedding patterns of herpesviruses and polyomaviruses in normal individuals. Results of virus reactivation studies in ground-based analogs of space flights can then be meaningfully interpreted in the context of "normal" reactivation patterns. The first three collection points have been analyzed for detection of polyomaviruses. JC virus (JCV) excretion has been detected in urine samples from 13 test subjects. Viral shedding was most consistently observed in subjects over 40 years of age (10/13 positive subjects). DNA sequence analyses showed that JCV isolates could be distinguished genetically, information that could be used to track viruses in transmission studies. Only sporadic urine samples contained detectable amounts of BK virus (BKV) DNA. None of the blood samples from the first three collection time points contained polyomavirus DNAs.

A QC-PCR assay for herpesvirus EBV has been perfected. This assay is being utilized in a collaborative study to measure EBV genome loads in HIV-infected persons before and after treatment with highly active antiretroviral therapy (HAART). The study is not yet complete, but preliminary indications are that different people show different patterns of latent virus reactivation during changes in immune status, emphasizing the importance of establishing baseline patterns of viral reactivation for several latent viruses in normal hosts.

A synergy project in collaboration with Dr. Janet Mullington of the Human Performance Team is currently being analyzed under code. Our role in the project is to test whether short-term partial sleep deprivation has a measurable effect on reactivation of latent viruses.

An animal experiment was completed testing the effects of anti-orthostatic suspension on clearance of a primary rotavirus infection and protection from virus challenge in outbred CD-1 mice. The experiment led to the following conclusions: (1) clearance of a primary rotavirus infection was delayed by short-term anti-orthostatic suspension (4 days prior to inoculation), (2) the delay in clearance did not appear to be due to a delay in development of intestinal antibodies, (3) short-term anti-orthostatic suspension during primary infection did not alter the induction or development of memory mucosal immune responses, and (4) once memory mucosal immune responses were established under normal conditions, short-term anti-orthostatic suspension at the

time of challenge did not alter the ability of the mucosal memory immune response to protect mice from reinfection with rotavirus. These results suggest that alterations in mucosal immune responses do occur under short-term simulated space flight conditions.

Data obtained from these studies will allow us to evaluate whether conditions that simulate certain aspects of space flight have serious enough effects on viral infections and mucosal immunity that they may jeopardize the success of long-term space flight missions. If so, appropriate countermeasures will be designed and tested. These studies will also provide a foundation from which rational experiments can be designed to monitor viral reactivation and shedding and immune changes in crew members participating in actual space flight missions.

RESEARCH AREA:	Immunology, Infection and Hematology
PRINCIPAL INVESTIGATOR:	George E. Fox, Ph.D.
ORGANIZATION:	University of Houston
PROJECT TITLE:	DNA Probe Design for Preflight and Inflight Microbial Monitoring
FUNDING:	\$48,000 (FY 1998); \$49,152 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Crew health is a dominant issue in manned space flight. Microbiological concerns, in particular, have repeatedly emerged as determinants of flight readiness. For example, in at least one case, suspected contamination of the potable water supply nearly forced a launch delay. In another instance, a crew member's urinary tract infection nearly led to early termination of the mission, in part due to the difficulty of accurately diagnosing the nature of the infection in-flight. Microbial problems are an increasing concern with the trend towards longer-duration missions. It is essential to the success of such missions that systems that deliver acceptable quality of air and water during the anticipated lifetime of the spacecraft be available. As mission duration and re-supply intervals increase, it will be necessary to rely on advanced life support systems which incorporate both biological and physical-chemical recycling methods for air and water as well as provide food for the crew. It therefore is necessary to develop real-time, robust, in-flight monitoring procedures that are sensitive enough to detect less than 100 CFU (colony forming units) of bacteria per 100 milliliters of water. It would be desirable if the monitoring system could be readily "reprogrammed" to identify specific pathogens if an in-flight incident were to occur. Thus, the monitoring technology must simultaneously detect many organisms of interest, be subject to miniaturization and be highly automated. The long range goal of project is to develop such monitoring systems.

Our underlying hypothesis is that the most appropriate target will be either ribosomal RNA or the DNA that encodes it. The small subunit rRNA sequence (16S rRNA) has been experimentally determined in several thousand bacterial species. Each of these sequences contains short sub-sequences that are widely conserved throughout the data set as well as other sub-sequences which are totally unique to, and hence characteristic of, a particular species. This pattern of sequence conservation makes it possible to design oligonucleotide hybridization probes that can distinguish individual organisms, or groupings of organisms. Once an appropriate set of target sub-sequences have been identified for a desired assay, any of a variety of formats can be used to implement the assays. Thus, the final assay system may utilize PCR amplified nucleic acids or, because rRNAs are high copy number molecules, direct detection systems such as chemiluminescence. Both type of assay are compatible with hybridization array technology (DNA chips) and hence can be readily miniaturized and data can be processed automatically or returned to Earth by telemetry. During the first project year we demonstrated the feasibility of a DNA chip based assay for monitoring of water quality using probes that target 16S rRNA. It was at the same time clear that three major difficulties needed to be overcome to make the approach useful. These are (1) development of an appropriate set of hybridization probes with minimal cross-reactivity, (2) the development of spacecraft compatible procedures for extracting and purifying the target nucleic acids and (3) increasing the sensitivity and ease of execution of the assay. The work undertaken in year 2 focused on these issues and considerable progress was made towards resolving them.

The prototype assay system for rapid examination of water quality from a microbial perspective will contain probes for (1) total bacteria, (2) enteric organisms as a group- i.e. as a measure fecal contamination, (3) specifically detect *E. coli*, (4) detect the genera *Enterococcus* and *Burkholderia*, (5) detect the presence of *Pseudomonas aeruginosa* and closely related organisms. The prototype system is being developed as a sandwich assay which utilizes both a capture probe and detector probe(s). The surface capture probe selectively acquires the target rRNA from a total RNA preparation. The detector probe provides a labeling group and assists in the denaturation of the target molecule by disrupting the secondary structure of the target rRNA in the region where it binds. The target capture probes were designed to be highly organism or group specific. For each capture probe, a detector probe is designed using the sequence adjacent (two bases away) to the target sequence used for the capture probe. Most of these detector probes are in fact degenerate at several positions to ensure binding to all targeted organisms.

Capture probes were initially synthesized with a 5' amino linker, to allow chemical coupling to surfaces such as glass slides or microtiter plates. In collaboration with Genosys Inc. we tested these probes in a hybridization array format. The results suggested this approach had great promise. However, these initial studies showed that most of these initial probes exhibited either too little specificity or too much cross reactivity for our purposes. It was clear that the next step was refinement of the probes. In order to accomplish this we therefore needed to develop a routine assay for examining probe specificity in our laboratories. To this end we have implemented two assays during the past year. The first is a dot-blot assay that utilizes biotinylated detector probes. The second is a traditional radioactive assay using alpha P³² ATP to end-label the DNAs. Since the radioactive label is on the 5' end and the biotin label is at the 3' end, the same DNA probes can be used with each experimental protocol. We first tested the initial set of oligonucleotide detector probes. The results showed that there is a considerable amount of non-specific binding evident at room temperature. Much of the non-specific binding is eliminated by higher temperature hybridization. For example, the *Burkholderia* probes all give a strong signal with *B. cepacia* RNA and only a background signal with the other organisms' RNAs. This level of specificity actually exceeds what is needed for a detector probe which need only bind the target 16S rRNA as well as they bind non-target 16S rRNAs. Experiments with capture probes revealed that several were not as specific as hoped and those which are problematic are now undergoing redesign. To assist in this, new computational tools were developed in the past year which allow us to check for probe specificity versus not only known 16S rRNAs but genomic sequences in general. In conducting these assays with biotinylated probes it was found that the EZNA RNA purification procedure, although extremely easy to use gave a RNA that was of lower quality than that obtained by the phenol/chloroform extraction procedure. It was uncertain if this significantly effected results but in view of the developmental nature of the work another variable is not needed and this procedure has been temporarily abandoned.

The development of monitoring systems for use in space environments presents several unique problems. In particular, sample preparation and sample processing must be done as expeditiously as possible. Ideally, the target 16S rRNA would need to be purified by a greatly simplified one or two step approach. Efforts to develop alternative simplified RNA isolation procedures during the past year focused on compaction precipitation using spermine and spermidine. These agents neutralize the highly charged phosphate backbone of nucleic acids and stabilize intermolecular interactions as well such that the nucleic acid is precipitated. We have identified conditions under which a total RNA mixture is precipitated with little contaminating protein or DNA. The RNA fractions in the precipitate can be resolved by anion-exchange chromatography. The 16S rRNA obtained appears to be as pure as that obtained with the phenol/chloroform procedure and is

currently being tested in hybridization experiments with the expectation that this protocol will soon be the method of choice in the ongoing probe studies.

In order to increase the sensitivity and the usability of the assay we are exploring molecular beacon technology. This approach would eliminate the need for washing steps. Such steps are required to remove unbound detector probes that would otherwise emit a false positive signal. Moreover, the beacon technology eliminates the need for the addition of reagents during hybridization. This technology is therefore very attractive for use in the space based assay. During the past year, experiments to evaluate the molecular beacon technology were undertaken. The experiments focused on a unique sequence in *Vibrio proteolyticus* 5S rRNA. This target sequence allows quantitative detection of this RNA in the presence of other 5S rRNAs, e.g. *E. coli*. However, only 25% of the expected signal was seen. This likely is due to quenching by RNA structure and is a problem that needs to be overcome. We have repeated the experiment using chaperon probes in analogy to the planned sandwich assay. This increased the signal somewhat. Further experiments in this area are contemplated in the coming year.

RESEARCH AREA:	Immunology, Infection and Hematology
PRINCIPAL INVESTIGATOR:	Clarence P. Alfrey, M.D., Ph.D.
ORGANIZATION:	Baylor College of Medicine
PROJECT TITLE:	Neocytolysis: Mechanisms and Limitations
FUNDING:	\$230,000 (FY 1998); \$235,520 (FY 1999)

PROJECT EXECUTIVE SUMMARY

We uncovered the physiologic process of neocytolysis through attempts to understand the cause of "spaceflight anemia". Astronauts spending just a few days in space invariably return to earth with a 10-15% decrement in their red cell mass. This is not a benign phenomena, rendering the astronaut weak and with orthostatic hypotension on re-entry into a gravitational field.

Out studies on SLS-1 and SLS-2 demonstrated normal red cell production during the first days in space, and also there was normal survival of red cells labeled with ⁵¹Cr twelve to fourteen days before launch. Our data could only be explained by the selective hemolysis of red cells younger than twelve days old; the process named "neocytolysis". On entering microgravity, the blood normally held in the extremities pools centrally. This leads to acute central plethora, rapid loss of plasma volume through third space transudation, and a shut-off of erythropoietin elaboration. We suspect that it is the depression of erythropoietin levels below a nadir threshold that precipitates neocytolysis. To confirm this, we studied individuals acclimated to the hypoxic environment at 14,500 feet in the Peruvian Andes. On transport to sea level, we observed the predicted 10-15% fall in red cell mass over seven days, and we found that the neocytolysis was totally prevented by administration of low doses of injected erythropoietin. Also confirming our theories are our studies of hemodialysis patients who suffer a substantial shortening of red cell survival for 7-10 days after erythropoietin therapy is with drawn.

Our current project will expand our understanding of neocytolysis in a number of ways. First we wish to dissect molecular mechanisms underlying the process. We have constructed a theoretic model in which the absence of erythropoietin effects a change in signals from endothelial cells to reticuloendothelial (RE) phagocytes leading to an altered interaction between RE cells and neocytes. Adhesion molecules selectively expressed by neocytes are targeted. Advancing our theory is the fact that the presence of erythropoietin receptors on certain types of endothelial cells is becoming widely acknowledged (see below). We have invested effort in developing assays for a panel of adhesion molecules and determining which are selectively expressed by neocytes and thus are candidate targets for neocytolysis.

In the past year, our results have pointed us to these potential targets: CR1 (CD35), LW antigen (ICAM-4), glycophorin A, wheat germ lectin receptor and CellTracker® Green supravital dye staining. With the perfection of these assays, we are poised to apply them in model systems before, during and after neocytolysis.

A second goal that has emerged from these studies is to establish an in vitro model of neocytolysis. We have found that a cell line of cultured human splenic endothelial cells responds to the withdrawal of erythropoietin by increasing its permeability. We can antigenically distinguish these endothelial cells from a cell line that is unresponsive to changes in erythropoietin. (Similarly, human umbilical vein endothelial cells, aortic endothelial cells and renal glomerular endothelial cells are erythropoietin unresponsive.) Continuation of these studies

will facilitate our dissection of endothelial cell-macrophage-red cell adhesion molecule interactions in neocytolysis.

A third goal of our project is the creation of a human in vivo model of neocytolysis. Now that our adhesion molecule assays are developed, we are beginning to inject volunteer subjects with erythropoietin for variable numbers of weeks, then withdraw the erythropoietin and study the dynamics of red cell changes. This model will allow us to explore the limits of neocytolysis: how high must the red cell mass be raised, how low must erythropoietin be suppressed. We will selectively label different aged cohorts of red cells with ^{13}C and ^{15}N to directly demonstrate the hemolysis of the youngest cells. We will study the changes in expression of adhesion molecules that accompany the process.

Finally, the establishment of a rodent model of neocytolysis would facilitate studies dissecting and manipulating the process. In the last year, we have achieved success in establishing stable high levels of erythropoietin secretion in mice injected with adenovirus vectors carrying the murine erythropoietin gene. We have also incorporated into these vectors a tetracycline response gene, which enables us to turn off erythropoietin production with tetracycline therapy. This development has allowed us to abandon our efforts to use the cumbersome and problematic ex-hypoxic mouse model. Mice rendered polycythemic by erythropoietin gene transfection can have neocytolysis precipitated by tetracycline therapy.

Our current research is making inroads into dissecting the process of neocytolysis, understanding its underpinnings and its limitations. Applications of the knowledge gained will not only apply to improving the safety of space travel, but also to the understanding and treatment of diseases on earth.

**NSBRI RESEARCH PROGRAM
MUSCLE ALTERATIONS AND ATROPHY**

Team Leader:	Schwartz, R. J.	Baylor		
Co-Leader:	Booth, F. W.	UT HSC at Houston		
Schwartz, R. J.	PI	Baylor	GH/IGF-I Transgene Expression on Muscle Homeostasis	B-64
Booth, F. W.	CO-I	UT HSC at Houston		
Demayo, F. J.	CO-I	Baylor		
O'Malley, B. W. Jr.	CO-I	Hopkins/SOM		
Goldberg, A. L.	PI	Harvard	Pharmacological Inhibitors of the Proteasome in Atrophying Muscles	B-65
Baldwin, K. M.	CO-I	UC, Irvine		
Epstein, H. F.	PI	Baylor	Molecular Signaling in Muscle Plasticity	B-69
Booth, F. W.	CO-I	UT HSC at Houston		
Schwartz, R. J.	CO-I	Baylor		
Hamilton, S. L.	PI	Baylor	Activity Dependent Signal Transduction in Skeletal Muscle	B-70
Armstrong, R. B.	CO-I	Texas A&M		
Reid, M. B.	CO-I	Baylor		
Rosenthal, N. A.	PI	Harvard	Molecular Mechanisms Regulating Muscle Fiber Composition Under Microgravity	B-73
Baldwin, K. M.	CO-I	UC, Irvine		
Mosier, D. R.	PI	Baylor	Motoneuron Influences on Muscle Atrophy in Simulated Microgravity Induced Muscle Atrophy	B-75
Appel, S. H.	CO-I	Baylor		
Booth, F. W.	CO-I	UT HSC at Houston		
Schwartz, R. J.	CO-I	Baylor		

MUSCLE ALTERATIONS AND ATROPHY TEAM PROGRAM EXECUTIVE SUMMARY

A current goal of the National Biological Research Institute is to develop countermeasures that allow humans to live and work in microgravity for durations over a year and to minimize readapting to Earth's gravity, and optimize crew safety, well-being, and performance. Exposure to reduced gravity during space travel profoundly alters the loads placed on muscle. Astronauts lose muscle mass and strength while in space. Their ability to work upon reexposure to gravity is thus reduced. This is a safety concern. Individuals with weaker muscles are less likely to survive an unexpected event requiring muscle strength to save life. Although, a large amount of work has been published assessing the efficacy of various exercise modalities the results of these studies can be summarized as follows: virtually all protocols of exercise and/or muscle loading do not prevent muscle atrophy.

The mission of the Muscle Alteration and Atrophy Team is to foster an investigative and highly interactive research program towards understanding basic mechanisms involved with maintenance of muscle mass and muscle function under conditions of long term microgravity. The most effective countermeasure to atrophy of muscle in space flight is likely to be developed from the mechanism producing the atrophy. Without knowing the fundamental molecular mechanisms underlying muscle atrophy, the development of effective countermeasures to muscle atrophy from unloading is less likely to be an optimal countermeasure. Similar wasting of muscles affects people on earth during prolonged bed rest, immobilization, and nerve crush injury, motor neuron diseases and aging. Likewise, knowledge of the mechanisms of muscle atrophy from unloading is likely to provide more effective countermeasures. Most mechanistic information about the cause of muscle atrophy with unloading will be obtained from animals. This is due to: 1) the work schedules of astronauts prohibiting their involvement as subjects, 2) the inability to collect enough muscle from astronauts, and 3) the future necessity to use transgenic animals in spaceflight. Experiments performed in animals will provide guidelines for design of human experiments and will provide molecular/biochemical markers of muscle atrophy

The proposed investigations will shed light on the pathogenesis of muscle atrophy and fiber type conversion at a system, cellular, and molecular level, drawing on the Muscle Team's depth of expertise on the neuromuscular junction (NMJ), excitation-contraction coupling (E-C), muscle gene regulation, and trophic interactions. The objectives of this proposal are to mount effective countermeasures by pharmacological, physiological, and gene-therapeutic means, to blunt muscle atrophy during weightlessness in long term space flight, and to provide important novel spin-back applications to ameliorate related human health problems of muscle wasting on earth. The proposed countermeasures encompass a complementary set of workable short term and longer-term interventions including:

- an emphasis on the growth hormone/insulin-like growth factor axis, and its interaction with physical countermeasures (resistive and concentric exercises);
- pharmacological inhibitors of muscle proteolysis;
- injectable gene-based medicines expressing growth hormone releasing hormone;
- fundamental mechanisms coupling muscle excitation and cellular stretch signaling via calcium fluxes, NFAT-calcineurin, myotonic dystrophy kinase to muscle gene expression;
- Basic helix-loop-helix transcription factors governing muscle fiber type during stimulated microgravity;
- longitudinal assessment of NMJ functions in animals and humans.

RESEARCH AREA:	Muscle Alterations and Atrophy
PRINCIPAL INVESTIGATOR:	Robert J. Schwartz, Ph.D.
ORGANIZATION:	Baylor College of Medicine
PROJECT TITLE:	GH/IGF-I Transgene Expression on Muscle Homeostasis
FUNDING:	\$239,674 (FY 1998); \$232,248 (FY 1999)

PROJECT EXECUTIVE SUMMARY

We propose to test the hypothesis that the growth hormone/ insulin like growth factor-I axis through autocrine/paracrine mechanisms may provide long term muscle homeostasis under conditions of prolonged weightlessness. As a key alternative to hormone replacement therapy, ectopic production of hGH, growth hormone releasing hormone (GHRH), and IGF-I will be studied for its potential on muscle mass impact in transgenic mice under simulated microgravity. Expression of either hGH or IGF-I would provide a chronic source of a growth-promoting protein whose biosynthesis or secretion is shut down in space. Muscle expression of the IGF-I transgene has demonstrated about a 20% increase in hind limb muscle mass over control nontransgenic litter mates. These recent experiments, also establish the utility of hind-limb suspension in mice as a workable model to study atrophy in weight bearing muscles. Thus, transgenic mice will be used in hind-limb suspension models to determine the role of GH/IGF-I on maintenance of muscle mass and whether concentric exercises might act in synergy with hormone treatment. As a means to engineer and ensure long-term protein production that would be workable in humans, gene therapy technology will be used by to monitor muscle mass preservation during hind-limb suspension, after direct intramuscular injection of a genetically engineered muscle-specific vector expressing GHRH. Effects of this gene-based therapy will be assessed in both fast twitch (medial gastrocnemius) and slow twitch muscle (soleus). End-points include muscle size, ultrastructure, fiber type, and contractile function, in normal animals, hind limb suspension, and reambulation.

RESEARCH AREA:	Muscle Alterations and Atrophy
PRINCIPAL INVESTIGATOR:	Alfred Goldberg, M.D.
ORGANIZATION:	Harvard Medical School
PROJECT TITLE:	Pharmacological Inhibitors of the Proteasome in Atrophying Muscles (Also Kenneth Baldwin, Ph.D., UC Irvine, Effects of Unloading on Myosin Content and Isoform Specific Regulation in Skeletal Muscle)
FUNDING:	\$338,945 (FY 1998); \$323,196 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Studies of the Ubiquitin-Proteasome Pathway (Dr. Alfred Goldberg)

It is now clear that the marked loss of muscle mass that occurs with disuse, denervation or in many systemic diseases (cancer cachexia, sepsis, acidosis, various endocrine disorders) is due primarily to accelerated degradation of muscle proteins, especially myofibrillar components. Recent work primarily in Dr. Goldberg's laboratory had suggested that in these diverse conditions, the enhancement of muscle proteolysis results mainly from activation of the Ub-proteasome degradative pathway. In various experimental models of atrophy, rat muscles show a common series of changes indicative of activation of this pathway, including increases in mRNA for Ub and proteasome subunits, content of ubiquitinated proteins, and sensitivity to inhibitors of the proteasome. In order to understand the muscle atrophy seen in weightlessness, Dr. Goldberg's laboratory is collaborating with Dr. Baldwin in studies to define the changes in these parameters upon hind-limb suspension. Related experiments will explore the effects on this degradative system of exercise regimens and also of glucocorticoids, which are known to rise in space personnel and to promote muscle, especially in inactive muscles. The main goals will be: A) to define the enzymatic changes leading to enhanced activity of the Ub-proteasome pathway in inactive muscles upon hind-limb suspension, and the effects on this system of exposure to glucocorticoids or exercise; and (B) to learn whether inhibitors of the Ub-proteasome pathway may be useful in retarding the excessive proteolysis in atrophying muscles.

Using muscle extracts, Dr. Goldberg's group hopes to define the rate-limiting, enzymatic changes that lead to the accelerated Ub-conjugation and protein degradation. They have recently developed cell-free preparations from atrophying rat muscles, in which Ub-conjugation to muscle proteins is increased above control levels. Because these new preparations seem to reproduce the changes occurring *in vivo*, they will analyze in depth extracts from normal and atrophying muscles to compare the activities of the Ub-activating enzyme (E1), the various Ub-carrier proteins (E2s), and Ub-protein ligases (E3s). Recent studies of other types of muscle wasting suggest a very important role in muscle proteolysis of certain ubiquitination enzymes, E2_{14k} and E3 α (i.e. components of the "N-end pathway"). Future studies will focus in understanding their role and test whether they are in fact critical for muscle atrophy *in vivo*. Since weightlessness leads to a specific loss of contractile proteins and to a switching of myosin isoforms, Dr. Goldberg's group will attempt to identify the ubiquitination enzymes specifically involved in myosin degradation both in normal muscle and after hind-limb suspension.

The other important goal of work in Dr. Goldberg's laboratory is to develop pharmacological inhibitors of this pathway (either inhibitors of the ubiquitination steps or of proteasome function) that may be useful in combatting the muscle wasting seen in space personnel. An exciting recent

development has been the identification of inhibitors of the 20S proteasome (peptide aldehydes, lactacystin) that can enter cells and reduce proteolysis selectively. A number of inhibitors have been shown to block the Ub-proteasome pathway in incubated rat muscles, including the increased degradation in atrophying muscles. Because of their potential as therapeutic agents, Dr. Goldberg's laboratory will study in depth their effects on protein turnover and their physiological consequences on isolated muscle cells. The eventual goal will be to test in intact rats the capacity of such inhibitors to reduce the rapid loss of muscle protein seen with hind-limb suspension and glucocorticoid treatment.

Specific Aims of Studies of the Ub-Proteasome System:

A. To determine how the activity of Ub-proteasome pathway is altered during muscle atrophy due to hind-limb suspension and related conditions.

1. To evaluate the muscle's content of Ub and Ub-protein conjugates and the level of expression of several genes, which have been shown to increase in other types of muscle wasting, including the polyUb gene, the Ub-carrier protein, E2_{14k}, and several 20S proteasome subunits. These studies will utilize Northern-blot analysis to follow the levels of these specific mRNAs and Western-blot analysis to assay the corresponding proteins.

2. To compare the capacity of extracts of normal and atrophying muscles to covalently link Ub to muscle proteins, generally as well as to individual myofibrillar proteins (e.g. specific myosin isoforms). These studies should lay the basis for subsequent work in defining the rate-limiting biochemical changes that accelerate Ub-dependent protein breakdown.

3. To define the biochemical basis for changes in the atrophying muscle found in the studies by Dr. Baldwin's laboratory concerning the effects of increased and decreased glucocorticoids and of administering intermittent exercise regimens.

B. How do the levels of Ub-conjugating enzymes change during accelerated proteolysis after hind-limb suspension? Prior studies indicate that Ub-conjugation is the rate-limiting step in the degradative pathway. These studies will compare cell-free extracts from normal rat muscles with muscles undergoing atrophy due to hind-limb suspension or to treatment with glucocorticoids. The goals of Dr. Goldberg's group will be:

1. To compare the abundance of the Ub-activating enzyme (E1) using an anti-E1 antibody and the amount of E1 activity using assays of Ub-thiolester formation.

2. To determine the abundance and activity of the various Ub-carrier proteins (E2s) using methods Dr. Goldberg's laboratory has recently developed a method to separate the major E2s in muscle extracts. E2 activity will be examined by the ability to form thiolester linkages with ¹²⁵I-Ub. A major goal will be to identify any E2s that increase specifically in association with the enhanced proteolysis during hind-limb suspension or glucocorticoid-induced wasting.

3. To define which Ub-protein ligases (E3) are important in the ubiquitination of the bulk of muscle proteins. A major goal will be to assay E3 α content in control muscles and ones after hind-limb suspension or treatment with glucocorticoids. Techniques are being developed to affinity-purify other muscle E3s as well, especially those responsible for Ub-conjugation to myosin and other myofibrillar proteins. E3 levels will then be compared in the extracts of normal and atrophying muscles.

4. To clarify the importance of the "N-end pathway" for ubiquitination (i.e. the enzymes E2_{14k} and E3 α) in proteolysis in the atrophying muscles. The best characterized enzyme system for ubiquitination of proteins is the so-called "N-end pathway," but its *in vivo* function has long been unclear. This enzyme system has generally been believed to catalyze only the degradation of certain highly abnormal proteins with large unblocked N-terminal residues. However, Solomon and Goldberg recently made the unexpected discovery that in normal rabbit muscles, ubiquitination of most soluble proteins is by E2_{14k} and E3 α , and that activation of this system is primarily responsible for increased ubiquitination in muscle extracts in cancer cachexia, sepsis, acidosis, and hyperthyroidism. Its importance in the degradation of different muscle proteins after hind-limb suspension or glucocorticoid-treatment will therefore be studied in depth in cell-free extracts. Competitive dipeptide inhibitors of E3 α , are available and will be used to measure the specific contribution of this E3 to muscle proteolysis. Finally, studies with mutant mice lacking E2_{14k} will test critically the functional importance of this system *in vivo*.

C. To test whether pharmacological inhibitors of the Ub-proteasome pathway may be useful in retarding muscle proteolysis and combatting muscle wasting. Recent studies have identified several types of inhibitors of the proteasome (e.g. peptide aldehydes and lactacystin) that can retard protein breakdown in cells, including skeletal muscle. Because of their potential as therapeutic agents, Dr. Goldberg's laboratory will systematically test the capacity of different proteasome inhibitors to selectively reduce the breakdown of different classes of muscle proteins and to promote an accumulation of proteins in cultured muscle cells. Eventually, the most effective agents will be studied *in vivo* for their ability to reduce the loss of muscle proteins upon hind-limb suspension and glucocorticoid treatment.

Effects of Unloading on Myosin Content and Isoform Specific regulation in Skeletal Muscle (Dr. Kenneth M. Baldwin)

Previous studies clearly show that the slow (type I) myosin heavy chain (MHC) and other contractile protein isoforms are down regulated as part of the atrophy process that occurs in antigravity muscles of mammals (rodents) in response to spaceflight and/or the ground-based model of hindlimb unloading. However, relatively little is known concerning the regulation of this process at the subcellular/molecular level. The primary objective of the proposal is to use the rodent hindlimb suspension model, in both the presence and absence of a) resistance training paradigms; and b) interventions altering the action of hormones known to regulate protein turnover such as glucocorticoids, in order to examine the regulation of type I MHC expression at three distinct, but interrelated levels of investigation. These include: 1) determining quantitative changes in MHC protein pools and altered protein synthesis rates for fast and slow MHC isoforms (Baldwin Team objective); 2) ascertaining the intrinsic level of activity of the ubiquitin-proteasome system, including changes in conjugating enzyme activity including E1, E2, and E3, as well as determining ubiquitin and ubiquitin-protein conjugate levels, and proteolytic activity of the proteasome complex [Goldberg Team objective]; and 3) determining the transcriptional control of the slow type I MHC gene by measuring nuclear run-on capacity (as well as activity of a transfected type I promoter construct) coupled with assessing the relative expression of a battery of transcription factors (e.g., transcriptional enhancing factor-1 (TEF-1), myogenin, Myo-D, and other putative factors) that interact with cis-regulatory elements in the type I MHC promoter (Baldwin Team objective).

To achieve these objectives and to test six working hypotheses (as defined in the original proposal), a series of experiments will be performed using adult female rats with initially stable

body and muscle mass (i.e., non-growing muscles). In the first series of experiments (designated as phase I), groups of rats will be studied after one, two and four weeks of suspension in order to determine the rates of protein synthesis for MHC isoforms, as well as the altered functional activity the ubiquitin-proteasome system. Included in this series will be analyses including its specificity for degrading slow type I and fast type IIb native myosin in the context of the atrophy response. The experiments at the four-week time-point will be performed in order to identify markers of altered transcriptional activity of the type I MHC gene. In the second series (phase #2) experiments will be performed to block the interactive effects of glucocorticoids with its receptor complex in the cascade of events causing muscle atrophy. Whereas, subsequent experiments (phase #3) will utilize a rodent heavy resistance training paradigm as a countermeasure for the atrophic response. Collectively, these experiments will more clearly define the role of several interactive processes in the control of muscle protein turnover along with associated transcriptional factors specifically involved in the control of slow MHC gene expression. The latter will be used as a marker protein for regulation of muscle atrophy. Also, these experiments will further delineate the role of specific hormonal and activity factors in the induction of atrophy and/or the prevention of atrophy during states of unloading.

RESEARCH AREA:	Muscle Alterations and Atrophy
PRINCIPAL INVESTIGATOR:	Henry F. Epstein, M.D.
ORGANIZATION:	Baylor College of Medicine
PROJECT TITLE:	Molecular Signaling in Muscle Plasticity
FUNDING:	\$109,500 (FY 1998); \$112,128 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Extended spaceflight under microgravity conditions leads to significant atrophy of weight-bearing muscles. Atrophy and hypertrophy are the extreme outcomes of the high degree of plasticity exhibited by skeletal muscle. Stimuli which control muscle plasticity include neuronal, hormonal, nutritional, and mechanical inputs. The mechanical stimulus for muscle is directly related to the work or exercise against a load performed. Little or no work is performed by weight-bearing muscles under microgravity conditions. A major hypothesis is that focal adhesion kinase (FAK) which is associated with integrin at the *adherens* junctions and costameres of all skeletal muscles is an integral part of the major mechanism for molecular signaling upon mechanical stimulation in all muscle fibers. Additionally, we propose that myotonic protein kinase (DMPK) and dystrophin (DYSTR) also participate in distinct mechanically stimulated molecular signaling pathways that are most critical in type I and type II muscle fibers, respectively. To test these hypotheses, we will use the paradigms of hindlimb unloading and overloading in mice as models for microgravity conditions and a potential exercise countermeasure, respectively, in mice. We expect that FAK loss-of-function will impair hypertrophy and enhance atrophy in all skeletal muscle fibers whereas DYSTR and DMPK loss-of-function will have similar but more selective effects on Type II and Type I fibers, respectively. Gene expression will be monitored by muscle-specific creatine kinase M promoter-reporter construct activity and specific mRNA and protein accumulation in the soleus (type I primarily) and plantaris (type II primarily) muscles. With these paradigms and assays, the following Specific Project Aims will be tested in genetically altered mice: 1) identify the roles of DYSTR and its pathway; 2) evaluate the roles of the DMPK and its pathway; 3) characterize the roles of FAK and its pathway and 4) genetically analyze the mechanisms and interactions between the FAK, DYSTR, and DMPK-associated pathways in single and specific combinations of mutants. The identification of potential signaling mechanisms may permit future development of pharmacological countermeasures for amelioration and prevention of the microgravity-induced atrophy in extended spaceflight, and the analysis of both overloading and unloading paradigms may provide further support for development of exercise-based countermeasures. Understanding the basic mechanisms of molecular signaling in muscle plasticity may aid our understanding and treatment of skeletal muscle atrophy not only in spaceflight but in similar problems of the aging population, in prolonged bed rest, and in cachexia associated with chronic disease.

RESEARCH AREA:	Muscle Alterations and Atrophy
PRINCIPAL INVESTIGATOR:	Susan L. Hamilton, Ph.D.
ORGANIZATION:	Baylor College of Medicine
PROJECT TITLE:	Activity Dependent Signal Transduction in Skeletal Muscle
FUNDING:	\$118,152 (FY 1998); \$122,178 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The overall goals of this project are: 1) to define the initial signal transduction events whereby the removal of gravitational load from antigravity muscles, such as the soleus, triggers muscle atrophy, and 2) to develop countermeasures to prevent this from happening. Our rationale for this approach is that, if countermeasures can be developed to regulate these early events, we could avoid having to deal with the multiple cascades of events that occur downstream from the initial event. One of our major findings is that hind limb suspension causes an early and sustained increase in intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$). In most cells the consequences of changes in $[\text{Ca}^{2+}]_i$ depend on the amplitude, frequency and duration of the Ca^{2+} signal and on other factors in the intracellular environment. We propose that muscle remodeling in microgravity represents a change in the balance among several Ca^{2+} regulated signal transduction pathways, in particular those involving the transcription factors NFAT and NF κ B and the pro-apoptotic protein BAD. Other Ca^{2+} sensitive pathways involving PKC, ras, rac, and CaM kinase II may also contribute to muscle remodeling.

Mechanisms by which hind limb suspension could alter the concentration of resting Ca^{2+}

In the 02 year of NSBRI funding our goals were to determine both the cause and the functional consequences of the rise in resting Ca^{2+} . Muscle inactivity increases the production of ROS (Hisao *et al*, *Am. J. Physiol.* 28: E839-E844, 1993) and decreases nitric oxide (NO) production (Tidball *et al*, *Am.J. Physiol.* 275: C260-C266, 1998). We demonstrated that, in muscle, there is a delicate balance between ROS, NO and calmodulin (CaM) regulation of Ca^{2+} leak via the skeletal muscle Ca^{2+} release channel (RYR1). Both oxidants and Ca^{2+} free CaM activate RYR1, but their interactions with the channel are mutually exclusive. When cytoplasmic Ca^{2+} rises, Ca^{2+} CaM helps to shut the channel, but this effect can be blocked by channel oxidation and, conversely, both Ca^{2+} CaM and Ca^{2+} free CaM partially protect RYR1 from oxidation. NO blocks oxidative activation of RYR1, has no effect on Ca^{2+} CaM inhibition of the channel, but prevents the activation of the channel by Ca^{2+} free CaM. The net effect of conditions that increase ROS but decrease NO would be prolonged opening of RYR1 and increased cytoplasmic Ca^{2+} . These findings have led to our current working hypothesis that the increase in resting Ca^{2+} in skeletal muscle during hind limb suspension arises, at least in part, from increased SR Ca^{2+} leak. Decreases in SR luminal Ca^{2+} could also activate store operated Ca^{2+} influx pathways. Mechanisms to regulate $[\text{Ca}^{2+}]_i$ will be investigated in the coming year.

Effects of sustained increases in $[\text{Ca}^{2+}]_i$ on muscle function

Increases in intracellular Ca^{2+} can alter a variety of signal transduction pathways and the actual pathways altered will depend on the amplitude, frequency and duration of the Ca^{2+} signal. Our studies show a sustained increased $[\text{Ca}^{2+}]_i$ after about 3 days of hind limb suspension. We are exploring the possibility that the increased $[\text{Ca}^{2+}]_i$ activates pro-apoptotic pathways leading to loss of myonuclei and muscle remodeling. Activation of apoptotic pathways has previously been

suggested to contribute to hind limb suspension induced muscle remodeling (Allen *et al*, Am. J. Physiology 273: C579-C587, 1997). In B cells low sustained increases in intracellular Ca^{2+} have been shown to activate NFAT while large Ca^{2+} transients activate NF κ B and JNK transcription factors (Dolmetsch *et al*, Nature 386:855-858, 1997). For the NFAT pathway, the increases in resting Ca^{2+} activate calcineurin and this dephosphorylates NFAT, allowing it to translocate to the nucleus. The transcriptional events activated by NFAT depend on the status of a number of other signal transduction pathways, but NFAT activation can increase the transcription of several pro-apoptotic genes. We have identified the presence of NFAT in skeletal muscle and have shown that cytoplasmic levels of NFAT decrease with hindlimb suspension. We have not, however, yet shown that this is due to translocation to the nucleus. We are currently assessing the nuclear translocation of NFAT with hind limb suspension.

In addition to its effects on NFAT, calcineurin can dephosphorylate the apoptotic protein BAD (Wang *et al*, Science 284:339-343, 1999), leading to its interaction with the anti-apoptotic proteins Bcl-2 and Bcl-xl. We have detected BAD in skeletal muscle and are currently attempting to assess whether hind limb suspension alters its phosphorylation status. We have, however, shown that there is a significant increase in cytosolic BAD with 14 days of hind limb suspension. We are currently assessing if this is due to new protein or decreased breakdown. An anti-apoptotic protein that can interact with Bcl-2 is smn (Iwahashi *et al*, Nature 390:413-417, 1997), the protein missing in spinal muscular atrophy. Our preliminary studies suggest a decrease in cytoplasmic smn with hind limb suspension. We also have preliminary evidence for a decrease in cytosolic I κ B.

Skeletal muscle specific FKBP12 deficient mice as models for effects of microgravity

FKBP12 is an endogenous modulator of both RYR1 and calcineurin. FKBP12 inhibits calcineurin and stabilizes a closed state of RYR1. The absence of FKBP12 is likely to lead to increases in both resting Ca^{2+} and calcineurin activity. If calcineurin activation produces muscle atrophy, the knockout of FKBP12 may mimic the effects of hind limb suspension on skeletal muscle. An animal model of muscle atrophy would be extremely useful for drug intervention. We have previously prepared FKBP12 deficient mice. Skeletal muscle force production was markedly diminished but, unfortunately these animals die of cardiac hypertrophy. To avoid the cardiac complications we are in the process of creating a skeletal muscle specific knockout of FKBP12 using the Cre-loxP system. To generate the skeletal muscle restricted FKBP12-deficient mice, two transgenic mouse lines will be used, the skeletal muscle specific Cre mouse and the FKBP12-loxP mouse. In collaboration with Dr. Weinian Shou, we now have both the FKBP12-loxP targeted ES cell lines and the linear myogenin-Cre construct. We anticipate having the skeletal muscle specific FKBP12 knockout mice within the next 6 months. We will compare soleus muscle from these mice to that obtained from hind limb suspended mice to determine if the mechanisms of atrophy are related.

Summary of Progress in 02 year

In the 02 year of NSBRI funding we have demonstrated that: 1) there is an early and sustained increase in intracellular Ca^{2+} , 2) an increase in oxidants or a decrease in NO can increase resting Ca^{2+} , 3) hind limb suspension alters NF κ B and possibly NFAT signaling in skeletal muscle, 4) NF κ B mediates proteolytic signaling in muscle by upregulating components of the ubiquitin/proteasome pathway, and 5) hind limb suspension increases the amount of the pro-apoptotic protein, BAD and decreases anti-apoptotic protein, SMN. In addition to this, we are well on our way to producing skeletal muscle specific FKBP12 deficient mice. These will be

used to test our hypothesis that increased cytoplasmic Ca^{2+} activates calcineurin, producing effects similar to those found with hind limb suspension.

In summary, we propose that skeletal muscle adaptation to microgravity represents an increase in both calcineurin and ubiquitin/proteasome activity and a shift in the balance between pro-apoptotic and anti-apoptotic pathways. We propose to test this hypothesis during the 03 year. The demonstration of the activation of these pathways by hind limb suspension will allow us then to design and test new countermeasures.

RESEARCH AREA:	Muscle Alterations and Atrophy
PRINCIPAL INVESTIGATOR:	Nadia A. Rosenthal, Ph.D.
ORGANIZATION:	Harvard Medical School
PROJECT TITLE:	Molecular Mechanisms Regulating Muscle Fiber Composition Under Microgravity
FUNDING:	\$134,384 (FY 1998); \$139,162 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The overall goal of this project is to reveal the molecular mechanisms underlying the selective and debilitating atrophy of specific skeletal muscle fiber types that accompanies sustained conditions of microgravity. Since little is currently known about the regulation of fiber-specific gene expression programs in mammalian muscle, elucidation of the basic mechanisms of fiber diversification is a necessary prerequisite to the generation of therapeutic strategies for attenuation of muscle atrophy on earth or in space.

Vertebrate skeletal muscle development involves the fusion of undifferentiated mononucleated myoblasts to form multinucleated myofibers, with a concomitant activation of muscle-specific genes encoding proteins that form the force-generating contractile apparatus. The regulatory circuitry controlling skeletal muscle gene expression has been well studied in a number of vertebrate animal systems. The goal of this project has been to achieve a similar level of understanding of the mechanisms underlying the further specification of muscles into different fiber types, and the role played by innervation and physical activity in the maintenance and adaptation of different fiber phenotypes into adulthood.

Our recent research on the genetic basis of fiber specificity has focused on the emergence of mature fiber types and have implicated a group of transcriptional regulatory proteins, known as E proteins, in the control of fiber specificity. The restriction of E proteins to selected muscle fiber types is an attractive hypothetical mechanism for the generation of muscle fiber-specific patterns of gene expression. To date our results support a model wherein different E proteins are selectively expressed in muscle cells to determine fiber-restricted gene expression. These studies are a first step to define the molecular mechanisms responsible for the shifts in fiber type under conditions of microgravity, and to determine the potential importance of E proteins as upstream targets for the effects of weightlessness.

In the past year we have determined that the expression of E Proteins is restricted to specific fiber types by post-transcriptional mechanisms. By far, the most prevalent mechanism of cellular control for achieving post-transcriptional regulation of gene expression is selective proteolysis through the ubiquitin-proteasome pathway. Steady-state levels of HEB message are similar in all fast and slow skeletal muscle fiber types, yet the protein is restricted to Type IIX fibers. HEB appears to be a nodal point for regulating fiber-specific transcription, as expression of the transcription factor is regulated at the post-transcriptional level. It is not clear at present whether the regulation is at the level of protein synthesis or degradation. We are now poised to evaluate the biological role of ubiquitination in fiber specific-gene expression by controlling the post-transcriptional expression of E Proteins. The use of metabolic labelling and pharmacological inhibitors of the ubiquitin pathway will be used to identify the mode of regulation of the Type IIX expression pattern. The potential role of specific kinases in effecting the restriction of HEB expression will be examined by using both inhibitors and activators. The results of these studies

will provide the necessary information to evaluate the biological role of E proteins in controlling fiber type transitions, and in potentially attenuating the atrophic effects of microgravity conditions.

We have also recently shown that ectopic expression of the HEB protein transactivates the Type IIX-specific skeletal α -actin reporter. The 218 bp skeletal α -actin promoter drives transgene expression solely in mature Type IIX fibers. A mouse also carrying the transgene MLC1/HEB (which ectopically expresses the E Protein HEB in Type IIB fibers) forces expression of the skeletal α -actin reporter gene in Type IIB fibers.

We can now dissect the composition of this fiber-specific *cis*-element. The skeletal α -actin promoter is quite compact and has been extensively characterized *in vitro* for activity and binding factors. The single E box may act as a binding target of myogenic factor/HEB heterodimer to allow for IIX expression. The HEB transcription factor may recognize either the precise flanking sequences of the E Box, or perhaps interacting with other proteins bound nearby, and activating expression in Type IIX fibers. This E box will be both ablated, and alternatively, as ablation may well destroy any muscle-specific transcriptional activity, flanking sequences substituted with those surrounding the E box (E1) of the myogenin promoter. Modification of fiber-specific transgene expression will be tested in transgenic mice. The results of these studies will provide basic information on the regulatory circuitry underlying fiber specificity, and will form the basis for building appropriate transgenic regulatory cassettes to effect fiber transitions in subsequent experimental manipulations on unweighted muscles.

RESEARCH AREA:	Muscle Alterations & Atrophy
PRINCIPAL INVESTIGATOR:	Dennis R. Mosier, M.D., Ph.D.
ORGANIZATION:	Baylor College of Medicine
PROJECT TITLE:	Motoneuron Influences on Muscle Atrophy in Simulated Microgravity Induced Muscle Atrophy
FUNDING:	\$116,800 (FY 1998); \$119,603 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Many alterations in motor unit structure and function occur with exposure to microgravity during spaceflight, and could lead to impaired motor performance. While much work is ongoing to ascertain the nature of biochemical, structural, and physiological changes occurring in muscle fibers, comparatively little attention has been paid to the changes reported in motoneuron terminals at the skeletal neuromuscular junction, and in motoneuron cell bodies, during exposure to microgravity. It is highly unlikely that these changes, whether they occur independently or secondary to changes in the innervated muscle fibers, are without consequences for the regulation of motor unit function. Accordingly, the central hypothesis of this study is that alterations in motoneuron structure and function occur during the process of microgravity-induced muscle atrophy, and that these alterations significantly influence muscle dysfunction, adaptation, and recovery from atrophy induced by microgravity. These changes may be manifested as early structural and functional alterations in the distal motoneuron terminal, in addition to alterations in motoneuron activity produced by changes in stretch reflexes and supraspinal pathways. Initiation of alterations in motoneuron terminals may be influenced by retrograde signals from muscle which induce, as an early event, changes in intracellular calcium and transmitter release.

To begin to address these hypotheses, a combination of electrophysiologic assays of transmitter release at neuro-muscular junctions, coupled with electron microscopic assays of junctional remodelling, synaptic vesicles, and intraterminal calcium, is being used to define quantitatively the nature, extent, and possible significance of changes in motoneuron terminals occurring in a mouse model of unloading-induced muscle atrophy. This comprehensive approach is being further extended to determine motoneuronal responses to treatments designed to ameliorate muscle atrophy induced by unloading, and to test the hypothesis that one or more activity-dependent factors released locally by skeletal muscle may induce alterations in the presynaptic terminals of innervating motoneurons. The data obtained from this study will be useful in defining the anatomic and physiologic consequences to motoneurons of manipulations which induce muscle atrophy, and will aid in designing further experiments to determine the mechanisms influencing motor unit dysfunction occurring during space travel. Information from this study will be of value to the design and refinement of countermeasures aimed at ameliorating the deleterious effects of microgravity on human motor performance. The results of this work may also provide new insights into important clinical problems such as mechanisms influencing muscle and motor nerve injury encountered in critical care settings, motoneuron dysfunction in devastating neurodegenerative illnesses such as amyotrophic lateral sclerosis, and the design of therapies to retard or prevent muscle atrophy produced by disuse or spinal cord injury.

**NSBRI RESEARCH PROGRAM
NEUROVESTIBULAR ADAPTATION**

Team Leader:	Oman, C. M.	MIT		
Shelhamer, M. J.	PI	Hopkins/SOM	Context-Specific Adaptation Of Gravity-Dependent Vestibular Reflex Responses	B-80
Goldberg, J.	CO-I	Baylor		
Minor, L. B.	CO-I	Hopkins/SOM		
Paloski, W. H.	CO-I	NASA JSC		
Young, L. R.	CO-I	MIT		
Zee, D. S.	CO-I	Hopkins/SOM		
Oman, C. M.	PI	MIT	Visual Orientation in Unfamiliar Gravito-Inertial Environments	B-83
Beall, A. C.	CO-I	MIT		
Howard, I. P.	CO-I	York University		
Shebilske, W. L.	CO-I	Wright University		
Taube, J. S.	CO-I	Dartmouth College		
Wall, C. C.	PI	Harvard	Advanced Techniques for Assessment of Postural and Locomotor Ataxia, Spatial Orientation and Gaze Stability	B-86
Bloomberg, J. J.	CO-I	NASA JSC		
Cohen, H. S.	CO-I	Baylor		
Krebs, D. E.	CO-I	Harvard		
Oddsson, L.	CO-I	Boston University		
Oman, C. M.	CO-I	MIT		
Raphan, T.	CO-I	Brooklyn College		
Young, L. R.	CO-I	MIT		

NEUROVESTIBULAR ADAPTATION TEAM PROGRAM EXECUTIVE SUMMARY

The NSBRI neurovestibular adaptation research program provides a framework for space human and animal physiological and behavioral research leading to the development of new scientifically based countermeasures against the neurovestibular problems associated with long duration spaceflight as well for vestibular patients.

Our current research portfolio of three projects address the following questions:

1. Can gravireceptor dependent motor responses be pre-adapted (conditioned) in context-specific ways, so astronauts can rapidly transition between alternative environments, i.e. between terrestrial, orbital, artificial, and planetary gravity, with minimal performance impairment? (Dr. Mark Shelhamer, Johns Hopkins University and 7 co-investigators)
2. How do visual and gravireceptor cues influence human orientation perception? How is our sense of direction neurally coded in 0-G? Does 1-G training in simulated "agravic" real or virtual environments improve three dimensional spatial memory and performance in orientation and navigation tasks? (Dr. Charles Oman, MIT, and 5 co-investigators)
3. What causes the profound impairment of posture, gaze, and locomotion stability seen in vestibular patients and many returning astronauts, and how can it be quantified? (Dr. Conrad Wall, Harvard Medical School/Massachusetts Eye and Ear Infirmary, and 6 co-investigators)

Also, a one year collaborative "synergy" pilot project with the Cardiovascular team is now underway. One of the goals is to demonstrate that visually induced illusions of static tilt produce cardiovascular regulatory responses (Dr. Craig Ramsdell, Harvard Medical School and 6 co-investigators).

Research highlights of programmatic significance are:

Project 1: Adaptation to weightlessness and readaptation to Earth's, planetary, or artificial gravity requires adaptive changes in many of the body's sensory-motor reflexes. Normally, adaptation to a series of new environments occurs sequentially, and crew members experience some degree of disorientation and ataxia until the process is complete. Can vestibular reflexes be pre-conditioned in context specific ways, so that adaptation occurs much more rapidly, or so the appropriate pre-adapted responses are immediately invoked? If so, what are the essential characteristics of the conditioning stimulus? Experimental evidence has been found for context-specificity in human saccades and in the linear vestibulo-ocular reflex (LVOR) eye movement responses to translatory movements of the body. Saccade gain in a target following task can be reprogrammed to depend on vertical eye position, or on head roll angle. Horizontal LVOR gain can be altered to depend on head pitch angle. (However, context specific changes could not be induced when head roll angle provided the context cue, perhaps because the stimulus and context cues are more difficult to distinguish.) In a squirrel monkey animal model, we have also found related preliminary evidence for stimulus frequency specific gain adaptation in the LVOR. Finally, we have found the human vestibulo-colic reflex adapts much more quickly to artificial increases in head inertia after several practice sessions on consecutive days.

Project 2: Astronauts report inversion and visual reorientation illusions, EVA acrophobia, and 3D spatial memory problems when moving between modules which can impair performance, and sometimes trigger space motion sickness. The design of ground based simulators and training experiences could undoubtedly be improved if we could better understand better what visual scene attributes determine perceived orientation in 3 dimensions, the role of experience in 3D spatial memory, and more about the physiology of our orientation sense in 3 dimensions. During the past year, we have shown that compelling visual scenes can produce much larger illusions of subjective tilt than had previously been thought. For example, many supine subjects feel erect which viewing an environment which is visually upright with respect to their bodies, and resulting in an interesting "levitation" sensation if subjects elevate their arms. A correlation between tilt illusion susceptibility and age has been found. (This finding has practical application in 1-G. It suggests, for example, that placing pictures or other polarized objects on the walls of stairways could make older people less prone to falls.) If the scene is sufficiently polarized and realistic, e.g. produced using an inclined mirror, the illusion of tilt can produce large transient cardiovascular changes, further evidence of visual/vestibular-autonomic coupling to the cardiovascular regulatory system. The strength of tilt illusions also depends on the "polarity" objects in the scene. This attribute depends both an object's familiar orientation in 1-G, and its means of physical support. We have also studied 3D spatial memory in a task analogous to that confronting astronauts in the node module of a space station. Though the experiments were performed in 1-G, spatial memory and learning was not strongly dependent on the gravitational orientation of the subject, nor on whether a virtual or real training environment was used. Instead, performance depended more on the mental image and mnemonic strategies used, and correlated significantly with performance on standard paper-and-pencil tests of 2 and 3 dimensional mental rotation ability, and visual field dependence. Lastly, we have studied the limbic coding of 3D orientation in an animal model in parabolic flight. Head direction cells in the anterior thalamic nuclei of rats showed normal allocentric responses in zero g and hypergravity, except that reversals in cell preferred direction have were seen when the animal locomoted on the ceiling. We believe it is the neural correlate of visual reorientation illusions reported by humans in similar situations. The finding also helps explain rat place cell results recently obtained on the Neurolab Spacelab mission by McNaughton and colleagues.

Project 3: In addition to inflight neurovestibular difficulties, astronauts returning from long duration missions typically report postflight problems with standing, walking, and gaze stabilization. The longer a crewmember flies, the more profound and long lasting the deficits usually are. We are currently developing a number of new methods for measuring gaze, head and body stability in quantitative, parametric fashion in normals and vestibular patients. Two of our most important findings this year derive from the concepts of "head fixation distance" and "ideal trajectory analysis" as applied to normal movement: First, we have found that during normal walking, the head pitches in phase with gait so it aimed consistently at a point which we call the "Head Fixation Distance", located about one meter ahead, and independent of gaze fixation distance. We believe this is partly the result of a linear vestibulo-collic reflex, responding to the vertical kinematic component of walking. When looking at a point far away during normal walking, the angular vestibulo-ocular reflex provides appropriate ocular stabilization. Looking near invokes the vertical LVOR, which may be affected by spaceflight. Computerized Dynamic Visual Acuity (DVA) testing on a treadmill presumably invokes both gaze stabilization mechanisms. This year, we obtained preliminary data showing changes in DVA after acute vestibular nerve section, and differences in the horizontal linear vestibulo-collic reflex of chronic vestibular patients as compared to normals. Second, by "ideal trajectory analysis" (ITA, which yields a measure of kinematic deviation from an ideal sinusoidal body center of mass trajectory), and analyzing data from normals and patients perform a repeated

“stepping up” task, we can statistically discriminate between normals and patients. ITA is being used to evaluate the effects of vestibular rehabilitation in patients, and may also prove useful for assessing the performance and rehabilitation of returning astronauts. Floquet Multiplier analysis is also being evaluated, using a more generalized technique. We also believe it is also important to study the recovery to specific perturbations of the gait cycle. This year, we have also developed a safe new perturbation technique which quickly moves one foot forward and laterally 200 msec. after heelstrike. Normals show an overshoot of the line of march of nearly the same amplitude as the perturbation, but recovery in four steps and about 0.75 sec.

By next year, several concepts and techniques under development by the individual projects may be suitable for transition to the NASA countermeasures evaluation/implementation process. These include a stepping test and associated method for center-of-mass trajectory analysis; a gait perturbation technique, methods for measuring head and eye fixation distances in returning astronauts, and computerized methods for assessing and improving 3D spatial memory and preflight visual orientation training. Methods for training head fixation distance and for altering the gain of the vestibular eye and neck reflexes in context specific ways are also under study.

Progress in each of the three core projects during the first sixteen months are detailed in separate Project reports. The body of this Program report outlines our team strategy, problems, plans and priorities. For readers who do not have time to read the individual reports, it provides an overview of results of the second year accomplishments of the individual projects. Our contribution to the NASA Critical Path project, our Synergy project, education and outreach projects and other collaborative activities are also summarized. The report concludes with recommendations for the third year and beyond.

RESEARCH AREA:	Neurovestibular Adaptation
PRINCIPAL INVESTIGATOR:	Mark J. Shelhamer, Sc.D.
ORGANIZATION:	Johns Hopkins School of Medicine
PROJECT TITLE:	Context-Specific Adaptation of Gravity-Dependent Vestibular Reflex Responses
FUNDING:	\$294,496 (FY 1998); \$321,114 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Stabilization of the eyes and head during body movements is important for maintaining balance and keeping the images of objects stationary on our retinas. Impairment of this ability can lead to disorientation and reduced performance in sensorimotor tasks such as piloting of spacecraft. In the absence of a normal earth gravity field, the dynamics of head stabilization, and the interpretation of vestibular signals that sense gravity and linear acceleration, are subject to change. Transitions between different gravito-inertial force environments – as during different phases of space flight – provide an extreme test of the adaptive mechanisms that maintain these reflexive abilities. It is vitally important to determine human adaptive capabilities in such a circumstance, so that we can know to what extent the sensorimotor skills acquired in one gravity environment will transfer to others. Our work lays the foundation for understanding these capabilities, and for determining how we can aid the processes of adaptation and readaptation.

An integrated set of experiments addresses this issue. We use the general approach of adapting some type of reflexive eye movement (saccades, the angular vestibulo-ocular reflex (AVOR), the linear vestibulo-ocular reflex (LVOR)), or the vestibulo-colic reflex (VCR), to a particular change in gain or phase in one condition of gravito-inertial force, and adapting to a different gain or phase (or asking for no change) in a second gravito-inertial force condition, and then seeing if the gravito-inertial force itself – the context cue – can recall the previously learned adapted responses. The majority of the experiments in the laboratory use the direction of vertical gaze or the direction of gravity (head tilt) as the context cue. This allows us to study context-specificity in a ground-based setting. One set of experiments, to be performed in parabolic flight (see below), specifically uses the magnitude of gravito-inertial force as a context cue. This is a much better analog of the situation encountered in space flight.

Various experiments investigate the behavioral properties, neurophysiological basis, and anatomical substrate of context-specific learning mechanisms. We use otolith (gravity) signals as the contextual cue for switching between adapted states of the saccadic system, the angular and linear vestibulo-ocular reflexes, and the VCR. (By LVOR we mean the oculomotor response – horizontal, vertical, and torsional – to linear translation of the head and body.) We are studying the effect of context on adaptation of saccade gain, phase and gain of the AVOR and LVOR, on ocular counterrolling (OCR) in response to static head tilt, and on head/neck reflexes (VCR) in response to rotation in different orientations. Such research is particularly germane to potential problems of postural and oculomotor control upon exposure to different gravitational environments.

The knowledge gained from these studies will help us to design potential pre-adaptation strategies to assist flight crews in making transitions between different gravito-inertial force situations, and can provide design data for spacecraft facilities (artificial gravity, exercise centrifuge) by delineating the limits of human adaptive capabilities.

In our work over the past two years, we have found increasingly solid evidence for context-specificity in human saccades and in the human LVOR in response to translation. An upcoming series of parabolic flight experiments on NASA's KC-135 aircraft is planned for the summer of 1999. These experiments will examine the use of instantaneous gravity level (alternating periods of 0 g and 1.8 g) as a context cue for adapted saccadic eye movements. Saccades, which are rapid eye motions that move the eyes between targets, can be adaptively altered by presenting a target, then moving that target to a new location before the eyes can get to its first location. After several trials, an adaptive sensorimotor mapping takes place, so that the eyes move directly to the new target location when presented with the original target (for example, the gain can be increased so that 20 deg saccades are made when a 15 deg target is presented, or the gain can be decreased so that 10 deg saccades are made when a 15 deg target is presented). Pilot experiments in our laboratory at Johns Hopkins have been made in preparation for the parabolic flights. We have successfully used vertical eye position as a context cue for this response, so that saccades are increased in gain (amplitude) when the subject looks upward, and decreased in gain when the subject looks down. Further experiments confirmed that head orientation with respect to gravity (tilted to the right or to the left) can also serve as a context cue; saccade gain was increased with the head tilted to the right and vice versa. This is strong evidence for the ability to use gravity as a context cue for saccades. Laboratory experiments on this phenomenon are continuing, using another gravity cue – upright versus supine – as a context.

While it is not clear if and how saccades are affected by space flight, we use saccade adaptation partly as a model for sensorimotor behavior since it is fast and easy. In addition, there is some evidence from our lab and others to indicate that gravity may indeed provide important reference information for the generation of accurate saccade trajectories, in which case saccade programming may be disrupted in the space environment.

Building on our earlier experiments (also at JHU) on context-specificity in the human LVOR, we have now demonstrated the ability to use a gravity cue (head orientation) as a context for switching between two different adapted versions of the reflex. The gain of the LVOR can be adaptively changed by having the subject view a visual field that moves with him or her on the sled (driving the gain down, since no eye movements in response to head/body translation are required to stabilize the visual field) or view a visual field that is fixed in space (driving the gain up or keeping it constant). We have been able to induce a context-specific gain decrease with the subject's head tilted forward (pitched), while maintaining a constant gain with the head upright. This effect could not be duplicated when the context was head tilt (roll) toward one shoulder (versus upright). This is likely due to the fact that the LVOR stimulus and the roll context cue both stimulate the vestibular otolith organs in the same way, whereas the head pitch experiment provides a context cue that stimulates the otoliths orthogonal to the direction of the stimulus that evokes the LVOR. This set of results is very important because it indicates to us the limitations of human context-specific abilities, and to what extent a vestibular stimulus and a vestibular context cue should be distinguishable from each other by the nervous system. This experiment has benefited greatly from considerable recent effort in improving our human linear acceleration equipment at Johns Hopkins.

In the squirrel monkey, we have completed baseline investigations of the dynamics of the AVOR with high frequencies and accelerations. The stimulus regime being studied revealed interesting nonlinearities in the AVOR response, which must be understood before adaptive effects can be investigated. We also recently completed the instrumentation needed for squirrel monkey LVOR studies at JHU (translator and rotator, scleral search coil system). Our first monkey LVOR

adaptation studies have been performed, demonstrating adaptive increases and decreases in the inter-aural translational LVOR using magnifying or minimizing goggles during 2 hours of training. After the gain increase paradigm, the gain was increased by 15% when measured at the adapting frequency of 1.0 Hz, and likewise after gain decrease adaptation the gain was decreased by 30%. Torsional eye movement responses to the linear translations increased following adaptation with the magnifying lenses and decreased after adaptation with the minimizing lenses, but not significantly in either case. (This shows that the translational and tilt components of the LVOR (horizontal and torsional eye movements, respectively) may be coupled under normal circumstances. This has implications for paradigms that are designed to change adaptively tilt-translation interpretation.) When the LVOR was tested at 0.5 Hz, there was a decrease in gain after either type of adaptation (gain increase or decrease). Similarly, when the LVOR was adapted at 0.2 Hz, there was a gain decrease at all testing frequencies (1.0, 0.5, and 0.2 Hz), regardless of the adaptation condition (magnifying or minimizing lenses).

Related JHU experiments have been performed on the rhesus monkey AVOR. As in our earlier work in humans, we have elicited AVOR phase adaptation in the monkey, making the velocity-to-position neural integrator leaky (after phase lead adaptation) or unstable (after phase lag adaptation). We also induced cross-axis AVOR gain adaptation, asking for a vertical eye movement component during yaw head rotations. Afterward, the AVOR was tested with the animal in different pitch orientations; the results suggest that gravity can be used to switch in or out the adapted response (i.e. adaptive changes were smaller when tested with the animals pitched away from the training position). Finally, we performed our first flocculectomy in the same monkey and will begin testing shortly to examine the role of the vestibulocerebellum in these adaptive changes.

Experiments at Baylor College of Medicine on adaptation of the VCR have also begun to show evidence of context-specificity. These experiments have continued to establish baseline properties of the response along different axes. Significant effort has been placed on identifying appropriate mathematical models and fitting parameters for each subject, to provide a basis for understanding adaptive changes as induced by subsequent experiments. Adaptation to an artificial increase in inertia of the head has been demonstrated, as manifest by a decrease in head oscillation during body perturbations. The appropriate adapted response to increased inertia was stored by the head-neck control system even after subsequent re-adaptation back to normal head inertia; the system responded appropriately to each inertial load to keep head oscillations at the same level. Pilot data suggest that this apparent capacity to switch rapidly between two sets of system parameters persists for at least 35 days after the initial adaptation: the appropriate head damping occurs immediately for both normal and increased inertia loads, showing that two sets of damping parameters can exist simultaneously and be switched in and out as needed.

Development of equipment and procedures continues at MIT for our study of the use of Coriolis force as a context cue. A pilot study was recently completed. Data from the pilot study are currently being analyzed and analysis software is being developed. Collection of preliminary data during the pilot study has validated the experimental setup. These early findings support the hypothesis that adaptation to a rotating (Coriolis) environment occurs following a period of ad-lib head movements in the light, so that inappropriate eye movement components are decreased.

RESEARCH AREA:	Neurovestibular Adaptation
PRINCIPAL INVESTIGATOR:	Charles M. Oman Ph.D.
ORGANIZATION:	Massachusetts Institute of Technology
PROJECT TITLE:	Visual Orientation in Unfamiliar Gravito-Inertial Environments
FUNDING:	\$324,700 (FY 1998); \$338,693 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The goal of this project is to better understand the process of spatial orientation and navigation in unfamiliar gravito-inertial environments, and ultimately to use this new information to develop effective countermeasures against the orientation and navigation problems experienced by astronauts. How do we know our location, orientation, and motion of our body with respect to the external environment? On earth, gravity provides a convenient "down" cue. Large body rotations normally occur only in a horizontal plane. In space, the gravitational down cue is absent. When astronauts roll or pitch upside down, they must recognize where things are around them by a process of mental rotation which involves three dimensions, rather than just one. While working in unfamiliar situations they occasionally misinterpret visual cues and experience striking "visual reorientation illusions" (VRIs), in which the walls, ceiling, and floors of the spacecraft exchange subjective identities. VRIs cause disorientation, reaching errors, trigger attacks of space motion sickness, and potentially complicate emergency escape. MIR crewmembers report that 3D relationships between modules - particularly those with different visual verticals - are difficult to visualize, and so navigating through the node that connects them is not instinctive. Crew members learn routes, but their apparent lack of survey knowledge is a concern should fire, power loss, or depressurization limit visibility. Anecdotally, experience in mockups, parabolic flight, neutral buoyancy and virtual reality (VR) simulators helps. However, no techniques have been developed to quantify individual differences in orientation and navigation abilities, or the effectiveness of preflight visual orientation training. Our understanding of the underlying physiology - for example how our sense of place and orientation is neurally coded in three dimensions in the limbic system of the brain - is incomplete.

During the 16 months that this human and animal research project has been underway, we have obtained several results that are not only of basic research interest, but which have practical implications for the architecture and layout of spacecraft interiors and for the development of astronaut spatial orientation training countermeasures:

- Interaction between scene and body orientation was studied in 12 human subjects inside an 8 foot tumbling room furnished with many polarized objects, such as a table, chair, bookshelf, etc. Subjects reported body tilt in 25 different combinations of room and body orientation relative to gravity. We found that subjective orientation usually was aligned with the orientation of the visual scene, particularly when body and room axes are coincident. Orientation with respect to gravity had only small effect, except when prone. Walls apparently provided more potent orientation cues than the floor or ceiling.

- Levitation and roll tumbling illusions were studied as a function of age in 96 subjects. It was found that when a gravitationally supine subject is placed in a room also pitched back 90°. The subject reports that the room and self are erect and a compelling sense of levitation when the arms or legs are lifted. The proportion of subjects experiencing the levitation illusion increases from about 20% in 10-year olds to 80% in 70-year olds. However, if the room was rolled at constant velocity, subjects of all ages reported a head over heels tumbling illusion. The results

suggest, for example, that placing pictures or other polarized objects on the walls of stairways may make older people less prone to falls.

- To define the minimum visual cues to the direction of gravity that induce a visual reorientation illusion, 30 subjects were tested while lying supine on a bed, viewing various scenes through a mirror set above their heads inclined at 45°. All subjects saw a natural scene as erect and in front of them and a blank surface as a ceiling above them. Both intrinsic polarity in familiar objects with recognizable tops and bottoms, and extrinsic polarity, arising from object support (e.g., ball and box vs. ball on box) and hanging objects produced strong effects on subjective tilt. Our inclined mirror display method has also been adopted by other NSBRI colleagues, who recently obtained preliminary evidence of cardiovascular responses at the onset of illusory tilt.

- Three dimensional spatial memory and learning was studied in a task analogous to that confronting astronauts who must learn the spatial relationships in a 6 ported space station node. Tests were performed in both a real environment (73 subjects) and a computer generated virtual equivalent (24 subjects). Subjects had to memorize the spatial relationships among pictures of familiar objects placed at the center of each of six walls of a cubic chamber. They had to learn them well enough so that they could imagine themselves in a different roll orientation within the chamber, and from that imaginary perspective correctly predict the relative direction of a specific target object. Subjects were trained in both erect and supine body positions, and their viewpoint was later switched so they faced a different direction. We found that most people could learn the object configuration within 10-20 trials from a given viewpoint. Trainee body position had little effect, so that the more practical erect position will be used for future experiments. Quantitatively similar results were obtained for the real and virtual environment subject groups. A statistically significant correlation was found between task performance measures and conventional paper-and-pencil tests of field independence and 2&3 dimensional figure rotation ability. Spatial memory proceeds so effortlessly our everyday lives, but our experiments clearly demonstrate the difficulty of spatial memory tasks when generalized to three dimensions. The our paradigm may be suitable for development into a 3D spatial orientation computer based training countermeasure.

- Head Direction cells in rat anterior dorsal thalamus were monitored in parabolic flight under 0-g, 1g, and 1.8 g conditions. The animals were in a clear Plexiglass rectangular cage that had wire mesh covering the floor, ceiling, and one wall, designed so that up-down visual cues were ambiguous. Cells maintained the same direction-specific discharge when the rat was on the cage floor during the 1-g, 0-g and 1.8 g pull-out periods. The cell's preferred direction was also maintained when the rat crawled on the wall in 0-g. When the animal was placed on the ceiling of the test chamber in 0-G, the preferred direction frequently shifted 180°, or increased its firing rate and became directionally nonspecific. These responses indicate that the rats maintained a normal allocentric frame of reference in 0-g and 1-g when on the floor or wall, but that when placed on the ceiling, the rat sometimes experienced a VRI, as evidenced by the reversal of HD cell preferred direction across the cage axis of symmetry. This is preliminary data from a limited number of cells, but changes were clear, and are the first demonstration in an animal model of a limbic correlate of a human 0-G spatial orientation illusion.

- In related 1-G animal experiments, we are studying the 3 dimensional characteristics of rat head direction cells to determine how response depends on the animal's orientation to gravity, visual cues, and the plane of locomotion. Animals have been successfully trained using behavior shaping techniques to crawl up a wall, across the ceiling, and down the opposite wall of a gridded test track. The track affords a view of the surrounding laboratory. Preliminary data has

been obtained from several cells. 3D response characteristics change temporally as the animal is crossing the ceiling, but return to normal after the animal regains the floor. Further experiments are planned to determine the effect of changing locomotion plane.

RESEARCH AREA:	Neurovestibular Adaptation
PRINCIPAL INVESTIGATOR:	Conrad Wall, III, Ph.D.
ORGANIZATION:	Harvard Medical School
PROJECT TITLE:	Advanced Techniques for Assessment of Postural and Locomotor Ataxia, Spatial Orientation, and Gaze Stability
FUNDING:	\$340,790 (FY 1998); \$369,278 (FY 1999)

PROJECT EXECUTIVE SUMMARY

In addition to adapting to microgravity, major neurovestibular problems of space flight include postflight difficulties with standing, walking, turning corners, and other activities that require stable upright posture and gaze stability. These difficulties inhibit astronauts' ability to stand or escape from their vehicle during emergencies. The long-term goal of the NSBRI is the development of countermeasures to ameliorate the effects of long duration space flight. These countermeasures must be tested with valid and reliable tools. This project aims to develop quantitative, parametric approaches for assessing gaze stability and spatial orientation during normal gait and when gait is perturbed.

Two of this year's most important findings concern head fixation distance and ideal trajectory analysis. During a normal cycle of walking the head moves up and down linearly. A simultaneous angular pitching motion of the head keeps it aligned toward an imaginary point in space at a distance of about one meter in front of a subject and along the line of march. This distance is called the head fixation distance. Head fixation distance provides the fundamental framework necessary for understanding the functional significance of the vestibular reflexes that couple head motion to eye motion. This framework facilitates the intelligent design of countermeasures for the effects of exposure to microgravity upon the vestibular ocular reflexes.

Ideal trajectory analysis is a simple candidate countermeasure based upon quantifying body sway during repeated up and down stair stepping. It provides one number that estimates the body sway deviation from an ideal sinusoidal body sway trajectory normalized on the subject's height. This concept has been developed with NSBRI funding in less than one year. These findings are explained in more detail below.

Compared to assessments of the vestibulo-ocular reflex, analysis of vestibular effects on locomotor function is relatively less well developed and quantified. We are improving this situation by applying methodologies such as nonlinear orbital stability to quantify responses and by using multivariate statistical approaches to link together the responses across separate tests. In this way we can exploit the information available and increase the ability to discriminate between normal and pathological responses. Measures of stability and orientation are compared to measures such as dynamic visual acuity and with balance function tests. The responses of normal human subjects and of patients having well documented pathophysiologies are being characterized. When these studies are completed, we should have a clearer idea about normal and abnormal patterns of eye, head, and body movements during locomotion and their stability in a wide range of environments. We plan eventually to use this information to validate the efficacy of candidate neurovestibular and neuromuscular rehabilitative techniques. Some representative studies made during this year are summarized below.

Linear and circular walking. To elucidate the role of the balance system during linear and circular locomotion, our studies have developed new methods for measuring and modeling head and trunk rotations during turning. One looks at the effects of the velocity of straight walking on trunk and head movements. Another, called head fixation distance investigates the effects of viewing distance on compensatory vertical eye movements. A third investigates the role of head and eye movements during circular turning and locomotion. Out of these studies we have developed new representational schemes for modeling and studying head and trunk rotations during turning.

For head fixation distance (HFD), the basic finding is that for optimal walking speeds (1.4-1.8 m/s), the HFD is fairly invariant at about 1 meter. The implication is that when subjects view objects further than 1 meter, compensatory eye movements would be in the direction of the angular vestibulo-ocular reflex (aVOR). The gain (eye velocity/head velocity) would become closer to the aVOR gain in dark, the further away one looks. Viewing closer targets would require a reduced gain or a change in phase. This gain change does in fact occur. Our hypothesis is that the linear vestibulo-ocular reflex (LVOR) and vision play important roles in the implementation of this altered gain that differ from that of the aVOR in dark. It also suggests that training astronauts with close visual targets may be an important countermeasure for maintaining their ability to use their IVOR and vision during natural locomotion. HFD does not appear to be affected by viewing distance, and therefore other countermeasures would have to be considered to maintain the HFD during space flight. It might be that the HFD will adapt to a far distance during space flight and so everything astronauts view will require the LVOR and vision. This would put a greater demand on linear compensatory systems which are now in adapted states. Thus, our hypothesis is that HFD is an important parameter to be controlled for maintaining stability of gait during straight walking following spaceflight. The functional relationship of HFD to walking velocity should be an important parameter for assessing the stability of gait.

Ideal Trajectory Analysis (ITA). A stair stepping study investigated the hypothesis that in an ambulatory task such as repeated stepping on to a 8 cm elevation, subjects with anomalies of their balance system will expend more energy and will have a significantly greater deviation from an ideal center of mass displacement trajectory as compared to healthy subjects. We developed a quantitative method to assess repeated stair stepping stability that yields one number which represents this deviation from ideal. Larger numbers correspond to larger deviations. The average values for subjects with balance disorders were more than twice those of healthy ones, indicating that the ideal trajectory analysis distinguishes between these groups. ITA will be used to validate various rehabilitation techniques by measuring a patient's stability before and after rehabilitation. This makes an earth-based analogue for validation of countermeasures.

Responses to single perturbations during locomotion. Six healthy subjects were asked to walk along a straight line marked on the ground while stepping at a constant cadence. A disturbance was introduced by quickly shifting the floor underneath their feet a short distance (10 cm) forward and to the right about 200 msec after right heel strike. As the subjects attempted to recover from the perturbation and walk along the line, their lateral trunk motion first proceeded to the right in the direction of the perturbation. Subsequent recovery produced an overshoot of the line of march in the left direction that was nearly the same amplitude as the initial perturbation response. The time constant of the recovery following the overshoot was approximately 0.75 seconds and nearly full recovery was within four additional steps. We hypothesize that the final recovery trajectory will be different for labyrinthine deficient (LD) versus healthy subjects because the balance systems of the LD's will yield less sensitive, or more

distorted, lateral position estimates. The longer time required to return to the unperturbed line of march will be reflected in the greater degree of instability as measured by our quantitative techniques. If this holds true, then we expect to find a similar effect in subjects upon immediate return from microgravity. After we have defined the most effective protocol for giving these perturbations then we anticipate simplifying the perturbation delivery device and adapting the protocol and its analysis for treadmill use at JSC.

Dynamic visual acuity test (DVA) Dynamic visual acuity is a composite measure of sensorimotor integration developed previously in the Neuroscience Laboratory at NASA/Johnson Space Center. There is an ongoing collaboration between an intramural investigator, and an extramural investigator with expertise in the development and testing of clinical rehabilitative interventions. Further evaluative research on the underlying concept is needed to determine if the test is sensitive to rapid change over time. To this end, a study was made on patients recovering from surgical resection of vestibular nerve tumors. The preliminary results of this study suggest that under certain test conditions the DVA test can measure rapid changes in vestibular reflex gain caused by the surgery and to the resulting compensatory processes that are elicited during the most acute phase of recovery.

Vestibulocolic reflex study. This experiment investigates the dynamic stability of the head relative to the body in response to linear accelerations and tilt. Subjects' head and body motions were recorded while they rode MIT's 4.7m linear acceleration sled (a computer-controlled, motor-driven cart). Head movements in response to linear acceleration were studied in normal and labyrinthine-defective (LD) subjects for anterior-posterior and for inter-aural axis acceleration, and were analyzed in frequency and time domains.

Analysis techniques overview

We are developing, adapting, or applying several techniques to advance the quantitative assessment of postural control and locomotion. These include: Ideal Trajectory Analysis, Floquet Multipliers and parametric linear system identification. These approaches are briefly described below.

Ideal trajectory analysis (ITA) is a new approach we have developed to characterize the sway of human subjects in response to a repeated stepping task. In this task, subjects perform metronome-paced stepping up and down a single wide step with four paces to a cycle. This maneuver causes a periodic sway pattern which can be fit with sinusoids. The sinusoids are considered to be "ideal trajectories" in the sense that they are "energy efficient." Thus, any deviation from these best fit sinusoids is less than ideal and is therefore considered to be an error. A dimensionless measure of this error is calculated by dividing the root mean squared deviation (over the duration of a stepping trial) by the subject's height. Large deviations from the ideal trajectory during repeated stepping yield larger dimensionless error coefficients. Thus, ITA is calculated from just the time series data taken continually over the test trial.

Floquet multipliers. Floquet multipliers, in contrast, work on a different basis. They are used to characterize the stability of a periodic system in response to one or more disturbances or perturbations, for example the response of a helicopter rotor blade to an abrupt change in angle of attack. The response is usually visualized in the phase plane which is a plot of displacement versus velocity. A frictionless pendulum has a phase plane trajectory that makes a repeated circular orbit. Some periodic systems, when disturbed from their steady orbits, return to them after a number of cycles. Other systems do not return when they are disturbed. Our primary use

of this technique is to quantify just how the former systems behave in terms of their stability. To do this, we take a once-per-cycle sample of the displacement and velocity of a subject's body parts over a number of cycles. From these samples, we can calculate the stability of the system in terms of how many cycles it takes to resume its original orbit. This experimental measure of stability can be formally related to a traditional theoretical measure of stability. Experimental versus theoretical estimates can be compared. Our working hypothesis is that exposure to microgravity will adversely affect the balance system which will, in turn increase the number of cycles it will take for the body parts to return to a steady state condition, as compared to the response of healthy subjects who have not had recent exposure to micro gravity.

General Floquet Theory. Our original Floquet multiplier method is somewhat limited in that it can completely identify only fairly simple systems. We are therefore adapting another method called General Floquet Theory (GFT) which can identify the more complex responses we believe we are starting to find. For this reason, we have delayed the complete analysis of some experimental data that we have already taken until we have verified this new approach. We compared the results obtained from our original and the GFT approaches with some theoretical results. While the original method does characterize the stability of the simple systems we simulated, it does not completely characterize the more complex ones. In contrast, the GFT method does characterize these more complex systems.

Parametric linear systems identification. We have applied linear systems identification techniques in order to quantify several of our experimental results. These techniques typically fit the responses in either the time or frequency domains with one or more models that have an assumed structure. The parameters which represent the variability in the structure are allowed to vary while the predicted response is compared with the actual one until a minimum error between predicted and actual responses is achieved.

Perturbation during steady walking. One such time domain application was made to the responses to single perturbations during steady walking. A 10 cm displacement was applied 200 ms after heel strike and at 45 ° to the right and forward of the direction of march. The medio-lateral sway in response to this disturbance was measured, low-pass filtered and fit with a model consisting of the sum of three exponential decays.

Vestibulocollic reflex in response to linear accelerations. A frequency domain application was made to the motion of the head on the neck during pseudorandom linear accelerations along the naso-occipital and medio-lateral body axes. These resulted in third order estimates of transfer functions of these motions, which showed differences between healthy and labyrinthine deficient (LD) subjects.

Summary of progress to date. At this point, some of our techniques have been well developed while some are still in development phases. This is not surprising since some are more complex than others and thus require more effort and time to get online. This progress parallels our countermeasures development. Both processes have been focused upon development in the individual sub-projects. Thus, part of our continuing effort at development will be to compare all methods and to make all methods available for use, as appropriate, for all subprojects. We will apply a similar approach to the dissemination and cross-fertilization of the countermeasures

Countermeasures. The various sub-projects have independently produced several candidate countermeasures. Head fixation distance (HFD). Training astronauts to view close targets before or during space flight could be important in helping them adjust their visual systems to the

increased demands following spaceflight. Ideal trajectory analysis (ITA) is an easy-to-implement technique that allows the quantification of sway during repeated stepping. ITA will be used to validate various vestibular rehabilitation techniques, which makes it a good earth-based analogue for recovery to exposure to microgravity. Dynamic Visual Acuity Test (DVA) is a composite measure of sensorimotor integration developed previously in the Neuroscience Laboratory at NASA/ Johnson Space Center. Its simplicity and portability makes it attractive for

synergistic application, for example with HFD and ITA. The results of the Vestibulo-Collic Reflex sub-project could contribute directly to the determination of a recommended head movement protocol for use during and following re-entry. Some of these countermeasures have potential synergies that must be integrated over the next year to make them more powerful. Others countermeasures are ready to consider for implementation now.

**NSBRI RESEARCH PROGRAM
RADIATION EFFECTS**

Team Leader:	Dicello, J. F.	Hopkins/SOM	
Dicello, J. F.	PI	Hopkins/SOM	Radiation Effects: Core Project B-96
Cucinotta, F. A.	CO-I	NASA JSC	
Gridley, D. S.	CO-I	Loma Linda	
Howard, S. P.	CO-I	Wisconsin	
Huso, D. L.	CO-I	Hopkins/SOM	
Mann, J.	CO-I	Hopkins/SOM	
Novak, G. R.	CO-I	Hopkins/SOM	
Piantadosi, S.	CO-I	Hopkins/SOM	
Ricart, R.	CO-I	Hopkins/SOM	
Strandberg, J. D.	CO-I	NCR/NIH	
Yang, T.	CO-I	NASA JSC (Deceased)	
Huso, D.L.	PI	Hopkins/SOM	Chemoprevention of Radiation-Induced Rat Mammary Neoplasms B-97
Dicello, J. F.	CO-I	Hopkins/SOM	
Howard, S. P.	CO-I	Wisconsin	
Strandberg, J. D.	CO-I	NCR/NIH	
Williams, J. R.	PI	Hopkins/SOM	Radiation-Induced Cytogenetic Damage as a Predictor of Cancer Risk for Protons and Fe Ions B-99
Griffin, C. A.	CO-I	Hopkins/SOM	
Sinden, R. R.	PI	Texas A&M	Quantitation of Radiation-Induced Deletion and Recombination Events Associated with Repeated DNA Sequences B-102
Braby, L. A.	CO-I	Texas A&M	

RADIATION EFFECTS TEAM PROGRAM EXECUTIVE SUMMARY

The Radiation Effects Team for the National Space Biomedical Research Institute has as its primary objective to study the consequences of radiations in space and to develop chemical countermeasures to reduce the risks of cancer and other diseases associated with such exposures. During the first year and a half, the team has assembled a group of outstanding collaborators with complementary specialties who are now focused on the NSBRI/NASA goals. They have obtained extensive data using a model system, cytogenetics, and DNA sequencing for beams of energetic heavy ions, protons, and photons.

During interplanetary missions, personnel in space will be exposed to galactic cosmic rays, including high-energy protons and energetic ions with atomic masses of iron or higher. In addition, solar events will produce radiation fields of high intensity for short but irregular durations. The level of intensity of these radiations is considerably higher than that on Earth's surface, and the biological risks to astronauts is consequently increased, including increased risks of carcinogenesis and other diseases. Moreover, it is likely that the environment to which the astronauts will be subjected in space for extended space missions, including but not limited to the stress and biological modifications introduced by the microgravitational environment, will alter the radiation susceptibilities of personnel, with the distinct likelihood of synergistic radiation response, not the least of these being those resulting from the combinations of different types of radiations, as discussed in last year's annual report.

This group is examining the risk of cancers resulting from low-dose, low-dose rate exposures of model systems to photons, protons, and iron by using ground-based accelerators which are capable of producing beams of protons, iron, and other heavy ions at energies comparable to those encountered in space. They have already investigated the effects of energetic iron beams at the Brookhaven National Laboratory and protons at the NASA research facility at Loma Linda University.

CORE (DICELLO)

The risks to personnel in space from the naturally occurring radiations are generally considered to be one of the most serious limitations to human space missions, as noted in two recent reports of the National Research Council/National Academy of Sciences. The Core Project is examining the consequences of radiations in space in vivo in order to develop countermeasure, both physical and pharmaceutical, to reduce the risks of cancer and other diseases associated with such exposures.

This group is examining the risk of cancers resulting from low-dose, low-dose rate exposures of model systems to photons, protons, and iron by using ground-based accelerators which are capable of producing beams of protons, iron, and other heavy ions at energies comparable to those encountered in space. They have begun the first series of experiments using a 1-GeV iron beam at the Brookhaven National Laboratory and 250-MeV protons at Loma Linda University Medical Center's proton synchrotron facility. As part of these studies, this group will be providing the exposed animals and cells for the Chemopreventive Project (Huso, PI) to investigate the potential for the pharmaceutical, Tamoxifen, to reduce the increased risk of breast cancer in astronauts.

Theoretical studies are being carried out in a collaboration between scientists at NASA's Johnson Space Center and Johns Hopkins University in parallel with the experimental program have provided methods and predictions which are being used to assess the levels of risks to be encountered and to evaluate appropriate strategies for countermeasures. We have begun analysis of the risks for carcinogenesis in the model system we are investigating, and we are examining synergistic effects resulting from exposures to particles of different ionization densities, i.e., microdosimetric distributions.

Although the work in this project is primarily directed toward problems associated with space travel, the problem of protracted exposures to low-levels of radiation is one of national interest in our energy and defense programs, and the results may suggest new paradigms for addressing such risks.

CHEMOPREVENTION (HUSO)

Tamoxifen antagonizes the action of estrogen by competing for the nuclear receptor complex thereby altering the association of the receptor complex and nuclear binding sites. Its effects in reducing the development of breast cancer could be accomplished by controlling clinically undetectable microcancers, arresting preneoplastic lesions, or correcting abnormal environments which predispose to high risk of malignant transformation.

In close collaboration with the NASA Radiation Effects Team, core project and Dr. John Dicello, we have begun to investigate the long term effects of low levels of exposure to iron ions and protons and are comparing them with the effects of photons. We have chosen the Sprague Dawley rat for our studies because it is a thoroughly studied model and will allow us to focus our studies on the mammary gland. We have made many important early observations on mammary carcinogenesis and chemoprevention in this model and are archiving tissue samples from all organs for potential additional future studies of other organ systems.

During the second year we have continued to follow this cohort and we initiated a pilot project to evaluate the effects of tamoxifen in preventing the development of mammary carcinomas in irradiated Sprague Dawleys. Though the animals numbers were limited for this pilot project, sixty days of tamoxifen treatment has had a dramatic effect in reducing the incidence of mammary tumors in irradiated Sprague Dawley rats.

Recently, we have begun large scale studies on the effectiveness of Tamoxifen in the prevention of mammary carcinomas induced by heavy ions and protons. A large group of animals have been exposed to iron ions at Brookhaven and animals from the same age cohort will be exposed to protons at Loma Linda within days. The animals from both groups will subsequently be shipped to JHU for Tamoxifen treatment and follow-up. These animals will be followed as a cohort using the techniques which we have in place from year one including regular palpation of the mammary glands, surgical removal of palpable tumors using survival surgery techniques, histopathological exam of each tumor, and complete necropsies of any animals which die or require euthanasia during the course of the studies.

In summary, we are accumulating data which should provide critical insights in predicting the long term effects of exposure to heavy ions, protons, and their secondaries at doses which astronauts may encounter during prolonged space travel, of relevance to the NSBRI mission. In addition, our studies test the hypothesis that pharmaceutical countermeasures may be used to mitigate the increased cancer risk associated with exposure to radiation in space. This hypothesis

will be tested for mammary gland, a radiation sensitive organ for which tamoxifen is an effective chemopreventative.

CYTOGENETICS (WILLIAMS)

We have successfully completed the series of experiments planned for year 1 and the first part of year 2 measuring the induction of chromosome aberrations induced in multiple cell types by Fe-ions, protons and photons. Most of these data have now been compiled and a significant part subjected to data analyses, although continuing data analysis is an important part of our current and future efforts. These analyses are directed toward defining the patterns of chromosomal damage induction by the three radiations and the extent to which such patterns are dependent on the type of cell irradiated. Our studies show significant differences, both quantitatively and qualitatively, between response of different cell types to these radiations however there is an overall pattern that characterizes each type of radiation in most cell lines. Thus our data identifies general dose-response patterns for each radiation for induction of multiple types of chromosomal aberrations but also identifies significant differences in response between some cell types. Specifically, we observe significant resistance for induction of aberrations in rat mammary epithelial cells when they are irradiated *in vivo* and assayed *in vitro*. Further, we have observed some remarkable differences in susceptibility to certain radiation-induced aberrations in cells whose genome has been modulated for two cancer-relevant genes, TP53 (p53) and CDKN1A (p21). This data, if confirmed, may represent the first evidence of gene-specific differences in cellular metabolism of damage induced by densely-ionizing radiation that confer substantial sensitivity to protons compared to photons.

Our data clearly demonstrate that dose-response patterns for induction of different types of aberrations is a complex function and varies in shape and intensity over different dose-ranges, with most variance between effects of Fe-ions compared to the effects of protons and photons. Our data suggest that it may be inappropriate to apply some models to predicting the relative biological efficiency (RBE) for Fe-ions, particularly at lower doses (< 0.5 Gy).

Our data show that Fe ions are more effective than photons in the induction of all types of aberrations over all dose ranges compared. There may be a trend that protons at some dose points may be slightly more effective compared to photons for inducing acentric fragments. We observe variation in response between cell lines based on their histological type, on their genotype and whether irradiated *in situ* within the animal or *in vitro*.

We have also completed studies in examining the dose-rate effect of photons for induction of aberrations. While not completely analyzed, these data show a large dose-rate effect that must be included in modeling of Fe-ion and proton data.

Finally, we have published a new model that we suggest better predicts induction of cancer and other endpoints over multiple dose ranges. The data we have acquired recently strongly supports this model and offers new insights into mechanisms of cellular processing of chromosomal radiation damage.

In the next research period, we will repeat selected studies as needed, extending the dose range where appropriate to better characterize dose-response patterns. We will also perform fractionation studies with the proton beam, to determine whether the small, densely-ionizing component of this radiation is more effective when delivered in small fractions. We will also initiate cooperative studies with Loma Linda in direct comparison of aberrations induced *in vivo*

in our animal model, the Sprague-Dawley rat and a mouse species that will be selected by Loma Linda. We will extend selected data points to spectral karyotyping (SKY) that will permit more detailed examination of aberrations induced and particularly the prevalence of multiple damages in individual cells, an extremely important data for modeling cell response with flux-based microdosimetry

REPEATED DNA SEQUENCES (SINDEN)

High-LET heavy ions are particularly damaging to cells as they do continual damage throughout their track. Differences in these energy deposition patterns can significantly influence the nature of DNA damage and the ability of cellular systems to repair such damage. It has been suspected that these differences also affect the spatial distribution of damage within the DNA of the interphase cell nucleus and produce corresponding differences in endpoints related to health effects. The interaction of a single high-LET particle with chromatin has been suggested to cause multiple double strand breaks within a relatively short distance. In part this is due to the organization of DNA into chromatin fibers in which distant regions of the DNA helix can be physically juxtaposed by the various levels of coiling of the DNA.

While it is clear that ionizing radiation can cause cytogenetic damage and cancer, relatively little is yet known about the mutagenic or carcinogenic effects of high energy HZE particles in cells. High-LET radiation produces proportionally more double-strand than single strand breaks compared with low-LET radiation. Nearly one-third of the human genome is composed of DNA repeats, which include simple mono-, di-, tri-, and tetranucleotide repeats; widely separated small and large repeats; and inverted repeats. Mutations associated with repetitive DNA are a source of many genetic diseases and cancer. Therefore, understanding how the various kinds of repeats contribute to the disease burden and understanding the impact of DNA damage on repeat-associated genomic instability is important for human health. Such repeated DNA sequences are likely to be very prone to mutation following exposure to high-Z high-energy (HZE) particles during space flight. Cells in the direct line of the HZE particle sustain a high dose of energy while cells surrounding the primary tract sustain a lower dose of energy from the energetic delta rays (electrons) produced by HZE particles. Therefore, the nature and pattern DNA damage to cells in tissue upon irradiation with HZE particles is particularly complex. It is important to understand the types of mutational changes induced by both the HZE particles as well as the delta rays. The molecular events that are responsible for cytogenetic damage (chromosomal breaks and rearrangements) and other mutations (point mutations, frameshifts, small deletions and duplications) in many cases will involve primer template misalignments. It is also possible that a cell sustaining substantial damage from a heavy iron particle hit may saturate some or all of its repair capability, or induce an error-prone mode of repair to mediate survival. The types of assays we are developing will provide sensitive reporters of the replication/repair fidelity of a cell following damage from HZE particles. With the sensitive reporter lines we are developing, the protective effects of chemopreventive measures or countermeasures can be quickly established. Through the coordination of these studies in the Sprague-Dawley rat mammary cells with the studies for the Johns Hopkins rat study we intend to provide a rapid way to test the efficacy of various countermeasures and chemopreventive drugs with respect to mutation minimization and cancer prevention.

RESEARCH AREA:	Radiation Effects: DNA Damage and Repair
PRINCIPAL INVESTIGATOR:	John F. Dicello, Ph.D.
ORGANIZATION:	Johns Hopkins Oncology Center
PROJECT TITLE:	Radiation Effects: Core Project
FUNDING:	\$560,100 (FY 1998); \$789,435 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The risks to personnel in space from the naturally occurring radiations are generally considered to be one of the most serious limitations to human space missions, as noted in two recent reports of the National Research Council/National Academy of Sciences. The Core Project of the Radiation Effects Team for the National Space Biomedical Research Institute is the consequences of radiations in space in order to develop countermeasure, both physical and pharmaceutical, to reduce the risks of cancer and other diseases associated with such exposures.

During interplanetary missions, personnel in space will be exposed to galactic cosmic rays, including high-energy protons and energetic ions with atomic masses of iron or higher. In addition, solar events will produce radiation fields of high intensity for short but irregular durations. The level of intensity of these radiations is considerably higher than that on Earth's surface, and the biological risks to astronauts is consequently increased, including increased risks of carcinogenesis and other diseases.

This group is examining the risk of cancers resulting from low-dose, low-dose rate exposures of model systems to photons, protons, and iron by using ground-based accelerators which are capable of producing beams of protons, iron, and other heavy ions at energies comparable to those encountered in space. They have begun the first series of experiments using a 1-GeV iron beam at the Brookhaven National Laboratory and 250-MeV protons at Loma Linda University Medical Center's proton synchrotron facility. As part of these studies, this group will be investigating the potential for the pharmaceutical, Tamoxifen, to reduce the risk of breast cancer in astronauts exposed to the level of doses and particle types expected in space.

Theoretical studies are being carried out in a collaboration between scientists at NASA's Johnson Space Center and Johns Hopkins University in parallel with the experimental program have provided methods and predictions which are being used to assess the levels of risks to be encountered and to evaluate appropriate strategies for countermeasures.

Although the work in this project is primarily directed toward problems associated with space travel, the problem of protracted exposures to low-levels of radiation is one of national interest in our energy and defense programs, and the results may suggest new paradigms for addressing such risks.

RESEARCH AREA:	Radiation Effects: DNA Damage and Repair
PRINCIPAL INVESTIGATOR:	David L. Huso, DVM, Ph.D. (Replacing S. Howard)
ORGANIZATION:	Johns Hopkins Oncology Center
PROJECT TITLE:	Chemoprevention of Radiation Induced Rat Mammary Neoplasms
FUNDING:	\$139,878 (FY 1998); \$136,582 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Radiations encountered in space include protons and heavy ions such as iron as well as their secondaries. The relative biological effect (RBE) of these ions is not known, particularly at the doses and dose-rates expected for planetary missions. Neutrons, are not particularly relevant to space travel, but have been found experimentally to have an increase in their RBE with decreasing dose. If a similar trend of increasing RBE with decreasing dose is present for heavy ions and protons during irradiation in space, the small doses received during space travel could potentially have substantial carcinogenic risk. Clearly more investigation of the effects of heavy ions and protons is needed before accurate risk assessment for prolonged travel in space can be done.

One means to mitigate the increased risk of cancer due to radiation exposure in space is by developing effective countermeasures that can reduce the incidence of tumor development. Tamoxifen has recently been shown to be an effective chemopreventive agent in both animal models and humans for the prevention of mammary tumors. Tamoxifen is a unique drug with a highly specific mechanism of action affecting a specific radiation-sensitive population of epithelial cells in the mammary gland. In human studies, the annual incidence of a primary tumor in the contralateral breast of women with previous breast cancer is about 8 per 1000, making them an exceedingly high-risk group for the development of breast cancer. In this high risk group, treated with tamoxifen, daily, for 2 years, the incidence of a new primary tumor in the contralateral breast was approximately one third of that noted in the non-tamoxifen treatment group. Tamoxifen antagonizes the action of estrogen by competing for the nuclear receptor complex thereby altering the association of the receptor complex and nuclear binding sites. Its effects in reducing the development of breast cancer could be accomplished by controlling clinically undetectable microcancers, arresting preneoplastic lesions, or correcting abnormal environments which predispose to high risk of malignant transformation.

Radiation exposure is a known risk factor for the development of breast cancer. Furthermore, the breast is one of the most sensitive organs in the body to the carcinogenic effects of radiation. The Sprague Dawley rat provides an excellent whole animal model system in which to determine the long term effects of exposure to low levels of heavy ions and protons. This strain has a high incidence of mammary neoplasms and has been shown to be a good model for studying radiation-induced mammary neoplasms. It therefore provides an excellent model system in which to investigate the hypothesis that increased cancer risks associated with exposures to low level radiation can be mitigated by specific pharmaceutical countermeasures. Emerging data on tamoxifen suggests that it would be an excellent compound to use to test the hypothesis in the setting of prevention of radiation-induced mammary carcinomas.

In close collaboration with the NASA Radiation Effects Team, core project and Dr. John Dicello, we have begun to investigate the long term effects of low levels of exposure to iron ions and protons and are comparing them with the effects of photons. We have chosen the Sprague

Dawley rat for our studies because it is a thoroughly studied model and will allow us to focus our studies on the mammary gland. We have made many important early observations on mammary carcinogenesis and chemoprevention in this model and are archiving tissue samples from all organs for potential additional future studies of other organ systems.

In summary, since year one we have been following a cohort of female Sprague Dawley rats that were exposed to various doses of heavy ions, protons, and photons. Mammary glands were palpated every three weeks and animals are weighed. Animals that develop palpable tumors are anesthetized to have tumors removed and evaluated histopathologically. Survival surgery techniques are used so that the rats remain in the study for long term follow-up. If necessary, animals are euthanized and complete necropsies are performed.

During the second year we have continued to follow this cohort and we initiated a pilot project to evaluate the effects of tamoxifen in preventing the development of mammary carcinomas in irradiated Sprague Dawleys. Though the animals numbers were limited for this pilot project, sixty days of tamoxifen treatment has had a dramatic effect in reducing the incidence of mammary tumors in irradiated Sprague Dawley rats.

Recently, we have begun large scale studies on the effectiveness of tamoxifen in the prevention of mammary carcinomas induced by heavy ions and protons (May 99). A large group of animals have been exposed to iron ions at Brookhaven and animals from the same age cohort will be exposed to protons at Loma Linda within days. The animals from both groups will subsequently be shipped to JHU for tamoxifen treatment and follow-up. These types of radiation are highly relevant to space travel and the NSBRI mission since this is the type of radiation that astronauts would likely be exposed to in space. These animals will be followed as a cohort using the techniques which we have in place from year one including regular palpation of the mammary glands, surgical removal of palpable tumors using survival surgery techniques, histopathological exam of each tumor, and complete necropsies of any animals which die or require euthanasia during the course of the studies.

The rat mammary tumor model has been used extensively to analyze the carcinogenic effects of both chemical xenobiotics and physical agents. The Sprague Dawley rat mammary tumor model is particularly well-suited for studies in the low dose range because it is prone to develop mammary neoplasms early in life. Previous studies using the Sprague Dawley model have shown that sublethal doses of radiation (xrays, gamma rays, neutrons-not particularly relevant to space travel) induced mammary tumors, often within one year, and with a linear dose-effect relationship. Thus the Sprague Dawley rat mammary carcinogenesis model not only closely resembles human breast cancer biologically, but it also is a highly sensitive model in which to examine the effects of radiation exposure and for testing pharmaceutical countermeasures against radiation effects.

In summary we are accumulating data which should provide critical insights in predicting the long term effects of exposure to heavy ions, protons, and their secondaries at doses which astronauts may encounter during prolonged space travel, of relevance to the NSBRI mission. In addition, our studies test the hypothesis that pharmaceutical countermeasures may be used to mitigate the increased cancer risk associated with exposure to radiation in space. This hypothesis will be tested for mammary gland, a radiation sensitive organ for which tamoxifen is an effective chemopreventative.

RESEARCH AREA:	Radiation Effects: DNA Damage and Repair
PRINCIPAL INVESTIGATOR:	Jerry R. Williams, Sc.D.
ORGANIZATION:	Johns Hopkins Oncology Center
PROJECT TITLE:	Radiation-Induced Cytogenetic Damage as a Predictor of Cancer Risk for Protons and Fe Ions
FUNDING:	\$200,000 (FY 1998); \$205,616 (FY 1999)

PROJECT EXECUTIVE SUMMARY

We have successfully completed the series of experiments planned for year 1 and the first part of year 2 measuring the induction of chromosome aberrations induced in multiple cell types by three model space radiations: Fe-ions, protons and photons. Most of these data have now been compiled and a significant part subjected to detailed data analyses, although continuing data analysis is an important part of our current and future efforts. These analyses are directed toward defining the patterns of chromosomal damage induction by the three radiations and the extent to which such patterns are dependent on the type of cell irradiated. Our studies show significant differences, both quantitatively and qualitatively, between response of different cell types to these radiations however there is an overall pattern that characterizes each type of radiation in most cell lines. Thus our data identifies general dose-response patterns for each radiation for induction of multiple types of chromosomal aberrations but also identifies significant differences in response between some cell types. Specifically, we observe significant resistance for induction of aberrations in rat mammary epithelial cells when they are irradiated in vivo and assayed in vitro. Further, we have observed some remarkable differences in susceptibility to certain radiation-induced aberrations in cells whose genome has been modulated for two cancer-relevant genes, TP53 (p53) and CDKN1A (p21). This data, if confirmed, may represent the first evidence of gene-specific differences in cellular metabolism of damage induced by densely-ionizing radiation that confers substantial sensitivity to protons compared to photons.

Differences between radiations: Our data clearly demonstrate that dose-response patterns for induction of different types of aberrations is a complex function and varies in shape and intensity over different dose-ranges, with most variance between effects of Fe-ions compared to the effects of protons and photons. Our data suggest that it may be inappropriate to apply some models to predicting the relative biological efficiency (RBE) for Fe-ions, particularly at lower doses (< 0.5 Gy). In the next budget period, we will perform modeling of our data, and other data from the literature, evaluating two different models: the linear-quadratic model and a new model, the subalpha-alpha-omega model, that we have proposed to represent better mechanisms that underlie radiation-induced cancer and cellular effects. We will incorporate particle-flux and microdosimetry in this modeling. This modeling will also focus on comparison of data from our cytogenetic studies and cancer induction in the Core Project. Our data show that Fe-ions are more effective than photons in the induction of all types of aberrations over all dose ranges compared. There may be a trend that protons, at some dose points, may be slightly more effective compared to photons for inducing a particular form of aberration, acentric fragments. Acentric fragments, by conventional wisdom, indicate unrepaired DNA double strand breaks that were induced when cells were in the G1/Go phases of the cell cycle. However some of our data suggest induction in G2/M which in turn suggest parallel break induction in homologous chromatids. Thus our work suggests that both Fe-ions and perhaps protons are more potent at inducing DNA double-strand breaks than photons; the effect of Fe-ions previously demonstrated by other methodology, but the effect of protons heretofore not demonstrated.

Differences between cell types: We observe variation in response between cell lines based on their histological type, on their genotype and whether irradiated in situ within the animal or in vitro. The cell type most resistant to induction of all aberrations is the rat mammary epithelial cell irradiated in vivo. The response is different both in magnitude (diminished) and in shape (extended plateau at lower doses) than the same cell type irradiated after explantation.

These data reflect the response of the target cell for mammary carcinogenesis that is being measured in parallel experiments. Thus our data for response of the rat mammary epithelial cell in vivo represents the data most relevant for seeking correlation between radiation-induced mammary cancer and radiation-induced chromosome aberrations.

Genetic determinants of response: As a secondary goal we have compared radiation-induced aberrations in human cells differing in expression of the TP53 (p53) and CDKN1A (p21) genes. We observe significant differences and these data offer a new approach to define better the molecular mechanisms that underlie different types of radiation-induced aberrations. These data, while needing repetition during the next budget period, suggest that background levels of both symmetrical and asymmetrical aberrations are elevated in cells with deficient p21 (double knockout). This increase is observed whether cells express dominant negative or wildtype p53. Most importantly, cells deficient in p53 (double knockout) show large differences between protons and photons for their induction of both asymmetrical and symmetrical aberrations, but particularly for the induction of acentric fragments. This suggests that the p53 protein is required for processing of DNA damage, perhaps that associated with DNA double-strand breaks that is reflected as acentric fragments. Additionally, a very rare form of aberration is observed in these cells after photon or at greatly increased levels after proton irradiation. This form of aberration is seen in all chromosomes in affected mitoses and is termed premature centromere separation (PCS). This observation supports earlier, unexplained studies that p53 modulates centromeric stability. The form of this aberration that we observe in the TP53-deficient cells, is observed only after larger doses of photon and proton irradiation (2.5, 5.0 Gy). If confirmed, these data offer a new approach to correlation between mechanisms of cancer and mechanisms of induction of chromosomal damage. TP53 is the gene most frequently altered in human cancer cells and these data suggest it may have a direct role in the metabolism of radiation-induced chromosomal damage. It also suggests that susceptibility to cancer induction by protons will depend on the genetic status of a given astronaut and the presence of "initiated" precancerous somatic cells in such astronauts may predispose them to promotion of cancer by proton exposure.

Dose-rate and dose-fractionation: We have also completed studies in examining the dose-rate effect of photons for induction of aberrations. While not completely analyzed, these data show a large dose-rate effect that must be included in modeling of Fe-ion and proton data. These studies are extremely important in comparing minimally-ionizing and densely-ionizing radiation, in that the latter delivers relatively large doses and dose-rates when a cell is traversed. Indeed one of the hypotheses that we are testing is that there is no low dose, low dose-rate radiation for Fe-ions in that if a cell is "hit" by this form of radiation, approximately 0.13 Gy is deposited within the cell. Thus, cell populations irradiated by Fe-ions contain cells with no dose, some with a single hit and some with multiple hits of approximately 13 rads each. Since the deposition of this radiation from a single traversal is over a very short time period, the instantaneous dose-rate is very high while the average dose-rate for the population is very low. We have approached this problem by defining partially the dose-rate effect in lymphocytes from photon exposure since the dose-rate is highest for this radiation. Future modeling will focus on combining these data with microdosimetric analyses.

Modeling: We have proposed a new model, the subalpha-alpha-omega model (SAO) that is described in an article now in press. We suggest this model better predicts induction of cancer and other endpoints over multiple dose ranges. The data we have acquired recently strongly supports this model and offers new insights into mechanisms of cellular processing of chromosomal radiation damage. The essential nature of this model is that there is a range of low doses for which radiation does not induce changes in gene expression and radiation-induced damage is processed by constitutive, homeostatic processes (subalpha response). At doses above 0.01 to 0.05 Gy for photons and above 0.05 Gy for photons and protons, cellular response genes are induced that increase survival of cell populations but with attendant increases in mutation, chromosome aberrations and susceptibility to malignant transformation (alpha response). At higher doses, above 0.5 Gy for Fe-ions and above 2.5 Gy for photons and protons, cells respond through the omega response that is characterized by altered chromosomal processing and by increased survival, decreased transformation and decreased mutation.

Studies for the next budget period: In the next research period, we will repeat selected studies as needed, extending the dose range where appropriate to better characterize dose-response patterns. We will also perform fractionation studies with the proton beam, to determine whether the small, densely-ionizing component of this radiation is more effective when delivered in small fractions. We will also initiate cooperative studies with Loma Linda in direct comparison of aberrations induced in vivo in our animal model, the Sprague-Dawley rat and a mouse species that will be selected by Loma Linda. We will extend selected data points to FISH and to spectral karyotyping (SKY) that will permit more detailed examination of aberrations induced and particularly the prevalence of multiple damages in individual cells, an extremely important data for modeling cell response with flux-based microdosimetry. These "painted chromosome studies will also define better the etiology of excess levels of acentric fragments observed after Fe-ion and proton irradiation.

RESEARCH AREA:	Radiation Effects: DNA Damage and Repair
PRINCIPAL INVESTIGATOR:	Richard R. Sinden, Ph.D.
ORGANIZATION:	Texas A&M University
PROJECT TITLE:	Quantitation of Radiation Induced Deletion and Recombination Events Associated with Repeated DNA Sequences
FUNDING:	\$50,000 (FY 1998); \$60,000 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Effects of Radiation on Biological Systems

Manned exploration of space exposes the explorers to a complex and novel radiation environment. The galactic cosmic ray and trapped belt radiation (predominantly proton) components of this environment are relatively constant, and the variations with the solar cycle are well understood and predictable. The level of radiation encountered in low earth orbits is determined by several factors, including altitude, inclination of orbit with respect to the equator, and spacecraft shielding. At higher altitudes, and on a Mars mission, the level of radiation exposure will increase significantly. A significant fraction of the dose may be delivered by solar particle events which vary dramatically in dose rate and incident particle spectrum. High-LET radiation is of particular concern. High-LET radiation, a component of galactic cosmic rays (GCR), is comprised of a variety of charged particles of various energies (10 MeV n^{-1} to 10 GeV n^{-1}), including about 87% photons, 12% helium ions, and heavy ions (including iron) (NCRP, 1989).

These high energy particles can cause significant damage to target cells. The different particle types and energies result in different patterns of energy deposition at the molecular and cellular level in a primary target cell. They can also cause significant damage to other, nearby cells as a result of secondary particles. Protons, for instance produce secondaries that include photons, neutrons, pions, heavy particles, as well as gamma rays. Heavy ions deposit energy in a "track" in which the magnitude of the damage varies as the particle loses energy. Heavy ions produce secondary delta rays, or electrons. The distribution of damage through tissue is described by a Bragg curve which will be characteristic for different energies. Needless to say there are differences in the RBE of protons and α particles, see for example (Belli et al., 1992; Goodhead et al., 1992; Jenner et al., 1992).

High-LET heavy ions are particularly damaging to cells as they do continual damage throughout their track. Differences in these energy deposition patterns can significantly influence the nature of DNA damage and the ability of cellular systems to repair such damage. It has been suspected that these differences also affect the spatial distribution of damage within the DNA of the interphase cell nucleus and produce corresponding differences in endpoints related to health effects. The interaction of a single high-LET particle with chromatin has been suggested to cause multiple double strand breaks within a relatively short distance. In part this is due to the organization of DNA into chromatin fibers in which distant regions of the DNA helix can be physically juxtaposed by the various levels of coiling of the DNA (Holley and Chatterjee, 1996). This prediction was confirmed by the detection of the generation of double strand DNA fragments of 100-2000 bp following exposure to high-LET ions (including iron) (Rydberg, 1996).

While it is very clear that ionizing radiation can cause cytogenetic damage and cancer, relatively little is yet known about the mutagenic or carcinogenic effects of high energy HZE particles in cells, for review see (Yang and Craise, 1997). High-LET radiation produces proportionally more double-strand than single strand breaks compared with low-LET radiation (Lett et al., 1987; Roots et al., 1985). Double-strand breaks are likely responsible for the cytogenetic damage visible as chromosomal aberrations, transformation, mutations, and delayed cell death (Yang et al., 1997; Kronenberg et al., 1995; Kronenberg and Little, 1989).

Nearly one-third of the human genome is composed of DNA repeats, which include simple mono-, di-, tri-, and tetranucleotide repeats; widely separated small and large repeats; and inverted repeats. Mutations associated with repetitive DNA are a source of many genetic diseases and cancer. Therefore, understanding how the various kinds of repeats contribute to the disease burden and understanding the impact of DNA damage on repeat-associated genomic instability is important for human health. Such repeated DNA sequences are likely to be very prone to mutation following exposure to high-Z high-energy (HZE) particles during space flight. Cells in the direct line of the HZE particle sustain a high dose of energy while cells surrounding the primary tract sustain a lower dose of energy from the energetic delta rays (electrons) produced by HZE particles. Therefore, the nature and pattern DNA damage to cells in tissue upon irradiation with HZE particles is particularly complex. It is important to understand the types of mutational changes induced by both the HZE particles as well as the delta rays.

Given the high frequency of occurrence of repeated DNA sequences it is highly likely breaks or base damage from radiation will occur within these sequences. Moreover certain processes of repair and recombination involve the generation of free 3' ends in DNA and extended single-strand regions that expose repeats to recombination or primer template misalignments. Therefore, the molecular events that are responsible for cytogenetic damage (chromosomal breaks and rearrangements) and other mutations (point mutations, frameshifts, small deletions and duplications) in many cases will involve primer template misalignments. (Note that we have shown that the molecular mechanism for a hotspot for several +1 frameshift mutations involves intermolecular strand switch events (primer template misalignments) that occur specifically in during leading strand replication at a region containing DNA repeats (Rosche et al., 1998).) It is also possible that a cell sustaining substantial damage from a heavy iron particle hit may saturate some or all of its repair capability, or induce an error prone mode of repair to mediate survival. The types of assays we are developing will provide sensitive reporters of the replication/repair fidelity of a cell following damage from HZE particles. It is the fidelity of this process which, if compromised, will ultimately lead to carcinogenesis or other detrimental effects of radiation damage. With the sensitive reporter lines we are developing, the protective effects of chemopreventive measures or countermeasures can be quickly established. Through the coordination of these studies in the Sprague-Dawley rat mammary cells with the studies for the Johns Hopkins rat study we intend to provide a rapid way to test the efficacy of various countermeasures and chemopreventive drugs with respect to mutation minimization and cancer prevention.

Goal:

The goal of this proposal is to develop data on the relationship between gene mutations, including deletions and recombination associated with direct repeats, and the quantity and quality of the radiation that interacts with the biological system so that countermeasures designed to minimize the health risks of radiation exposure in space can be devised. We will accomplish this by quantifying the rate of deletions between direct repeats, which may involve primer-template

misalignment, recombination, or gene conversion in human cells following exposure to radiations which reproduce the energy deposition patterns produced in individual cells by the radiation environment in space. Using cell lines that provide sensitive reporters of mutations involving deletions between direct repeats and recombination events, we will quantitate the rate of mutations in irradiated cells and in progeny of irradiated cells, following exposure to high energy alpha particles. We will also analyze several biological endpoints in other cells lines that do not contain genetically selectable end points, but which contain long tracts of direct repeats (1.8 mb) or inverted repeats (15.3 kb). In addition, we are developing additional reporter constructs in Sprague-Dawley rat mammary cells to increase the sensitivity of measuring deletions and recombination events mediated by DNA repeats. This will complement the long-term rat carcinogenesis study of the Radiation Effects Group, by providing a rapid, sensitive screen for the effects of chemopreventive and radioprotective drugs on genome instability following exposure to HZE particles and protons.

Hypothesis:

The hypothesis driving this proposal is that DNA damage introduced by high-energy (HZE) particles induces aberrant DNA repair events, involving repeated DNA sequences that lead to recombination, gene conversion, or other mutation, that initiate the sequence of cytogenetic and functional changes which manifest themselves as the long term health effects of radiation exposure in space, including cancer. Knowing the types of mutational events induced by different radiations will contribute to sound decisions for optimizing shielding and reducing biological consequences through use of radioprotective drugs or various countermeasures. The cell lines and procedures utilized in this proposal will be useful for testing the efficacy of various countermeasures and chemopreventive drugs.

Summary of Results to Date.

The results are discussed in section III of the Annual Progress Report. The following highlights significant accomplishments.

- The survival of four cell lines (122-2, F14C-23, 7#7-7, and 3134) following exposure to 250 KeV X-rays has been measured.
- The frequency of deletion of an inverted repeat and a nonpalindromic sequence from a *neo* gene in human 122-2 and F14C-23 cells have been measured (by isolating clones resistant to the antibiotic G-418) following exposure to 250 KeV X-rays.
- The nature of the reversion events, which involve precise deletions between direct repeats, has been analyzed by PCR analysis.
- The rate of reversion or the mutant frequency for the deletion mutations in the *neo* gene have been calculated for control and X-ray exposed cells. The frequencies are about $1-2 \times 10^{-7}$ in sham (non irradiated) cells. The rate increases by as much as a factor of 60 following exposure to X-rays.
- The survival of 122-2 and 3134 cells following Cu-244 alpha particle radiation has been determined.
- The survival and G-418 reversion frequencies following exposure to 1000 MeV Fe particles at the BNL4 run have been measured. Following Cu-244 or Fe exposure, the rate of G-418 reversion increases as much as a factor of 100.

A 650 bp *Alu* inverted repeat has been assembled and is being cloned into a selectable *neo* gene in bacterial plasmids. The construct, a retroviral construct, is also being introduced into Sprague-Dawley rat mammary cancer cells.

**NSBRI RESEARCH PROGRAM
TECHNOLOGY DEVELOPMENT**

Team Leader:	Pisacane, V. L.	Hopkins/APL	
Charles, H. K. Jr.	PI	Hopkins/APL	Miniature X-Ray Bone Densitometer
			B-108
Beck, T. J.	CO-I	Hopkins/SOM	
Feldmesser, H. S.	CO-I	Hopkins/APL	
Pisacane, V. L.	CO-I	Hopkins/APL	
Cohen, R. J.	PI	MIT	Instrumentation for Non-Invasive Assessment of Cardiovascular Regulation
			B-110
Sherman, D. A.	CO-I	MIT	
Potember, R. S.	PI	Hopkins/APL	Miniature Time-of-Flight Mass Spectrometer
			B-111
Bryden, W. A.	CO-I	Hopkins/APL	
Cotter, R. J.	CO-I	Hopkins/SOM	
Pisacane, V. L.	CO-I	Hopkins/APL	
Risby, T. H.	CO-I	Hopkins/SOM	
Maurer, R. H.	PI	Hopkins/APL	In-Situ Spectrometry of Neutrons
			B-114
Dicello, J. F.	CO-I	Hopkins/SOM	
Fainchtein, R.	CO-I	Hopkins/APL	
Gold, R. E.	CO-I	Hopkins/APL	
Goldsten, J. O.	CO-I	Hopkins/APL	
Kinnison, J. D.	CO-I	Hopkins/APL	
Roth, D. R.	CO-I	Hopkins/APL	

TECHNOLOGY DEVELOPMENT TEAM PROGRAM EXECUTIVE SUMMARY

The objective of the Technology Development Program of the National Space Biomedical Research Institute is to develop systems, instrumentation, devices, algorithms, etc., that are important to the work of the other Research Teams in the Institute and the at-large space life science community. The unique feature of the program's effort is the opportunity to bring an integrated engineering systems perspective to bear on technological developments to support basic research. Multi-disciplinary development teams have been established to work on strategically focused projects that integrate individuals with vastly different capabilities into a cohesive team.

Four development projects were selected, by independent review, for pursuit under the technology development program. All projects are active and continue to show progress in achieving their individual goals and objectives. Designs have all been completed and prototype development accomplishments to date portend ultimate success for the projects, though definitive science results are pending. Rigorous design reviews have been conducted in order to preclude unexpected technology issues.

The Compact, High Precision, Multiple Projection DEXA Scanner project is developing a low volume, low power, high accuracy dual x-ray absorptiometer that will afford the ability to measure bone mineral density and composition of soft tissues. This development supports the explicit needs of the Bone Demineralization/Calcium Metabolism and the Muscle Alterations and Atrophy research teams. The project team has completed construction of a laboratory prototype and images are being successfully acquired.

The Instrumentation for Non-Invasive Assessment of Cardiovascular Regulation project is developing instrumentation to non-invasively apply cardiovascular systems identification to identify mechanisms responsible for cardiovascular regulation and alterations. This project directly addresses the needs of the Cardiovascular Alterations research team and may be used to support studies conducted under other team protocols. The project team has completed the development of an engineering prototype system. The prototype has been configured with data acquisition and processing applications. The current goal is to automate all system operations.

The In-Situ Spectrometry of Neutrons project is developing a portable, real-time neutron spectrometer, for the range of 10 KeV to 500 MeV, to support the needs of the Radiation Effects/DNA Damage and Repair research team. The project team has completed a design of the system, which includes three detector subsystems. Test prototypes have been implemented and have been submitted to characterization tests carried out with alpha particles at APL and with neutrons at different energies at Clemson University, Columbia University, and the National Institute of Science and Technology. Additional funding has been granted to pursue measurements from high-altitude aircraft flights.

The Miniature Time-of-Flight Spectrometer project is adapting a high resolution, portable time-of-flight mass spectrometer (TOFMS) for quantitative measurement of human biomarker compounds in space flight. The biomarkers are important to Bone Demineralization/Calcium Metabolism and the Muscle Alterations and Atrophy research teams. Key elements of this project are the development of a reliable sampling method and the quantitation of measurements. The team has demonstrated the ability to routinely detect and accurately quantify (1-2%)

3-methylhistidine in urine. Membrane and electro-spray sample collection processes have been demonstrated. Pursuit of a high molecular weight biomarker (i.e., IGF-1) is under way.

A Technology Development Working Group, composed of representatives from the other research teams, continues to monitor and established technology development needs. The working group continues to participate in teleconferences, team site reviews, and the integration of a technology requirements document (available under separate cover).

The Technology Development team embodies a sense of synergy that is unique to the institute. There is a cohesiveness that exists between the individual project teams and researchers within other research teams. As well, there is a strong intra-team coalition that enables free and open technology interchange. All of these attributes provide a strong basis for contribution to, and support of, the Institute's mission

RESEARCH AREA:	Technology Development
PRINCIPAL INVESTIGATOR:	Harry K. Charles, Jr., Ph.D.
ORGANIZATION:	Johns Hopkins University Applied Physics Laboratory
PROJECT TITLE:	Miniature X-ray Bone Densitometer
FUNDING:	\$310,000 (FY 1998); \$317,440 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The purpose of the Dual Energy X-ray Absorptiometry (DEXA) project is to design, build, and test an advanced X-ray absorptiometry scanner capable of being used to monitor the deleterious effects of weightlessness on the human musculoskeletal system during prolonged spaceflight. The instrument is based on the principles of dual energy x-ray absorptiometry and is designed not only to measure bone, muscle, and fat masses but also to generate structural information about these tissues so that the effects on mechanical integrity may be assessed using biomechanical principles. A skeletal strength assessment could be particularly important for an astronaut embarking on a remote planet where the consequences of a fragility fracture may be catastrophic. The scanner will employ multiple projection images about the long axis of the scanned subject to provide geometric properties in three dimensions, suitable for a three-dimensional structural analysis of the scanned region. The instrument will employ advanced fabrication techniques to minimize volume and mass (100 kg current target with a long-term goal of 60 kg) of the scanner as appropriate for the space environment, while maintaining the required mechanical stability for high precision measurement. The unit will have the precision required to detect changes in bone mass and geometry as small as 1% and changes in muscle mass as small as 5%.

As the system evolves, advanced electronic fabrication technologies such as chip-on-board and multichip modules will be combined with commercial (off-the-shelf) parts to produce a reliable, integrated system which not only minimizes size and weight, but, because of its simplicity, is also cost effective to build and maintain. Additionally, the system is being designed to minimize power consumption. Methods of heat dissipation and mechanical stowage (for the unit when not in use) are being optimized for the space environment.

The DEXA Project is a joint effort among the Technology Development Team and the Bone Demineralization/Calcium Metabolism Team and the Muscle Alterations and Atrophy Team. It will provide the high precision monitoring system necessary to fully assess both the deleterious effects of weightlessness on the bones and muscles and the effectiveness of any countermeasures. We believe that any pharmacological or exercise-related countermeasures used by astronauts to mitigate microgravity effects will require efficient and timely monitoring. Moreover, the monitoring device must be capable of being used by astronauts during spaceflight so that feedback can be dynamically employed to regulate countermeasure doses. The system design will be such that intelligent but not necessarily medically trained personnel will be able to create scans that will provide all of the accuracy and precision necessary. Readouts and displays for the DEXA instrumentation will be specifically designed to provide useful (real-time) feedback information to both the astronauts and the ground-based physician monitoring team (as permitted by the mission dynamics).

There have been several significant accomplishments during Year 2 on the DEXA project with progress in several key areas. (1) The bench-top test bed system was refined by changing the

motor control software to make it simple to translate and rotate for detectors other than the two-line diode array and/or the 256-line CCD array. (2) A third detector was tried and proved to be far superior in spatial and contrast resolution than either of the detectors tried last year. It will also prove to provide a system that uses far less power than a system utilizing either the diode or CCD arrays. (3) The bench-top test bed with the new detector has made some extremely impressive images and we have begun to develop the software to process them. (4) We have developed an advanced 3-element beam monitor detector module for dynamically monitoring x-ray fluence and spectral characteristics during image acquisition. Use of a dynamic beam monitor will enable the achievement of higher short and long-term measurement precision.

There are several new commercial tie-ins and relationships which have been or promise to be advantageous to the DEXA project. In addition to the x-ray source, Varian Medical Systems loaned us a version of their flat panel detector and electronics. They will provide us a more efficient version of the flat panel detector as soon as that is available. CompuMed has signed a letter of intent with us to use our technology and work with them to develop, among other things, smaller versions, perhaps with detectors that we have tried but will not use for the whole body DEXA, for use in ground based clinics for checking fracture risk of extremities.

We will continue to spend considerable time this year optimizing source and detector scenarios (scan rates, tube power, detector types, etc.) utilizing the bench-top test bed. Radiation patterns and detector sensitivity measurements will be performed. Based on these, x-ray technique factors will be selected so that the design for the space-flight-capable high voltage power supply can be started. While working on that, we will be constructing a gantry, procuring a detector that meets our final criteria, and developing the control and image processing software. It is our plan to have a unit capable of measuring patient parameters by the end of calendar 1999 and beginning those patient studies early in calendar 2000.

RESEARCH AREA:	Technology Development
PRINCIPAL INVESTIGATOR:	Richard J. Cohen, M.D., Ph.D.
ORGANIZATION:	Massachusetts Institute of Technology
PROJECT TITLE:	Instrumentation for Non-Invasive Assessment of Cardiovascular Regulation
FUNDING:	\$110,000 (FY 1998); \$112,640 (FY 1999)

PROJECT EXECUTIVE SUMMARY

It is critically important to be able to assess alterations in cardiovascular regulation during and after space flight. We propose to develop an instrument for the non-invasive assessment of such alterations that can be used on the ground and potentially during space flight. This instrumentation would be used by the Cardiovascular Alterations Team at multiple sites for the study of the effects of space flight on the cardiovascular system and the evaluation of countermeasures. In particular, the Cardiovascular Alterations Team will use this instrumentation in conjunction with ground-based human bed-rest studies and during application of acute stresses *e.g.*, tilt, lower body negative pressure, and exercise. In future studies, the Cardiovascular Alterations Team anticipates using this instrumentation to study astronauts before and after space flight and ultimately, during space flight. The instrumentation may also be used by the Bone Demineralization/Calcium Metabolism Team, the Neurovestibular Team and the Human Performance Factors, Sleep and Chronobiology Team to measure changes in autonomic nervous function.

The instrumentation will be based on a powerful new technology – cardiovascular system identification (CSI) – which has been developed in our laboratory. CSI provides a non-invasive approach for the study of alterations in cardiovascular regulation. This approach involves the analysis of second-to-second fluctuations in physiologic signals such as heart rate and non-invasively measured arterial blood pressure in order to characterize quantitatively the physiologic mechanisms responsible for the couplings between these signals. Through the characterization of multiple physiologic mechanisms, CSI provides a closed-loop model of the cardiovascular regulatory state in an individual subject.

The application of CSI currently requires off-line computerized analysis of recorded physiologic signals by an expert user. The user interacts iteratively with the computer to preprocess the data, select data segments for analysis, run the CSI analyses, and evaluate and interpret the results. Thus the availability of this technology is currently limited to highly expert users located in Professor Cohen's laboratory. In this project, we will develop integrated instrumentation capable of acquiring the physiologic signals, performing the CSI analysis in a fully automated fashion, and displaying the results on-line. The design of this instrumentation will be such that users with minimal training (including astronauts and other NSBRI investigators) can perform CSI onsite, conveniently and effectively.

The availability of this instrumentation is essential for effectively studying the cardiovascular effects of space flight and for the subsequent development and evaluation of appropriate countermeasures. The development of such instrumentation may also have significant clinical impact on the diagnosis and treatment of patients with a variety of cardiovascular and neurological disorders.

RESEARCH AREA:	Technology Development
PRINCIPAL INVESTIGATOR:	Richard S. Potember, Ph.D.
ORGANIZATION:	Johns Hopkins University Applied Physics Laboratory
PROJECT TITLE:	Miniature Time-of-Flight Mass Spectrometer
FUNDING:	\$250,000 (FY 1998); \$256,000 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Major advances must occur to protect astronauts from prolonged periods in near-zero gravity and high radiation associated with extended space travel. The dangers of living in space must be thoroughly understood and methods developed to reverse those effects that cannot be avoided. Six of the seven research teams established by the National Space Biomedical Research Institute (NSBRI) are studying biomedical factors for prolonged space travel to deliver effective countermeasures. To develop effective countermeasures, each of these teams require identification of and quantitation of complex pharmacological, hormonal, and growth factor compounds (biomarkers) in humans and in experimental animals to develop an in-depth knowledge of the physiological changes associated with space travel.

At present, identification of each biomarker requires a separate protocol. Many of these procedures are complicated and the identification of each biomarker requires a separate protocol and associated laboratory equipment. To carry all of this equipment and chemicals on a spacecraft would require a complex clinical laboratory; and it would occupy much of the astronaut's time. What is needed is a small, efficient, broadband medical diagnostic instrument to rapidly identify important biomarkers for human space exploration. The Miniature Time-Of-Flight Mass Spectrometer Project in the Technology Development Team is developing a small, high resolution, time-of-flight mass spectrometer (TOFMS) to quantitatively measure biomarkers for human space exploration. Virtues of the JHU/APL TOFMS technologies reside in the promise for a small (less than one cubic ft), lightweight (less than 5 kg), low-power (less than 50 watts), rugged device that can be used continuously with advanced signal processing diagnostics. To date, the JHU/APL program has demonstrated mass capability from under 100 to beyond 10,000 atomic mass units (amu) in a very small, low power prototype for biological analysis. Further, the electronic nature of the TOFMS output makes it ideal for rapid telemetry to earth for in-depth analysis by ground support teams.

The TOFMS will be used to identify and quantify biomarkers and support biomedical research and medical care. Several miniature TOF mass spectrometers are presently under development at The Johns Hopkins University Applied Physics Laboratory (JHU/APL) for a DARPA program to analyze chemical and biological weapons. These prototype instruments have demonstrated the sensitivity and mass range required for monitoring human space exploration. These instruments do not currently perform rigorously quantitative sample analysis. The goal of this program is to demonstrate a quantitative TOF mass spectrometer system from engineering model instruments available from the DARPA program. To achieve this goal, this program will develop the methodology to perform quantitative sample analysis using the MALDI technique. The TOFMS team is using isotopically labeled internal standards to demonstrate that the MALDI-TOF MS can provide quantitative sample analysis of biological analytes. The TOFMS team is also working to minimize crystallization of the analyte with matrix material to improve shot-to-shot repeatability.

The TOFMS Team has completed initial laboratory studies with critical biomarkers identified by the Muscle Alterations and Atrophy Team. The TOFMS Team has recorded full spectrum mass spectral signature of key target biomarker analytes using the MALDI technique at physiological concentrations found in urine. Sampling from urine has been chosen as a high priority in the first year of this program. Compounds under investigation in year one included: insulin-like growth factors (IGF-1), Urinary 3-methylhistidine, and estradiol. IGF-1 is a potent anabolic factor that mimics most of the growth promoting actions of GH *in vivo*. IGF-1 has also been identified by the Bone Demineralization / Calcium Metabolism Team as an important biomarker. Urinary 3-methylhistidine is a measure of myofibrillar protein degradation. 3-methylhistidine cannot be re-utilized by the body. It is rapidly and quantitatively excreted in the urine. Estradiol is a steroid hormone important for the maintenance of muscle mass and bone density. It is widely speculated that steroid hormones such as estradiol play a central role in the early stages of muscle atrophy and bone demineralization.

In addition to IGF-1 and estradiol, the TOFMS Team has also completed initial laboratory studies with biomarkers specific to the Bone Demineralization / Calcium Metabolism Team. These include trivalent hydroxypyridinium crosslinks and creatinine. Trivalent hydroxypyridinium crosslinks are released into the circulation during bone resorption and are excreted as both free pyridinolines. In bone and cartilage, the collagen is bound by pyridinoline or deoxypyridinoline crosslinks. Deoxypyridinoline is found exclusively in bone while pyridinoline is found in skin, joint and cartilage. Creatinine is used to extrapolate the status of bone remodeling activity in various metabolic bone conditions.

In year 2, the TOFMS team used matrix-assisted laser desorption mass spectrometry as tool to quantitatively measure 3-MH in biological fluids. The TOFMS team analyzed various concentrations of 3-methylhistidine in water and in urine to determine the relationship between analyte concentration and analyte molecular ion intensity. The concentrations used in this study were based on 3-methylhistidine concentration typically found in urine, i.e. 20pmole – 3.5nmole. The team examined the utility of two types of internal standards, histidine, a structural analogue, and d_3 -3-methylhistidine, a stable-isotope labeled analogue. 3-Methylhistidine (3-MH) samples in water and urine were prepared ranging from 5 μ M – 10mM, keeping the (3MH)/(histidine) ratio constant at 1:10. Protonated molecular ions for 3MH and histidine could be identified in the corresponding MALDI spectra. A plot of the ratio of relative peak intensities of (3MH)/(d_3 -3-MH) versus 3-MH concentration gave a linear response with a correlation coefficient, $R^2 = 0.9799$ and a relative standard deviation of the slope of 4.00%.

The TOFMS team continued to perform design and development of mass spectrometer system components that can be utilized for diagnostics based on complex, non-volatile biomarkers species. Because this requires multiple (and generally incompatible) ionization sources, we have designed an orthogonal extraction time-of-flight (TOF) mass spectrometer analyzer that will incorporate a dual matrix-assisted laser desorption/ionization (MALDI) and electron ionization (EI) source.

The TOFMS team has also used a breath monitoring system to examine human subjects in order to select molecules that may serve as biomarkers of normal and abnormal physiology. These molecules will be used to direct the selection of molecules to be monitored with the time of flight miniature mass spectrometer.

In year 3, the TOFMS team will continue to explore methods to process urine samples to increase the signal strength of large biomolecules (proteins) in urine. The team will also study a

range of biomarkers found in blood. Sampling from blood will be performed because of the wealth of information that can be collected from blood. Prefiltration or processing of whole blood is expected before the sample can be analyzed because of the large number of other biological compounds that are present in blood.

The TOFMS team will select from the various requirements to one focused on design for the next generation TOFMS for space application. This decision will be based on considerations of sampling (urine, mucous, blood, breath), the classes of biomarkers selected, the technical feasibility, cost, operational concept, user interface, and signal processing decision aids.

RESEARCH AREA:	Technology Development
PRINCIPAL INVESTIGATOR:	Richard H. Maurer, Ph.D.
ORGANIZATION:	Johns Hopkins University Applied Physics Laboratory
PROJECT TITLE:	In-Situ Spectrometry of Neutrons
FUNDING:	\$280,000 (FY 1998); \$316,720 (FY 1999)

PROJECT EXECUTIVE SUMMARY

High energy charged particles of extra-galactic, galactic and solar origin collide with spacecraft structures in Earth orbit outside the atmosphere and in interplanetary travel beyond the Earth's magnetosphere. These primaries create a number of secondary particles inside the structures that can produce a significant ionizing radiation environment. This radiation is a threat to long term inhabitants or travelers for space missions and produces an increased risk of cancer and DNA damage. The primary high energy cosmic rays and trapped protons collide with common spacecraft materials such as aluminum and silicon and create secondary particles inside structures that are mostly protons and neutrons. Charged protons are readily detected and instruments are already in existence for this task. Neutrons are electrically neutral and therefore much more difficult to measure and detect. These neutrons are reported to contribute 30-60% of the dose inside space structures and cannot be ignored. Currently there is no compact, portable and real time neutron detector instrumentation available for use inside spacecraft or on planetary surfaces where astronauts will live and work.

Present neutron detection systems use gas tube proportional counters for the monitoring of low energy (0.025 eV to 1 MeV) neutrons. However for higher energies the detector systems are quite large and massive and often employ passive detection methods which must be recycled and read out after the fact. Physically large neutron diffraction tables are used for accelerator experiments. Emulsions are flown on the Space Shuttle and returned to Earth for analysis. The NASA Ames aircraft uses an instrument built with Bonner spheres which are large spheres of polyethylene moderator some tens of centimeters in diameter with a photodiode in the center and weighing 1500 pounds.

We propose to design and build a portable, low power and robust neutron spectrometer that will measure the neutron spectrum from 10 KeV to 500 MeV with at least 10% energy resolution in the various energy intervals. This instrument will monitor the existing neutron environment both inside spacecraft structures and on planetary surfaces to determine the safest living areas, warn of high fluxes associated with solar storms and assist the NSBRI Radiation Effects Team in making an accurate assessment of increased cancer risk and DNA damage to astronauts. The instrument uses a highly efficient proportional counter Helium 3 tube at the lowest energy intervals where equivalent damage factors for tissue are the highest (10 KeV-2 MeV). The Helium 3 tube may be shielded with a cadmium absorber to eliminate the much less damaging, but more prevalent, thermal and epithermal neutrons and to make the structure of the spectrum more accurate in the 20 KeV-2 MeV range; or a pair of tubes, one shielded and one unshielded, can be combined so that the difference in their counts yields the thermal neutron contribution. The spectrometer also uses a 5mm lithium drifted bulk silicon solid state detector in the medium energy range of 2-20 MeV and two standard silicon surface barrier detectors separated by tens of millimeters behind a 1 cm thick polyethylene moderator in a stack or telescope arrangement for the high energy neutrons (>20 MeV). In the medium and high energy regions equivalent damage factors are lower but hits from one or a small number of neutrons may prove to be important. The silicon detector systems for medium and high energy neutrons will discriminate against charged

particles by using a plastic cesium iodide scintillator of an appropriate geometry monitored by a silicon PIN photodiode.

Presently, we are analyzing the results of a first round of experiments with monoenergetic neutron beams on the Helium 3 tube and 5mm silicon detector systems. Both detector systems have previously been evaluated with Californium (mean energy ~ 1 MeV) and Americium/Beryllium (mean energy ~ 5 MeV) radioactive neutron sources at NIST. The Helium 3 tube exhibited energy resolution of at least 1 KeV over the energy range from 10 KeV to 3 MeV. The efficiency of detection of the tube decreased from 80% at energies of tens to hundreds of KeV to 0.1% as 1 MeV was approached as would be expected from the behavior of the neutron capture cross section for the neutron-Helium 3 reaction over this energy range. The best performing high energy silicon detector from the set of FY 1999 tests proved to be the 5mm thick lithium drifted silicon detector. It demonstrated surprisingly good efficiencies of 1-5% at the Columbia RARAF for neutron beam energies of 2.46, 5.89 and 14 MeV.

The 5 millimeter thickness of the silicon detector is a reasonable fraction of the neutrons' mean free paths in silicon in the 2-20 MeV medium energy range thereby significantly increasing the probability of a neutron-silicon nucleus interaction. We will not use any moderator in this energy interval since we will need to overlap with the Helium 3 tube at this energy without distorting the spectrum and since secondary protons do not readily emerge from polyethylene thicknesses of greater than 1mm. In the high energy region above 20 MeV the substantial progress that we have made with the modeling in FY 1999 has yielded a conceptual design of a stack or telescope of two standard silicon detectors, a 300 micron transmission detector and a 500 micron surface barrier detector, separated by tens of millimeters behind a 1 centimeter thick polyethylene moderator and possibly a tantalum degrader foil. Preliminary results from simulations of the high energy stack show that efficiencies of 5×10^{-4} can be achieved while maintaining 10% energy resolution for neutrons of greater than 50 MeV.

During the remaining part of FY 1999 we are purchasing a second set of detectors together with some needed timing electronics and battery packs for our aircraft flight package. NASA/Dryden has committed several late summer F 18 flights for a version of our spectrometer to monitor avionics environment neutrons and check out our design. After receipt of the purchases, we will resolve some timing discrimination issues with a radioactive Californium source and conduct a second round of experiments at Columbia's RARAF neutron facility. This second visit to Columbia will help us resolve some details that occurred due to the first set of experiments, increase our statistics for better resolution of deposited energy structure in the 5mm detector due to 5.89 MeV neutrons and calibrate both helium tubes and the 5mm detector for the aircraft flights.

**NSBRI RESEARCH PROGRAM
SYNERGY PROJECTS**

Cohen, R. J.	PI	MIT	Alterations in Cardiovascular Regulation and Function During Long-Term Simulated Microgravity (Cardiovascular Alterations – Bone Loss)	B-117
LeBlanc, A.	CO-I	Baylor		
Ramsdell, C. D.	CO-I	Harvard		
Shackelford, L.	CO-I	NASA JSC		
Yelle, J. M.	CO-I	NASA JSC		
Dijk, D.	PI	Harvard	Acute Total and Chronic Partial Sleep Deprivation: Effects on Neurobehavioral Function, Waking EEG and the Renin-Angiotensin System (Cardiovascular Alterations – Human Performance)	B-119
Cajochen, C.	CO-I	Harvard		
Williams, G. H.	CO-I	Harvard		
Ramsdell, C.D.	PI	Harvard	Visual- and Vestibular-Autonomic Influence on Short-Term Cardiovascular Regulatory Mechanisms (Cardiovascular Alterations – Neurovestibular Adaptation)	B-121
Beall, A. C.	CO-I	MIT		
Mullen, T. J.	CO-I	Harvard		
Oman, C. M.	CO-I	MIT		
Paloski, W.	CO-I	NASA JSC		
Wood, S.	CO-I	Baylor		
Yelle, J. M.	CO-I	NASA JSC		
Mullington, J. M.	PI	Harvard	Sustained Partial Sleep Deprivation: Effects on Immune Modulation & Growth Factors (Human Performance – Immunology, Infection & Hematology – Muscle Alterations)	B-123
Butel, J. S.	CO-I	Baylor		
Dinges, D. F.	CO-I	Penn		
Lednický, J. A.	CO-I	Baylor		
Ling, P. D.	CO-I	Baylor		
Schwartz, R. J.	CO-I	Baylor		

SYNERGY AREA: Cardiovascular Alterations - Bone Loss
PRINCIPAL INVESTIGATOR: Richard J. Cohen, M.D., Ph.D.
ORGANIZATION: Harvard Medical School/MIT
PROJECT TITLE: Alterations in Cardiovascular Regulation and Function During Long-Term Simulated Microgravity
FUNDING: \$24,969 (FY 1998); \$224,969 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The Cardiovascular Alterations Team is conducting studies of hemodynamic regulation and susceptibility to arrhythmias resulting from sixteen days of simulated microgravity exposure. In these studies very intensive measurements are made during a short duration of bed rest. In this collaborative effort are making many of the same measurements, however much less frequently, on subjects who are exposed to a much longer duration of simulated microgravity.

Alterations in cardiovascular regulation and function that occur during and after space flight have been reported. These alterations are manifested, for example, by reduced orthostatic tolerance upon reentry to the earth's gravity from space. However, the precise physiologic mechanisms responsible for these alterations remain to be fully elucidated. Perhaps, as a result, effective countermeasures have yet to be developed. In addition, numerous reports from the past 30 years suggest that the incidence of ventricular arrhythmias among astronauts is increased during space flight [Charles *et al.*, 1994, Fritsch-Yelle, *et al.*, 1998]. However, the effects of space flight and the associated physiologic stresses on cardiac conduction processes are not known, and an increase in cardiac susceptibility to arrhythmias has never been quantified.

In this project we are applying the most powerful technologies available to determine, in a ground-based study of long duration space flight, the mechanisms by which space flight affects cardiovascular function, and then on the basis of an understanding of these mechanisms to develop rational and specific countermeasures. To this end we are conducting a collaborative project with the Bone Demineralization/Calcium Metabolism Team of the National Space Biomedical Research Institute (NSBRI). The Bone Team is conducting bed rest studies in human subjects lasting 17 weeks, which provides a unique opportunity to study the effects of long duration microgravity exposure on the human cardiovascular system. We are applying a number of powerful new methods to these long term bed rest subjects, including cardiovascular system identification (CSI), microvolt level T wave alternans analysis, and cardiac magnetic resonance imaging to assess non-invasively the effects of simulated long duration space flight on the cardiovascular system.

CSI involves the mathematical analysis of second-to-second fluctuations in non-invasively measured heart rate, arterial blood pressure (ABP), and instantaneous lung volume (ILV – respiratory activity) in order to characterize quantitatively the physiologic mechanisms responsible for the couplings between these signals. Through the characterization of all the physiologic mechanisms coupling these signals, CSI provides a model of the closed-loop cardiovascular regulatory state in an individual subject. The model includes quantitative descriptions of the heart rate baroreflex as well as other important physiologic mechanisms. With an additional non-invasive measurement of stroke volume (SV – ultrasound Doppler method), the model may be extended to also include the characterization of the peripheral resistance baroreflex – which may play a central role in the development of orthostatic intolerance – and measures of systolic and diastolic function.

To determine whether simulated long-term space flight increases the risk of developing life-threatening heart rhythm disturbances such as sustained ventricular tachycardia (defined as ventricular tachycardia lasting at least 30 seconds or resulting in hemodynamic collapse) and ventricular fibrillation, we are applying a powerful new non-invasive technology, developed in Professor Cohen's laboratory at MIT, for the quantitative assessment of the risk of life-threatening ventricular arrhythmias. This technology involves the measurement of microvolt levels of T wave alternans during exercise stress. In addition, we are obtaining 24-hour Holter monitoring to detect non-sustained ventricular tachycardia and to assess heart rate variability. Finally, in order to investigate the effect of long duration microgravity on cardiac mass, cardiac magnetic resonance images are being obtained before and after the bed rest period.

To date, measurements for CSI, 24-hour Holter monitoring, and cardiac magnetic resonance imaging have been made on seven long-term bed rest subjects. Measurements for TWA analysis have been made in four of these subjects. The studies are still ongoing, and only preliminary analysis of the data has been completed. During Year 3 we will complete the analysis of the data generated in this study.

SYNERGY AREA: Human Performance - Cardiovascular Alterations
PRINCIPAL INVESTIGATOR: Derk-Jan Dijk, Ph.D.
ORGANIZATION: Harvard Medical School
PROJECT TITLE: Acute Total and Chronic Partial Sleep Deprivation: Effects on Neurobehavioral Function, Waking EEG and Renin-Angiotensin System
FUNDING: \$24,896 (FY 1998); \$24,896 (FY 1999)

PROJECT EXECUTIVE SUMMARY

Total sleep deprivation leads to decrements in neurobehavioral performance and changes in electroencephalographic (EEG) oscillations as well as the incidence of slow eye movements as detected in the electro-oculogram (EOG) during wakefulness. Although total sleep deprivation is a powerful tool to investigate the association of EEG/EOG and neurobehavioral decrements, sleep loss during space flight is usually only partial. Furthermore, exposure to the microgravity environment leads to changes in sodium and volume homeostasis and associated renal and cardio-endocrine responses. Some of these changes can be induced in head-down tilt bedrest studies. We integrate research tools and research projects to enhance the fidelity of the simulated conditions of space flight which are characterized by complexity and mutual interactions. The effectiveness of countermeasures and physiologic mechanisms underlying neurobehavioral changes and renal-cardio endocrine changes are investigated in Project 3 of the Human Performance Team and Project 3 of the Cardiovascular Alterations Team respectively. Although the specific aims of these two projects are very different, they employ very similar research protocols. Thus, both projects investigate the effects of posture/bedrest and sleep deprivation (total or partial) on outcome measures relevant to their specific aims. The main aim of this enhancement grant is to exploit the similarities in research protocols by including the assessment of outcome variables relevant to the Renal-Cardio project in the research protocol of Project 3 of the Human Performance Team and by including the assessment of outcome variables relevant to the Quantitative EEG and Sleep Deprivation Project in the research protocols of Project 3 of the Cardiovascular Alterations team. In particular, we will assess Neurobehavioral Function and Waking EEG in the research protocols of the renal-cardio endocrine project and renin-angiotensin and cardiac function in the research protocol of the Quantitative EEG and Waking Neurobehavioral Function project. This will allow us to investigate two additional specific aims:

- 1) Test the hypothesis that chronic partial sleep deprivation during a 17 day bed rest experiment results in deterioration of neurobehavioral function during waking and increases in EEG power density in the theta frequencies, especially in frontal areas of the brain, as well as the nonREM-REM cycle dependent modulation of heart-rate variability.
- 2) Test the hypothesis that acute total sleep deprivation modifies the circadian rhythm of the renin-angiotensin system, changes the acute responsiveness of this system to posture beyond what a microgravity environment alone does and affects the nonREM-REM cycle dependent modulation of heart-rate variability.

The data obtained on the waking EEG and neurobehavioral function in the chronic partial sleep deprivation experiment will complement the data obtained on the effects of total sleep deprivation which are collected in project 3 of the Human Performance Team. The data obtained on the renin-angiotensin levels in the acute total sleep deprivation experiment will complement data obtained on the effects of chronic partial sleep deprivation which will be collected in project

3 of the Cardiovascular Alterations team. We have obtained recording in two subjects who participated in a 24 day laboratory study with 21 days of continuous bedrest. The application of identical research tools and outcome measures in research protocols across the Cardiovascular and Human Performance team will greatly enhance the overall science return of these projects and emphasizes the synergistic nature of this application.

SYNERGY AREA: Cardiovascular Alterations - Neurovestibular Adaptation
PRINCIPAL INVESTIGATOR: Thomas J. Mullen, Ph.D. (1998) Craig D. Ramsdell, M. D. (1999)
ORGANIZATION: Harvard Medical School
PROJECT TITLE: Visual and Vestibular-Autonomic Influence on Short-term Cardiovascular Regulatory Mechanisms
FUNDING: \$24,983 (FY 1998); \$24,983 (FY 1999)

PROJECT EXECUTIVE SUMMARY

This synergy project was a one-year effort conducted cooperatively by members of the NSBRI Cardiovascular Alterations and Neurovestibular Adaptation Teams in collaboration with NASA-Johnson Space Center (JSC) colleagues. The objective of this study was to evaluate visual-autonomic interactions on short-term cardiovascular regulatory mechanisms. Based on established visual-vestibular and vestibular-autonomic shared neural pathways, we hypothesized that visually induced changes in orientation will trigger autonomic cardiovascular reflexes. A second objective was to compare baroreflex changes during postural changes as measured with the new Cardiovascular System Identification (CSI) technique with those measured using a neck barocuff. While the neck barocuff stimulates only the carotid baroreceptors, CSI provides a measure of overall baroreflex responsiveness.

This study involved a repeated measures design with 16 healthy human subjects (8 M, 8 F) to examine cardiovascular regulatory responses during actual and virtual head-upright tilts. Baroreflex sensitivity was first evaluated with subjects in supine and upright positions during actual tilt-table testing using both neck barocuff and CSI methods. The responses to actual tilts during this first session were then compared to responses during visually induced tilt and/or rotation obtained during a second session.

Effect of actual changes in posture on baroreflex responses. CSI involves the mathematical analysis of second-to-second fluctuations in non-invasively measured heart rate (HR), arterial blood pressure (ABP), and instantaneous lung volume (ILV, respiratory activity) in order to characterize quantitatively the physiologic mechanisms responsible for the couplings between these signals. A random interval breathing protocol (mean rate of 12 breaths per minute, inter-breath intervals randomly varying between one and 15 seconds) is utilized to broaden the frequency content of the recorded physiological signals, thereby facilitating CSI. Using the CSI technique, we have previously observed significant alterations to the autonomically mediated coupling mechanisms with a change in posture from supine to upright, while non-autonomically mediated mechanisms are left essentially unchanged. Further analysis of data from this first session will utilize CSI measurements to confirm this result, and to quantitatively compare the neck barocuff method with CSI in estimating baroreflex sensitivity.

Carotid baroreflex responses were obtained in both supine and head upright tilt positions using the neck barocuff employed according to the method described by Fritsch *et al.* (1992). This technique allows assessment of vagally mediated carotid baroreceptor-cardiac reflex responses provoked by neck pressure and suction steps during held expiration. Pressure was increased to 40 mmHg for 5 cardiac cycles, reduced by 15 mmHg decrements after each of the next seven R waves to -65 mmHg, and finally returned to ambient levels. Responses from up to four successful repetitions of this stimulus sequence during both supine and upright positions were

averaged. R-R intervals were plotted against carotid distending pressure (taken to be systolic minus neck chamber pressures). There were significant differences between male and female subjects for minimum, maximum and control RR interval ($p < 0.01$). For both male and female subjects, there were highly significant decreases ($p < 0.0001$) in minimum, maximum and control RR intervals when subjects were tilted from the supine to upright position. There were not; however, significant differences in either the RR interval ranges or maximum slopes between these positions.

Cardiovascular responses during virtual tilt and/or rotation. A second session with the same subjects was then used to examine the effects of visually induced virtual tilt and/or rotation stimuli in modulating autonomic cardiovascular reflexes. One of the stimuli involved a simple "mirror bed" to provide an illusion of body tilt without rotation. This device involved mounting a mirror over a subject in a supine orientation to align surrounding visual vertical cues with the subject's longitudinal body axis. In addition to the mirror bed, visually induced tilt and/or rotation illusions were elicited by a full-field virtual environment generator at NASA known as the Preflight Adaptation Trainer DOME. The subject was supine with the head positioned near the center of this large spherical DOME. A virtual scene aligned with the longitudinal body axis was then rotated in the subject's pitch, yaw or roll planes to elicit sensations of tilt and/or rotation. The pitch and yaw DOME visual stimuli rotated about an earth horizontal axis producing the paradoxical sense of tilt and rotation. The roll visual stimulus, on the other hand, rotated about an earth vertical axis typically resulting in the sense of rotation without tilt.

The visual conditions were therefore chosen to provide the following combinations of perceived tilt and/or rotation:

- Mirror bed – perceived tilt without rotation
- DOME Pitch and Yaw – perceived tilt and rotation
- DOME Roll – perceived rotation without tilt

Although there was a high degree of variability across subjects, the mean responses reflect the expected combinations of perceived tilt and rotation described above. The mirror bed was rated by subjects to be the most compelling, with the perceived orientation of the head (54.7 ± 6.7 , mean \pm SEM) slightly greater than the perceived orientation of the body (45.0 ± 5.7). Cardiovascular responses were recorded during 2 min prior to the start of each virtual tilt and during the initial three minutes with eyes open. Although the data appear to be quite variable, there were a few instances when the changes were quite dramatic. For example, rapid decreases in both systolic and diastolic pressure were observed in some subjects at the onset of the virtual tilt similar to the changes in blood pressure to an actual change in body posture on a tilt table.

Our preliminary results suggest that visually induced virtual tilt can elicit at least transient cardiovascular changes in some individuals. Pending further analysis, we expect to find that the degree of change in cardiovascular reflexes will correlate with individual measures of tilt perception. We will further characterize these effects on cardiovascular regulatory mechanisms using CSI, and expect that visually induced tilts will result in reductions in HR baroreflex sensitivity. The significance of these findings is that virtual environment stimuli may be used in the future to enhance cardiovascular and/or vestibular countermeasures for long-duration spaceflight.

**SYNERGY AREA: Human Performance - Immunology, Infection and Hematology -
Muscle Alterations**

PRINCIPAL INVESTIGATOR: Janet M. Mullington, Ph.D.

ORGANIZATION: Harvard Medical School

**PROJECT TITLE: Sustained Partial Sleep Deprivation: Effects on Immune Modulation
& Growth Factors**

FUNDING: \$25,000 (FY 1998); \$25,000 (FY 1999)

PROJECT EXECUTIVE SUMMARY

The vulnerability to medical emergencies is greatest in space where there are real limits to the availability or effectiveness of ground based assistance. Moreover, astronaut safety and health maintenance will be of increasing importance as we venture out into space for extended periods of time. It is therefore critical to understand the mechanisms of the regulatory physiology of homeostatic systems (sleep, circadian, neuroendocrine, fluid and nutritional balance) and the key roles played in adaptation. This synergy project has combined aims of the "*Human Performance Factors, Sleep and Chronobiology Team*"; the "*Immunology, Infection and Hematology Team*"; and the "*Muscle Alterations and Atrophy Team*", to broadly address the effects of long term sleep reduction, as is frequently encountered in space exploration, on neuroendocrine, neuroimmune and circulating growth factors. Astronaut sleep is frequently curtailed to averages of between 4-6.5 hours per night. There is evidence that this amount of sleep is inadequate for maintaining optimal daytime functioning. However, there is a lack of information concerning the effects of chronic sleep restriction, or reduction, on regulatory physiology in general, and there have been no controlled studies of the cumulative effects of chronic sleep reduction on neuroendocrine and neuroimmune parameters.

This synergy project represents a pilot study designed to characterize the effects of chronic partial sleep deprivation (PSD) on neuroendocrine, neuroimmune and growth factors. This project draws its subjects from two (of 18) conditions of the larger NSBRI project, "*Countermeasures to Neurobehavioral Deficits from Cumulative Partial Sleep Deprivation During Space Flight*" (PI: David Dinges), one of the projects on the "*Human Performance Factors, Sleep and Chronobiology Team*". For the purposes of this study, to investigate the effects of chronic sleep loss on neuroendocrine and neuroimmune function, we have focused on the two extreme sleep conditions from this larger study: a 4.2 hour per night condition, and a 8.2 hour per night condition.

During space flight, muscle mass and bone density are reduced, apparently due to loss of GH and IGF-I, associated with microgravity. Since >70% of growth hormone (GH) is secreted at night in normal adults, we hypothesized that the chronic sleep restriction to 4 hours per night would reduce GH levels as measured in the periphery. In this synergy project, in collaboration with the "*Muscle Alterations and Atrophy Team*", we are measuring insulin-like growth factor-I (IGF-I) in peripheral circulation to test the prediction that it will be reduced by chronic sleep restriction.

In addition to stress modulation of immune function, recent research suggests that sleep is also involved. While we all have the common experience of being sleepy when suffering from infection, and being susceptible to infection when not getting enough sleep, the mechanisms involved in this process are not understood and until recently have gone largely overlooked. We believe that the immune function changes seen in spaceflight may also be related to the cumulative effects of sleep loss. Moreover, in space flight, the possibility of compromised

immune function or of the reactivation of latent viruses are serious potential hazards for the success of long term missions. Confined living conditions, reduced sleep, altered diet and stress are all factors that may compromise immune function, thereby increasing the risks of developing and transmitting disease. Medical complications, which would not pose serious problems on earth, may be disastrous if they emerged in space.

**NIDCD-NSBRI JOINT PROGRAM FOR THE SUPPORT OF
VESTIBULAR RESEARCH**

Proposals Received: October 1998

Proposals Selected: June - September 1999

Year 1 Funding: \$1,413 K
(NIH - \$1,168 K; NSBRI private - \$245 K)

Total Funding: \$7,018 K
(NIH - \$6,126 K; NSBRI private - \$892 K)

- | | | |
|--|----------|------------------------------------|
| 1. Baylor College of Medicine: Helen COHEN, Ed.D. | Funding: | Yr. 1: \$112 K
Total: \$501 K |
| <i>MANAGEMENT OF ADAPTATION TO ALTERED SENSORIMOTOR STATES</i> | | |
| Co-Is: Jacob Bloomberg, Ph.D. (NASA JSC) | | |
| 2. Harvard University: Daniel MERFELD, Ph.D. | Funding: | Yr. 1: \$299 K
Total: \$1,465 K |
| <i>DECODING OF GRAVICEPTOR CUES, INCLUDING ADAPTIVE CHANGES</i> | | |
| Co-Is: Conrad Wall, Ph.D.
Lionel Zupan, Ph.D.
Robert Peterka, Ph.D. (Oregon Health Sciences U.)
Mark Shelhamer, D.Sc. (Johns Hopkins Univ.) | | |
| 3. Stanford University: Jennifer RAYMOND, Ph.D. | Funding: | Yr. 1: \$287 K
Total: \$1,659 |
| <i>VESTIBULAR AND VISUAL CONTROL OF EYE MOVEMENT</i> | | |
| 4. *Univ. of Mississippi Medical Ctr: W. Michael KING, Ph.D. | Funding: | Yr. 1: \$245 K
Total: \$892 K |
| <i>SIGNAL PROCESSING AND ADAPTATION IN CENTRAL OTOLITH PATHWAYS</i> | | |
| Co-Is: Wu Zhou, Ph.D. | | |
| 5. University of Rochester: Scott SEIDMAN, Ph.D. | Funding: | Yr. 1: \$241 K
Total: \$1,318 K |
| <i>PLASTICITY IN THE VESTIBULOOCULAR REFLEXES AND PERCEPTION</i> | | |
| Co-Is: Gary Paige, M.D., Ph.D. | | |
| 6. Wash. Univ. School of Medicine: Dora ANGELAKI, Ph.D. | Funding: | Yr. 1: \$229 K
Total: \$1,183 K |
| <i>NEURAL MECHANISMS OF VESTIBULAR ADAPTATION</i> | | |
| Co-Is: J. David Dickman, Ph.D. | | |

*NSBRI supported from private funding sources.

**Agreement of Cooperation
Between the
Institute for Space Physiology and Medicine (MEDES)
and the
National Space Biomedical Research Institute**

June 16, 1999

**AGREEMENT OF COOPERATION BETWEEN
THE INSTITUTE FOR SPACE PHYSIOLOGY AND MEDICINE (MEDES)
AND THE NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE**

This agreement is between the **INSTITUTE FOR SPACE PHYSIOLOGY AND MEDICINE** (Institut de Médecine et de Physiologie Spatiales, MEDES), and the **NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE** (NSBRI) and is effective as of the date set forth herein.

WHEREAS the **INSTITUTE FOR SPACE PHYSIOLOGY AND MEDICINE (MEDES)** CHU Rangueil, 1, Av. Jean Poulhès, 31403 Toulouse Cedex 4, France, and the **NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE**, One Baylor Plaza, NA-425, Houston, Texas 77030-3498, U.S.A, share a common interest in the human exploration and development of space and similar scientific, academic and professional objectives; and

WHEREAS both institutions are desirous of increasing the human and scientific relations which would contribute to the achievement of aims which both pursue.

NOW, THEREFORE, the parties do agree as follows:

- 1) Because of their general interest in the human exploration and development of space, the Parties agree to consider developing cooperative projects that support the following general categories of activity:
 - (a) Basic and applied research related to the development of countermeasures to the deleterious effects of space flight, including research on physiological adaptation to the spaceflight environment;
 - (b) Biomedical, psychosocial and performance research utilizing analog environments, model systems and simulation techniques;
 - (c) Special studies involving advanced technology, telemedicine, telescience, and advanced life support systems;
 - (d) Development of education and outreach programs for the schools and the general public; and
 - (e) Application of space research to the improvement of human health on Earth.

- 2) Within these general categories, the parties agree to undertake specific activities from time to time aimed at furthering the following general objectives:
 - (a) joint projects involving research, technological development, or education and outreach;
 - (b) exchange of scientists;
 - (c) joint or coordinated organization of seminars and meetings on subjects of mutual interest;
 - (d) reciprocal use of research findings and other published information;
 - (e) exchange of research and teaching materials and use of facilities;
 - (f) exchange of publications; and
 - (g) development of appropriate postgraduate, graduate and undergraduate student exchange programs according to academic rules jointly adopted, but subject to legislation in force in each country and within cooperating institutions.

All such activities shall be subject to the budgetary resources available to, and any legal restrictions applicable to the activities of, the parties.

Appendix D

- 3) Each project created under this agreement must be reduced to a separate, formal, written agreement which must be signed by authorized representatives of the parties before such a project can be deemed in effect and, accordingly, binding on either party.
- 4) By means of the special agreements reduced to writing and signed by authorized persons, the parties shall determine specific areas and programs of cooperation, as well as the terms, methods, financial conditions and procedures of specific projects. As a governing principle for all such agreements, and unless otherwise agreed to in writing, all costs and expenses related to implementation of a project – direct or indirect costs and expenses, costs of equipment and supplies, travel, etc. – and all expenses as are created pursuant to said agreements – travel, housing, living expenses, stipends, benefits (including, but not limited to, health and life insurance), licensure, malpractice insurance, etc. – will be paid by the sending party. Neither party will be responsible for any costs and expenses incurred in any respect by the other party or its students, residents or faculty unless expressly agreed to by separate written agreement signed by authorized representatives of the parties.
- 5) The parties agree that, within the scope of this instrument and upon approval of the parties, other qualified institutions may be invited to participate in the various projects envisioned by this agreement.
- 6) The parties agree that, as an essential proposition to any cooperative endeavor, all individual participants in projects created pursuant to this agreement will be selected with full respect for equal opportunity for all persons in accordance with the policies of each party and without regard to the race, sex, age, national origin or religious affiliation of participants or candidates for participation.
- 7) The parties acknowledge that, due to the unique professional, institutional, and legal requirements for registration, enrollment and certification applicable to each party, student participants in the various projects envisioned by this agreement will be registered and/or enrolled in and will receive certification and/or degrees from only the sending party. Accordingly, project participants will not automatically be registered and/or enrolled in, nor will they receive degrees from the receiving party, unless specifically accepted by the receiving institution and meeting their requirements.
- 8) While it is not contemplated that any projects implemented pursuant to this agreement will involve the rendition of health care services by professionals out of their country, the parties acknowledge that all physicians or other health care professionals who wish to participate in the rendition of patient care shall be solely responsible, at their expense or the expense of the sending party, for securing requisite licensure and all other authorization and any malpractice or other insurance coverage as may be required by law or applicable institutional and hospital policies and procedures.
- 9) This agreement is not exclusive and does not restrict either party from developing agreements with other institutes, institutions, or agencies.
- 10) This agreement will enter into force on June 16, 1999 and will continue in effect for five (5) years from that date. It shall be renewed for equal periods, unless one of the parties notifies the other in writing of its desire to terminate such agreement at least three (3) months prior to the date of termination.

11) Entered into in the City of Paris, France, by means of the execution of two counterpart originals.

FOR THE INSTITUTE FOR SPACE PHYSIOLOGY AND MEDICINE (MEDES), TOULOUSE, FRANCE

By: Original Signed By June 16, 1999

René Rettig
President of MEDES

Date

FOR THE NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE, HOUSTON, TEXAS, U.S.A.

By: Original Signed By June 16, 1999

Laurence R. Young, Sc.D.
Director, NSBRI

Date

Approval:

By: Original Signed By June 16, 1999

Bobby R. Alford, M.D.
Chairman of the Board and Chief Executive Officer, NSBRI

Date

**Framework Agreement
Between
The Politecnico di Milano
and the
National Space Biomedical Research Institute**

April 15, 1999

FRAMEWORK AGREEMENT

The **POLITECNICO DI MILANO**, with legal domicile at piazza Leonardo da Vinci 32, 20133 Milano (Italy), and represented by the Rector, Prof. Adriano De Maio

and

the **NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE**, with legal domicile at One Baylor Plaza, NA-425, Houston, Texas 77030-3498, U.S.A., and represented by the Director, Prof. Laurence Young, Sc.D.

pledge

to promote activities and projects of mutual interest in the human exploration and development of space and in space biomedical research, particularly concerning:

- the organization of seminars, courses, workshops, summer schools, internships/ placements, and other similar initiatives;
- the development of cooperative studies and collaborative research projects;
- the organization of lectures, meetings, congresses, and/or symposia to exchange knowledge and experience;
- the exchange of documentation: works, reviews, pedagogical documentation, and exhibitions; and
- the exchange of teachers, researchers, technicians and students.

The joint actions and cooperative projects under this framework will be defined through separate formal, written project agreements signed by both parties. In order to determine the most effective joint activities to develop into projects, a committee of members belonging to the parties may be established.

This framework agreement will come into force on the date of the signature of both parties and will have a term of five years. This agreement can be renewed after verification of the activities developed during its duration and previously defined by specific project agreements.

This agreement may be amended by the mutual consent of the parties hereto. Any party may withdraw from this agreement on six months written notice, provided that all activities in effect at the time of such notice shall be permitted to be completed in the same manner as if no such notice was given.

This agreement is written in Italian and English with the same content.

The signing of this framework agreement does not entail any financial obligation for the parties. This agreement consists only of a declaration of intent for cooperation and collaboration in the field of teaching and research programs in accordance with the terms explained above. All project agreements concerning specific activities between the parties must be implemented within the framework defined by this agreement. The parties agree to resolve any controversy arising from the interpretation of the present framework agreement in a friendly manner. In case such a resolution cannot be achieved, the controversy will be submitted for arbitration to an *ad hoc* three-member panel; each party will appoint one member of the arbitration panel, and the third member will be chosen by mutual consent.

FOR THE POLITECNICO DI MILANO

By: Original Signed By April 15, 1999

Prof. Adriano De Maio
The Rector

Date

FOR THE NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

By: Original Signed By April 15, 1999

Laurence R. Young, Sc.D.
Director

Date

Approval:

By: Original Signed By April 29, 1999

Bobby R. Alford, M.D.
Chairman of the Board and Chief Executive Officer

Contract
Between the
State Research Center of Russian Federation - Institute for
Biomedical Problems of the Ministry of Health
and the
National Space Biomedical Research Institute

August 9, 1999

CONTRACT

This contract is between the National Space Biomedical Research Institute, Houston, Texas, USA (hereinafter referred to as the NSBRI) and the State Research Center of Russian Federation - Institute for Biomedical Problems of the Ministry of Health, Moscow, Russia (hereinafter referred to as IBMP).

The NSBRI and the IBMP, hereinafter referred to as the "Parties," have agreed to the following articles.

ARTICLE 1: SUBJECT OF THE CONTRACT

The subject of this Contract between the NSBRI and the IBMP is the performance of the experiments proposed by the NSBRI and listed below, within the framework of Russian SFINCSS-99 (Simulation of Flight of International Crew on Space Station) program:

1. Latent Virus Reactivation During a 240-Day Chamber Study of SFINCSS Program (Description of the experiment is attached in the Appendix 1).
2. Use of Venipuncture to Monitor Wound Healing During a Chamber Study of SFINCSS Program (Description of the experiment is attached in the Appendix 2).

ARTICLE 2: OBLIGATIONS OF THE PARTIES

2.1. Obligations of IBMP

The IBMP takes upon itself the following obligations:

- 1) To support the performance of the two experiments, "Latent Virus Reactivation During a 240-Day Chamber Study of SFINCSS Program" and "Use of Venipuncture to Monitor Wound Healing During a Chamber Study of SFINCSS Program," in accordance with Appendixes 1 and 2.
- 2) To prepare the data, biological samples, films and other material resulting from and obtained for these two experiments for transferal to the USA.
- 3) To prepare the technical-operational report (one copy in English), and to transfer it to the NSBRI within 60 days after the final readaptation period of SFINCSS program ends. The table of contents of the report is attached in Appendix 3.

2.2. Obligations of the NSBRI

- 1) To deliver the supplies necessary for the performance of the experiment "Latent Virus Reactivation During a 240-Day Chamber Study of SFINCSS Program" in a timely manner. The list of supplies is attached in Appendix 4.
- 2) To deliver the equipment and supplies necessary for the performance of the experiment "Use of Venipuncture to Monitor Wound Healing During a Chamber Study of SFINCSS Program" in a timely manner. The list of equipment and supplies is attached in Appendix 5.
- 3) To familiarize IBMP specialists with the special methodologies required to carry out the protocols that support both experiments.
- 4) To transfer the data, biological samples, films, and other materials mentioned in item 2.1 (2) above from Russia to the USA.

ARTICLE 3: FINANCIAL CONDITIONS

3.1. The cost of the work carried out by the IBMP to implement the Russian SFINCSS-99 program, resulting in the report whose contents are listed in Appendix 3, is US\$ 25,000 (twenty five thousand US dollars). This price shall be final and definitive except when the Parties agree on any revision of the price reflecting future modification of the experiment protocols described in Appendixes 1 and 2. The cost of equipment and supplies provided by the NSBRI in accordance with Article 2 (item 2.2) is not included in the cost above.

3.2. The payment of the price shall be made as follows:

3.2.1. US\$ 15,000 shall be paid within 30 days from the date of signing of the Contract by both Parties.

3.2.2. US\$ 10,000 shall be paid within 45 days from the date of receipt by NSBRI of technical-operational report.

3.3. All payments shall be made by NSBRI by cable remittance to the IBMP's account No.40502840400000000555 in VNESH TORGBANK, SWIFT VTBRUMM

or

to the account of the DONAU-BANK AG, Vienna in Credit Lyonnais, New York No. 0100-678000-100 in favour of a/c of VNESH TORGBANK No. 617203-413. Beneficiary: the State Research Center of Russian Federation - Institute for Biomedical Problems (76-A, Khoroshevskoye Shosse, 123007, Moscow, Russia), No. 40502840400000000555 in VNESH TORGBANK.

SWIFT DONAU BANK AG, VIENNA: DOBA AT WW

SWIFT Credit Lyonnais, New York: CRLY US-33

Address of VNESH TORGBANK: 103031

16 Kuznetsky Most,
Moscow
Russia

Phone: +007-095-204-64-40/41/42

Telex: 412362 BFTR RU

Fax: +007-095-956-37-27

All payments on this Contract are accepted as net payments in favor of the IBMP without any deductions.

ARTICLE 4: TAXES AND DUTIES

4.1. All duties, taxes and other expenses in connection with this Contract charged in the territory of the USA, as well as expenses charged in the USA in connection with currency exchange and transfer of all the payments to the IBMP's account above mentioned shall be borne by the NSBRI.

4.2. All duties, taxes and other expenses in connection with this Contract charged in the territory of Russia, shall be borne by IBMP. However, customs payments or duties imposed

in Russia on the data, information, materials and samples (including biological ones) obtained under this Contract, as well as equipment and supplies necessary for the implementation of this Contract, shall be borne by the NSBRI.

ARTICLE 5: CONFIDENTIALITY

Each Party maintains ownership of results of patented and non-patented work, derived from experience and knowledge obtained before this Contract came into force. The IBMP and the NSBRI will preserve confidentiality of all written and oral information and data related to this Contract, using such information solely in performing work covered by this Contract. Each Party will take appropriate measures to ensure preservation of confidentiality of the said data by its personnel. All results of the study will be presented anonymously so that the subjects may not be identified. Investigators will make every attempt to ensure that the results of this study will never be used against the subjects.

ARTICLE 6: USE OF INFORMATION, PUBLICATIONS

The NSBRI will be free to use, disclose to a third party, and publish results of investigations performed under this Contract, making appropriate reference to the IBMP.

ARTICLE 7. CUSTOMS CLEARANCE

7.1. The IBMP shall assist the NSBRI by facilitating prompt customs clearance to and from Russia, of: (1) the data, information, materials and samples (including biological ones) obtained under this Contract; and (2) the equipment and supplies of the NSBRI necessary to implement this Agreement.

7.2. The NSBRI shall provide the IBMP with all documents and permissions, if any, required by the Russian Customs Authorities for entering into and exiting from Russia in connection with ARTICLE 7.1.

ARTICLE 8: FORCE MAJEURE

8.1. In cases of force majeure circumstances (fire, flood, earthquake, war) which are beyond the Parties control and prevent fulfillment of obligations under this Contract, the schedule and timelines for the fulfillment of such obligations shall be appropriately extended in accordance with the duration of force majeure circumstances.

8.2. The Parties will immediately inform each other about the beginning and the end of force majeure circumstances. A certificate given by the Chamber of Commerce of the appropriate country will be proof of the existence of force majeure circumstances. Failure to notify or untimely notification will result in the loss of right to refer to any such circumstance as a factor freeing a Party of responsibility for failure to fulfill its obligations.

8.3. If force majeure circumstances last longer than three (3) months, either of the parties will be free to cancel this Contract, notifying the other side of its intention in writing 30 days before the proposed cancellation date, without any material claims to each other.

ARTICLE 9: ARBITRATION

9.1. In case of any dispute and/or differences between the NSBRI and the IBMP resulting from this Contract or related to its fulfillment, the Parties will take all possible measures to settle them by negotiations.

9.2. If the Parties fail to settle disputes in accordance with article 9.1. by negotiations, such disputes will be finally settled under the Rules of Conciliation and Arbitration of the International Chamber of Commerce by one or more arbitrators appointed in accordance with the said Rules.

ARTICLE 10: OTHER TERMS

10.1. All amendments to this Contract will be in writing and signed by both Parties.

10.2. This Contract has been written and signed in two original copies in English. The NSBRI and the IBMP get one copy each.

ARTICLE 11: DURATION

This Contract will become effective as of the date of the last signature of the Parties and will remain in force until such time as the works and the payments of all financial obligations set forth herein have been completed.

ARTICLE 12: LEGAL ADDRESSES OF THE PARTIES

The NSBRI

The National Space Biomedical Research Institute
One Baylor Plaza, NA-425
Houston, Texas 77030-3498
Tel.: 713-798-7412
Fax: 713-798-7413

The IBMP

Russia
123007, Moscow,
Khoroshevskoye shosse, 76A
Tel.: +007 095195 23 63
Fax: +007 095 195 22 53
Telex: 411048 VUAL SU

For the NSBRI (USA):

For the IBMP (Russia):

Associate Director, NSBRI

Director

Original Signed By July 16, 1999
R. J. White Date

Original Signed By August 9, 1999
A. I. Grigoriev Date

Appendix 1

Description of the experiment “Latent Virus Reactivation During a 240-Day Chamber Study of SFINCSS Program”

Principal investigator: Janet S. Butel, Ph.D

Co-Investigators: John A. Lednicky, Ph.D., NSBRI
Paul D. Ling, Ph.D., NSBRI
Duane L. Pierson, Ph.D., JSC, NASA
Satish K. Mehta, Ph.D., JSC, NASA

Study plan and schedule:

Dates/duration: The planned duration of the study will extend from 4 weeks before chamber entry, throughout the 240-day chamber isolation, and for another 4 weeks after termination of chamber isolation.

Subjects: Crew members of SFINCSS-99, including the members of Crew 1, Crew 2, and Crew 3.

Regularity:

- 1) saliva samples will be collected upon arising at defined intervals before isolation (weekly, beginning four weeks before isolation in Groups 2 and 3; and three times, 11, 8, and 5 days before isolation in Group 1), and weekly during and after the isolation, ending four weeks after the isolation.
- 2) urine samples will be collected at defined intervals before isolation (weekly, beginning four weeks before isolation in Groups 2 and 3; and three times, 11, 8, and 5 days before isolation in Group 1), and weekly during and after the isolation, ending four weeks after the isolation.
- 3) blood samples will be collected 31 and 17 days before isolation in Groups 2 and 3 and 11 days before isolation in Group 1, then at monthly intervals during isolation and 1 month after isolation.

If necessary, sample collections may end at Recovery +15 days rather than R + 30 days for members of Groups 2 and 3. This would result in 2 fewer saliva and urine samples from each of those participants, and in the final blood sample being taken at 2 weeks rather than 1 month after isolation.

For the entire study, each member of Crew #1 will provide a total of 41 saliva samples, 41 urine specimens, and 10 blood samples. Each member of Crew #2 and Crew #3 will provide a total of 22 saliva samples, 22 urine specimens, and 7 blood samples (assuming that collections from Crews #2 and #3 end at R + 15 days).

Procedure for Collection and Processing of Saliva Samples

Collection of Saliva Samples:

1. Saliva is collected using saliva collection kits, which consist of a sterile plastic vial containing a sterile cotton-wool dental roll (Saliva Pledgettes, Sarstedt).
2. The cotton roll is removed from the vial and placed in the mouth.
3. The person chews on the cotton roll (for about 1 minute) until it is saturated with saliva.
4. The cotton roll is spit back into the plastic vial.
5. The vial is labeled.

Processing of Saliva Samples for Storage:

1. Collection tubes containing saliva-soaked cotton rolls are centrifuged at $1000 \times g$ for 5 min at 25°C .
2. Saliva is removed and aliquoted into two or three 1-ml samples (two or three screwcap cryovials), depending on the amount of saliva.
3. Freeze at -60 to -70°C .

Note: No preservative is added.

Procedure for Collection and Processing of Urine Samples

Collection of Urine Samples:

1. Collect at least 20 ml midstream urine in sterile cup.
2. Label the cup.

Processing of Urine Samples for Storage:

1. The cup containing the urine specimen is gently swirled to mix contents (soluble as well as particulate material) thoroughly.
2. Using a sterile 25-ml pipet, aseptically withdraw 20 ml of urine (including particulate material); transfer 10 ml of urine into each of two (2) sterile 15-ml polypropylene tubes.
3. Label tubes.
4. Store at -20°C .

Note 1: Urine should be transferred into tubes for freezing as soon as possible. However, urine can be stored at $0-4^{\circ}\text{C}$ for short periods of time prior to preparation for storage (≤ 4 hours).

Note 2: No preservative is added.

Procedure for Collection and Processing of Blood Samples

Collection of Blood Samples:

1. Blood is collected aseptically in ACD (acid-citrate dextrose) Vacutainer Venous Blood Collection Tubes (Becton Dickinson). These tubes have a capacity of up to 8.5 ml; three tubes will suffice per person (total of 15–20 ml of whole blood, anticoagulated).
2. Label the ACD blood tubes.

Processing of Blood Samples for Storage:

1. Lymphocytes and other mononuclear cells (WBCs) are separated from the whole blood by centrifugation through a Histopaque solution in sterile tubes (Accuspin™ System-Histopaque-1077) as described below.
2. Anticoagulated blood from the 3 ACD tubes is layered onto two Accuspin Histopaque-containing tubes (10 ml blood/Accuspin tube).
3. The Accuspin tubes are labeled.
4. The Accuspin tubes containing the blood are centrifuged at $1000 \times g$ for 10 min at room temperature. Red blood cells are pelleted and white blood cells (WBCs) form a band that appears intermediate between a porous cell barrier (“frit”) and the clear plasma layer.
5. The clear plasma layer is aseptically removed (from the top down close to the WBC band) using a 10-ml pipet.
6. The plasma is transferred to two sterile polypropylene tubes for storage.
7. The plasma tubes are labeled.
8. The plasma tubes are stored at -20°C .
Note: No preservative is added.
9. The white blood cell (WBC) layer is collected using a sterile 5-ml pipet and transferred to a sterile 50-ml polypropylene centrifuge tube.
10. The 50-ml tubes are labeled.
11. The tubes are brought up to ≈ 40 ml in volume with phosphate-buffered saline (PBS) (pH 7.2), the cells are gently mixed, and then centrifuged for 10 min at $2000 \times g$ at 25°C .
12. Most of the fluid is removed and discarded using a sterile pre-wrapped 25-ml pipet, leaving about 3 ml of buffer inside the tube covering the pelleted cells.
13. The cells are resuspended in the 3 ml of buffer and, using a sterile 5-ml pipet, 1-ml aliquots are transferred to each of 3 screwcap cryovial tubes.
14. The cryovial tubes are labeled.
15. The cryovial tubes are centrifuged for 5 min at 5000 rpm in a centrifuge. The liquid is removed using a sterile 1-ml pipet and discarded.
16. The vials containing the pelleted cells are stored at -60 to -70°C .

Appendix 2

Description of the experiment “Use of Venipuncture to Monitor Wound Healing During a Chamber Study of SFINCSS Program”

Investigators: James E. Smolen, Ph.D.; Kirsten Poehlmann, Ph.D.

Schedule:

Pre-isolation training and baseline data collection: Assign photographer to take pictures and plan Venipuncture Information Sheets. Take initial photographs of recoveries from pre-isolation blood draws.

Isolation activities: Photograph recoveries from blood draws taken from isolated cosmonauts.

Post-isolation activities: Take photographs of recoveries from blood draws taken from cosmonauts after they are removed from isolation.

Procedure: At the time of each venipuncture, it is important to record relevant information. The phlebotomists involved in the study will be asked to complete a Venipuncture Information Sheet immediately following the procedure. This sheet will include information about the identity of the phlebotomist, if there were any problems at the time of the puncture, the amount of blood drawn and the test for which the blood was drawn, etc.

For each wound, 3 photographs at 1/2 stop exposure intervals should be taken just prior to blood draw, 1 hour after blood draw, and at one day intervals thereafter, out to 7 days. A standard-sized label that also bears a code number that can be used to identify the wound and time of photography will be placed adjacent to the puncture mark to account for magnification and angulation errors.

After photographing the wound site, the phlebotomist will bandage the puncture and instruct the subject to avoid removing the bandage until 5 hours following the time of venipuncture. It is important that all wounds receive the same treatment following venipuncture; thus it will be easiest if any bandaging can be controlled.

Appendix 3

Contents of the Report

1. Organization and actual conditions of the study

- 1.1. Objectives of the study.
- 1.2. Human subjects (general information).
- 1.3. Time-line of the study.
- 1.4. Engineer-technical conditions.

2. Obtained data

- 2.1. Environment monitoring data
- 2.2. Medical monitoring data

3. Time-line fulfillment

Appendix 4

**List of supplies provided by the NSBRI for the experiment “Latent Virus Reactivation
During a 240-Day Chamber Study of SFINCSS Program”**

ITEM/DESCRIPTION	QUANTITY
1. 15 ml plastic conical centrifuge tube, racked sterile	20 racks of 50 tubes each
2. 50 ml plastic conical centrifuge tube, racked sterile	20 racks of 25 tubes each
3. 2 ml screwcap microtube skirted, sterile (cryovial)	15 bags of 100 tubes each
4. 1 ml serological , disposable pipets, sterile	20 bags of 25 pipetes each
5. 5 ml serological, disposable pipets, sterile	30 bags of 25 pipets each
6. 10 ml serological, disposable pipets, sterile	40 bags of 25 pipets each
7. 25 ml serological, disposable pipets, sterile	24 bags of 25 pipets each
8. Latex gloves, nonsterile	10 boxes of 100 gloves each
9. Accuspin System Histopaque 1077 tubes, 15 ml	200 tubes
10. Salivette pledgettes tubes	400 tubes
11. Phosphate buffered saline liquid solution	2 bottles of 500 mls per bottle, 10X stock
12. Plastic storage boxes	18 boxes, with 81 inserts in each
13. Labels	2 boxes of 25 sheets each, 80 labels per sheet
14. ACD blood collection tubes (acid-citrate-dextrose)	400 tubes
15. Alcohol swabs	1 box of 200 each
16. Cotton balls	1 bag of 200 each
17. Band-aids	1 box of 100 each
18. Vacutainer butterflies	2 boxes of 50 each
19. Vacutainer sheaths, reusable	1 package of 10 each
20. Tourniquet, reusable	1 bag of 10 each
21. Specimen cups	4 cases of 100 each

Appendix 5

List of equipment and supplies provided by the NSBRI for the experiment “Use of Venipuncture to Monitor Wound Healing During a Chamber Study of SFINCSS Program”

1. Two (2) 35 mm cameras, Nikon N70QD
Serial No. B2438455
Serial No. 2440132
2. Two (2) Nikkor 60 mm F/2.8 Micro Lens
Serial No. L3109618
Serial No. L3109602
3. Sixty (60) rolls of film, Kodak ISO 400 print film, 135-36 exp.
4. Twelve (12) pads Post-It notes (to serve as labels)
5. Four (4) rulers
6. Fifty (50) venipuncture information sheets and four (4) protocol sheets

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**July 1998 Letter from Mr. Goldin
Plus
NSBRI Augmentation Plan**

**Unsolicited Proposal to NASA Johnson Space Center
Submitted
November 18, 1998**

National Aeronautics and
Space Administration
Office of the Administrator
Washington, DC 20546-0001



Jul 9 1998

Dr. Bobby Alford
Chairman of the Board and Chief Executive
Officer, Department of National
Space Biomedical Research Institute
Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030-3498

Dear Dr. Alford:

As I noted when we met during the STS-90 prelaunch activities at the Kennedy Space Center on April 16, 1998, we humans have this incredible drive to keep on exploring. We are going to send spacecraft toward distant worlds in the cosmic ocean. We have set 25-year goals for ourselves that will transition us from the Century of Air Travel to the Century of Space Travel. In the 21st century, we will become citizens of the solar system. The American people have shown tremendous excitement for all that we have been doing. Recently, we seem to have struck a chord with our plans for the International Space Station, exploring Mars and the solar system with robots, with our plans to search for planets around other stars, to look for life beyond the Earth, and to solve the mysteries of the universe. The National Space Biomedical Research Institute (NSBRI) is a crucial element in that transition, enabling space missions through ground breaking, revolutionary research which will provide future space travelers the means and countermeasures to achieve this dream.

To assist in accomplishing our vision of the future, and per your request, I want to share with you my perspective of the research priorities addressing the biomedical activities. I have developed this perspective by reading research reports, getting inputs from the community, and visiting astronauts after their returns from space flight and observing first hand their reactions postflight. I know Johnson Space Center (JSC) has already initiated an effort that upon completion should provide in detail the type of information that you requested. I also am very pleased that you are working together with JSC to identify critical milestones and a schedule of deliverables to make exploration possible. In 1996, I requested the NASA Advisory Council to form a special task force to develop a countermeasures research strategy for human space exploration. The resulting Countermeasures Report document was produced in late 1997 and accepted by NASA. I am confident that this report will help your team to plan and execute an outstanding research program.

From my perspective, high priority research efforts addressing long lead-time human health and performance risks and associated solutions for exploration should include the following, as a minimum:

- Radiation protection from both protons and heavy ions. We are fortunate to be associated with an excellent team of researchers and outstanding ground research facilities such as the Loma Linda University Medical School proton beam facility and the Department of Energy's heavy ion beam at Brookhaven. The inclusion of this infrastructure into your planning activities will undoubtedly contribute to your efforts. Coordination with international researchers will also be beneficial in this area.
- Research into human machine interfaces, psychosocial compatibility, and design of virtual immersion tools for mission planning, crew training, proficiency and operations, will extend human capabilities to explore and conduct research in alien and hostile environments, while providing safety and improving comfort.
- So far, the development of advanced and smart medical care systems to assist in the treatment of sick and/or injured crewmembers has not been adequately researched or tested in actual remote settings. I believe we need to put a sizable effort in addressing this issue in a systematic fashion. Your team and affiliates seem to be uniquely equipped to undertake this challenge
- Finally, the maintenance of astronauts' fitness while allowing adaptation to various extreme environments, including fractional gravity in space and on planetary surfaces, while conducting a wide range of exploration activities, is of essence. This will ensure that crews can function properly after long missions lasting well over 3 years. Astronauts should be able to work and perform in various extreme environments on the Moon and Mars, including rapid readaptation to the gravity on Earth upon return.

We did release a NASA Research Announcement on June 1, 1998, requesting proposals in most of the above areas. Please make sure that you participate in and respond to this solicitation. Feel free to contact Dr. Nicogossian for further discussions on this matter.

Sincerely,

Original Signed by

Daniel S. Goldin
Administrator

National Space Biomedical Research Institute

VISION 2005

A COMPREHENSIVE NATIONAL PROGRAM TO PAVE THE WAY TO GO BEYOND EARTH ORBIT

As the first of the NASA Institutes, the National Space Biomedical Research Institute (NSBRI) has already clearly demonstrated its ability to engage leading members of the university life science community in a partnership with experienced, operationally oriented NASA researchers to identify and begin to solve the difficult problems which lie between us and the human exploration of the Solar System.

We have already formed 8 research teams, incorporating 41 projects and 133 investigators from 25 institutions, including NASA, to begin to carry out our research mission to develop countermeasures against the effects of long duration weightlessness and space radiation.

But the current funding level of \$10 M/yr for our basic program, even with an additional \$4-5 M/yr from other sources, forces us to select only a few programs for study from among the many critical areas that require further research and severely restricts the scope of the NSBRI's programs. In addition, large numbers of interested and potentially valuable collaborators cannot be included in the Institute's existing research efforts.

The NSBRI is squarely focussed on research at the heart of NASA's interests. In fact, the "Fundamental Question" in the NASA Strategic Plan central to the NSBRI mission is

- What is the fundamental role of gravity and cosmic radiation in vital biological ... systems in space, on other planetary bodies, and on Earth, and how do we apply this fundamental knowledge to the establishment of permanent human presence in space to improve life on Earth?

Our initial success, combined with our alignment with the goals of the NASA Strategic Plan and the long lead time required to go from biomedical research to proven space countermeasures, makes this an opportune time to enhance and augment the NSBRI and attack the larger problem of the Whole Healthy Human on Earth and in Space.

In response to the letter from Mr. Goldin to the NSBRI identifying NASA's priorities in space biomedical research, we have prepared a plan for a significant funding augmentation of the NSBRI. If carried out, it will involve more than three times the number of investigators within the Institute's intramural program and a like number in an extramurally-based partnership program with the NIH. It should lead to a doubling of the consortium base comprising the Institute, and add four new integrated research teams. This will result in a comprehensive, cooperative national program to prepare us for further exploration of space.

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

FY 2000 AUGMENTATION

CURRENT NASA FUNDING (FY 99) - \$10.2 M NASA FUNDING REQUEST (FY 2000) - \$48 M
TOTAL PROGRAM VALUE (FY 99) - \$14.8 M TOTAL PROGRAM VALUE (FY 2000) - \$63 M

NSBRI's VISION 2005: A COMPREHENSIVE NATIONAL PROGRAM TO PREPARE THE WAY TO GO BEYOND EARTH ORBIT

- **NEW THEME: The Whole Healthy Human on Earth and in Space**
 - **Whole ⇒ Emphasis Shift to Integrated Physiology & Medicine**
 - **Healthy ⇒ Unique Focus on Environmental Challenge to Healthy People**
 - **Human ⇒ Clear Research Aim to Apply Molecular and Cellular Medicine to Human Beings**
 - **Earth & Space ⇒ Synergistic Approach to Promoting Astronaut Well Being and Improving Life on Earth**

- **IMPLEMENTATION: Four New Integrated Core Research Teams**
 - **Integrated Human Function – Integrating Molecular & Systems Approaches to Human Health**
 - **Neurobehavioral and Psychosocial Health – Integrating Physiological and Psychological Elements Critical to Sustained Health and Performance**
 - **Nutrition, Physical Fitness and Rapid Rehabilitation – Integrating Nutritional, Physical Fitness, and Pharmacological Approaches into a Unified Countermeasure Protocol that Maintains Mental and Physical Health During Flight and Speeds Up Recovery After Flight**
 - **Smart Medical Care Systems – Integrating New and Emergent Technologies for Non-Invasive Data Gathering, Evaluation, Robotic Medical Assistance, and Data Systems with Individualized Models of Human Function**

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

FY 2000 AUGMENTATION

NSBRI's VISION 2005: A COMPREHENSIVE NATIONAL PROGRAM TO PREPARE THE WAY TO GO BEYOND EARTH ORBIT

- **IMPLEMENTATION: New Partnerships**
 - **Scientific Research Community** – Development of Significant, Stable Extramural (to NSBRI) **Competitive Research Program Tied Closely to the VISION 2005 THEME.** Acts as Extramural Seed Program to Enable the Best Ideas of the Community to Enter the NSBRI. **Annual Competition: At least \$10 M for new awards (4 year grants), i.e., ~ 50 awards annually**
 - **Other Federal Agencies** – Development of Full Partnerships, Primarily with the NIH and NSF, to Implement the “Earth and Space” Focus of the Vision – Should Reduce NASA Cost of Extramural Program by 50%. Peer Review of Extramural Grants Would Become the Responsibility of Partner Agency
 - **Academic Biomedical Research Community** – Enlargement of NSBRI Consortium Base with Additional Prominent Medical and Scientific Research Institutions using an Open, Competitive Solicitation.
 - **Industry** – Building a Stronger National Partnership with Industry
 - **International Research Community** – Developing Additional International Partnerships to Enable World-Wide Resources to be Focused on Critical Biomedical Problems

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

FY 2000 AUGMENTATION

NSBRI's VISION 2005: A COMPREHENSIVE NATIONAL PROGRAM TO PREPARE THE WAY TO GO BEYOND EARTH ORBIT

- **IMPLEMENTATION: Building on the Strength of the Current NSBRI Program**
 - **Integration and Expansion of Discipline Research – Creation of Integrated Human Function Team Provides Central Focus for All Existing Research Teams**
 - **Task Expansion – Growth in Number of Intramural Tasks per Research Area from Current Level of Only 4-5 to That of 12-15**
 - **Rational Development Phases – Full Four-Phase Approach to Countermeasures:**
 - **Molecular Mechanism Phase (Payoff in 5 or more years)**
 - **Systems Concept Testing Phase (Payoff in 3-5 years)**
 - **Ground/Flight (Model) Testing of Countermeasure (Payoff in 1-2 years)**
 - **Flight Validation of Countermeasure and of Emergent Medically-Related Technologies**
 - **Educating Future Leaders – Space Biomedical Research Graduate & Postgraduate Training Programs**
 - **Outreach – Robust Outreach Program to Utilize Latest Technology to Bring Space Biomedical Research to the School, Home, and Hospital**

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

FY 2000 AUGMENTATION

NSBRI's VISION 2005: A COMPREHENSIVE NATIONAL PROGRAM TO
PREPARE THE WAY TO GO BEYOND EARTH ORBIT

Background & Rationale

- NASA's Vision for Human Space Exploration: To Move Ahead from Today's Century of Air Travel to Tomorrow's Century of Space Travel and, Simultaneously, From the Century of Physics to the Century of Biology
- BUT, TO REALIZE THIS VISION
 - The Biomedical Risks of Space Flight to Health and Performance Must be Understood and Eliminated or Reduced to Minimal & Acceptable Levels.
 - Thus, Focused Biomedical Research
 - ❖ Is Critical to Future Human Space Exploration
 - ❖ Requires Long Lead Times to Address & Answer Key Questions
 - Optimum Low Cost/High Yield Management Approach
 - ❖ Should Involve the Leading Researchers of the Biomedical Community & the Latest, Strongest Weapons of Medical Science
 - ❖ Should Utilize the Well-Developed Infrastructure of the Nation's Leading Biomedical Research Institutions
 - ❖ Should Involve Strong Partnerships With the NIH Community
 - ❖ Should be Coordinated Through Solid Program/Project Management

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

FY 2000 AUGMENTATION

NSBRI's VISION 2005: A COMPREHENSIVE NATIONAL PROGRAM TO PREPARE THE WAY TO GO BEYOND EARTH ORBIT

Background & Rationale (continued)

- The National Space Biomedical Research Institute (NSBRI)
 - Has Clear Responsibility (Through Competitive Award) for the Leadership Role in Biomedical Research Supporting the Human Space Exploration Vision
 - Is Supported & Managed by Unique Consortium of Top Medical/Research Institutions in Country
 - Already Involves Some of the Strongest Researchers in the Biomedical Community
 - Has Developed a Strong, Peer-Reviewed Research Program in One Year
 - Has a Functioning Synergy with the NASA Intramural Research Community
 - Has Close Connections & Joint Demonstration Program with the NIH
 - Has Developed Strong Connections with Non-U.S. Space Agencies & International Science Community, Including Model Program with Germany
 - Has Infrastructure Already in Place to Rapidly Implement Full Program

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

FY 2000 AUGMENTATION

**NSBRI's VISION 2005: A COMPREHENSIVE NATIONAL PROGRAM TO
PREPARE THE WAY TO GO BEYOND EARTH ORBIT**

Background & Rationale (continued)

- **Current NSBRI Funding (~\$10 M) is Inconsistent with Critical Space Biomedical Research Needs and the Full Scope of Institute Responsibility**
 - **Only 4-5 Tasks/Research Area are Funded – A Selective, Strong Initial Program**
 - **Only 8 Research Areas are Included: Important Areas (Psychosocial Aspects of Health and Performance, Nutrition, Rehabilitation, Development of Intelligent Medical Care Systems, etc.) Are Absent**
 - **Many Valuable and Interested Collaborators Cannot Now be Included**
 - **Joint Program with NIH involves Only One Institute (NIDCD)**
 - **Minimal Attention is Paid to Multidisciplinary, Integrative Issues**
 - **Insufficient Funds to Undertake Necessary Space Investigations Required for Countermeasure Evaluation**

**NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE
FY 2000 AUGMENTATION**

**BUDGET SUMMARY
FY 1999-2003**

	<u>FY 1999</u>	<u>FY 2000</u>	<u>FY 2001</u>	<u>FY 2002</u>	<u>FY 2003</u>
		(Thousands of Dollars)			
NASA	10,155	48,000	57,000	67,000	77,000
Other Federal Agency	1,600	7,500	15,150	20,800	26,800
Non-U.S. Agency	450	900	1,500	2,500	4,000
Private	2,648	6,225	7,050	8,100	9,350
TOTAL PROGRAM	14,853	62,625	80,700	98,400	117,150
<u>Intramural Research Program (total)</u>	<u>10,099</u>	<u>41,050</u>	<u>47,950</u>	<u>54,100</u>	<u>60,350</u>
NASA Funding	8,317	36,000	40,000	45,000	50,000
Other Federal Agency Funding	800	1,200	3,600	4,000	4,500
Private Funding	982	3,850	4,350	5,100	5,850
<u>Cooperative National Research Initiatives (total)</u>	<u>1,600</u>	<u>11,600</u>	<u>21,600</u>	<u>31,600</u>	<u>42,000</u>
NASA Funding	0	5,000	10,000	15,000	20,000
Other Federal Agency Funding	800	5,800	10,800	15,800	21,000
Private Funding	800	800	800	800	1,000
<u>Cooperative International Research Activity (total)</u>	<u>500</u>	<u>1,050</u>	<u>1,750</u>	<u>2,800</u>	<u>4,350</u>
Non-U.S. Agency Funding	450	900	1,500	2,500	4,000
Private Funding	50	150	250	300	350
<u>Training, Education and Outreach (total)</u>	<u>1,271</u>	<u>5,060</u>	<u>5,510</u>	<u>5,960</u>	<u>6,460</u>
NASA Funding	655	3,600	3,600	3,600	3,600
Other Federal Agency Funding	0	500	750	1,000	1,300
Private Funding	616	960	1,160	1,360	1,560
<u>Core Supporting Elements (total)</u>	<u>1,383</u>	<u>3,865</u>	<u>3,890</u>	<u>3,940</u>	<u>3,990</u>
NASA Funding	1,183	3,400	3,400	3,400	3,400
Private Funding	200	465	490	540	590

National Space Biomedical Research Institute

Ensuring Human Health and Productivity in the Exploration and Development of Space

Mission

The National Space Biomedical Research Institute (NSBRI) is a mission-driven research entity, dedicated and committed to sponsoring, integrating and promoting fundamental and applied advances in space biomedical research. The mission of the NSBRI is to lead a world-class, national effort in integrated, critical path space biomedical research that supports NASA's Human Exploration and Development of Space (HEDS) Strategic Plan by focusing on the enabling of safe, long-term human presence in, development of, and exploration of space. This will be accomplished by:

- designing, implementing, and validating effective countermeasures to address the biological and environmental impediments to safe, long-term human space flight;
- defining the molecular, cellular, organ-level, integrated responses and mechanistic relationships that are responsible for these impediments, where such activity fosters the development of novel countermeasures;
- establishing biomedical support technologies to maximize human performance in space, eliminate biomedical hazards or reduce them to an acceptable level, and deliver quality medical care;
- transferring and disseminating the biomedical advances in knowledge and technology acquired through living and working in space to the benefit of mankind in space and on earth, including the treatment of patients suffering from gravity- and radiation-related conditions on earth; and
- ensuring open involvement in the Institute's activities by the scientific community, industry, and the public at large, and a robust exchange with NASA, particularly through Johnson Space Center.

Background

The engineering accomplishments of the last 100 years have provided unprecedented opportunities for people to become mobile and travel rapidly on or near the surface of the earth. With these opportunities, we have become citizens of the world, taking to the skies so often that this century will surely be known as the Century of Air Travel. However, even now the tools are in our hands to enable us to travel away from our home planet and become citizens of the solar system. We are seriously beginning to develop a vision that will make the 21st century the Century of Space Travel. But to take this bold step with due concern for the health and safety of future space explorers, we must assemble a critical mass of people and resources to develop and validate effective countermeasures against the risks posed by the potentially dangerous levels of radiation and extended weightlessness associated with space exploration. This action must be taken today because many of the key biomedical questions require long lead-times to answer and the solutions must be ready once technological advances permit prolonged human exploration beyond earth and before fundamental decisions are reached concerning the appropriate time to implement our vision for the 21st Century.

NASA, recognizing these needs, satisfied them through the creation of a special partnership with a new academically-based research institute, the National Space Biomedical Research Institute. In 1997, following a national competition, NASA selected a consortium of premier medical schools and research universities led by Baylor College of Medicine, which included Harvard Medical School, The Johns Hopkins University School of Medicine and the Applied Physics Laboratory, Massachusetts Institute of Technology, Morehouse School of Medicine, Rice University, and Texas A&M University. The primary mission of this new institute is to support human space exploration through focussed biomedical research by combining the basic research capabilities of leading academic research institutions with the operational capability of NASA and the applied research capability of industry. From the beginning, it has been clear that pursuit of this mission would lead to discoveries and products of clinical benefit to mankind on earth and enhance the treatment of patients suffering from gravity- and radiation-related conditions. It is intended that this dual contribution to health be developed to its maximum potential.

Funding for the NSBRI is at an annual level of \$10 million (FY 1997 \$\$) in order to encourage the cost-effective development of the Institute's research infrastructure and management plan. The vision for the NSBRI has been that it could operate as a strong NASA partner by implementing a plan that would involve some of the best researchers of the biomedical community using the most modern techniques of medical science and would include strong national and international research partnerships.

Current Status

The National Space Biomedical Research Institute, established in April 1997, is a private, non-profit organization charged to lead a national effort to carry out the research required to assure safe, long duration human exploration of space. It is governed by a consortium of educational institutions (including Baylor College of Medicine, Harvard Medical School, The Johns Hopkins University School of Medicine and the Applied Physics Laboratory, Massachusetts Institute of Technology, Morehouse School of Medicine, Rice University, and Texas A&M University) and has its headquarters in Houston at Baylor College of Medicine.

The NSBRI's research program is carried out at nineteen universities and government laboratories in addition to the consortium institutions. At all of these institutions, the NSBRI's research activities are built upon the considerable infrastructure already developed through existing Federal programs. Ten companies and non-profit organizations serve as industrial partners of the Institute. The management plan for the Institute is based on the NIH model, with an independent Board of Scientific Counselors responsible for assuring excellence in the Institute's intramural program through peer review; and an External Advisory Council, consisting of leaders in the research fields central to the Institute's mission, that is responsible for advising Institute management concerning programmatic effectiveness. In addition, the NSBRI has a User Panel of former and current astronauts and flight surgeons responsible for assuring that the focus of the research program is squarely on astronaut health and safety and that proposed countermeasures are practical to implement, and an Industry Forum of representatives of space and biomedically-related industries responsible for assisting the Institute in developing industry participation in NSBRI and the timely transfer of technology.

The strategic research agenda of the NSBRI currently involves eight teams of research scientists focussed on:

- *Bone Loss* – Addressing the loss of bone during space flight with the inherent risks of fracture;
- *Cardiovascular Alterations* – Addressing the inflight increase of cardiac dysrhythmias and the postflight impairment of the cardiovascular response to orthostatic and exercise stress;
- *Human Performance* – Addressing maintenance of high cognitive performance and vigilance while operating and monitoring sophisticated instrumentation despite environmental or psychosocial stress;
- *Immunology, Infection and Hematology* – Addressing the potential for immune system impairment and altered susceptibility to infection, increased allergic response, microgravity-induced anemia, and postflight decreased blood volume;
- *Muscle Alterations and Atrophy* – Addressing the loss of skeletal muscle mass, strength and endurance that accompanies space flight;
- *Neurovestibular Adaptation* – Addressing the problems of space motion sickness and disorientation during flight and the postflight problems of balance and gaze disability;

- *Radiation Effects* – Addressing the problems and increased cancer risk caused by the natural space radiation environment; and
- *Technology Development* – Developing instrumentation that will enhance the research of the other teams and transfer the technology to industry to benefit society.

The total current intramural research program, including all eight research areas, involves 41 projects, with an average funding per project of approximately \$200,000 (Direct + Indirect Costs). The NSBRI also has signed an agreement of affiliation with the Institute of Aerospace Medicine of the German Aerospace Center (Deutsches Zentrum für Luft- und Raumfahrt e. V., DLR) enabling German-funded projects to become part of the NSBRI's intramural program.

In addition, the NSBRI has developed partnerships with both the National Science Foundation and one of the institutes of the National Institutes of Health (National Institute on Deafness and Other Communication Disorders, NIDCD) to jointly fund competitive extramural research grants focussing simultaneously on health on earth and in space while complementing the NSBRI's intramural tasks. Peer reviews for these programs are managed by the partner, while the NSBRI's funds for these activities presently come from private sources.

Finally, the NSBRI has developed a vigorous program of education and outreach, serving the needs of the lay community by translating cutting-edge research from the laboratory for use in the classroom and home. Several types of classroom materials have been developed, a summer teacher training program has been started; preparation of a public television documentary program on space biomedical research has begun, and of a television series (*Liftoff to Health, The Story of Medicine and Space*) depicting the benefits medicine has received from the space program.

In summary, the NSBRI has established itself as the preeminent NASA-sponsored organization responsible for the research necessary to understand the effects of the space environment on humans and for using that information to develop countermeasures to mitigate the risks of space flight. In the short time that it has been in existence, the NSBRI has successfully implemented a sound management plan overseen by a unique consortium of some of the top medical and research universities in the country and has developed the infrastructure necessary to manage a complete biomedical research program. The NSBRI's current research program involves a core of strong biomedical researchers, selected through careful peer review and utilizing the modern tools of biomedical science. In addition, the Institute has begun to invest in the education of school children and in raising public awareness of the benefits of space research. Finally, the NSBRI has established close connections and joint model programs with other Federal agencies, including the NIH and the NSF, and has developed good relations and partnerships with non-U.S. space agencies and the international biomedical science community, including a program with Germany that enables German-funded projects to be incorporated into the NSBRI's intramural teams.

Although the NSBRI has made great strides in developing and implementing its research program with the current annual NASA funding level of \$10 million, its research program and other activities are, in fact, hampered by this limited support. In fact, the current level of

funding is inconsistent with both the critical research needs of space biomedical research and the full scope of the Institute's responsibility. This was clear at the NSBRI's outset; in development of the initial research plan, NSBRI devoted itself to eight of the most critical research areas and delayed research on other important issues. The result is that the current program has specific inadequacies because insufficient funds exist to pursue research in all of the research areas vital to human exploration. No NSBRI activity is currently devoted to the psychosocial and behavioral aspects of long-duration space flight, or to the importance and effects of nutrition on the body's adaptation to space flight, or to the development of intelligent medical care systems appropriate to a remote mission. In addition, even within each research area, current funding will support only four to five tasks and this level of effort represents that typical of a demonstration program, not of a complete countermeasure-oriented program. With current funding, large numbers of interested and potentially valuable collaborators cannot be included in the Institute's program. Because of funding limitations, only minimal attention is currently focussed on the multidisciplinary, integrative physiologic aspects of the research questions and these are of paramount importance in the development of a strategy to deal effectively with the complex reactions of the whole body to space flight. For example, countermeasures that affect muscle also certainly affect bone and may affect the cardiovascular system and the autonomic nervous system as well. This fundamental shortcoming is directly attributable to lack of funds. The joint programs that the NSBRI has developed with the NIDCD and the NSF are laudable, but are too small to have the desired impact. Finally, no funds or other resources are available to undertake the necessary space-flight studies required for countermeasure evaluation.

Augmentation

OVERALL BUDGET SUMMARY (FY 1999-2003)

	<u>FY 1999</u>	<u>FY 2000</u>	<u>FY 2001</u>	<u>FY 2002</u>	<u>FY 2003</u>
	(Thousands of Dollars)				
NASA	10,155	48,000	57,000	67,000	77,000
Other Federal Agency	1,600	7,500	15,150	20,800	26,800
Non-U.S. Agency	450	900	1,500	2,500	4,000
Private	2,648	6,225	7,050	8,100	9,350
TOTAL PROGRAM	<u>14,853</u>	<u>62,625</u>	<u>80,700</u>	<u>98,400</u>	<u>117,150</u>

This augmentation request enables the NSBRI to adopt a new theme that embodies the essence of the NSBRI's defined mission responsibilities: the whole healthy human on earth and in space. The new activities that the NSBRI would undertake with the enhanced funding would be dedicated to developing primary research activities directed at a fully integrated approach to physiology and medicine with a focus on health rather than disease. To accomplish this expansion, the Institute consortium will be expanded by the addition of four to eight new members between 1999 and 2001.

Thus, in order to enable the National Space Biomedical Research Institute to fulfill its mission responsibilities to lead a world-class, national effort in integrated, critical path space biomedical research, its NASA-supported budget would be increased from \$10,155 K in FY 1999 to \$48,000 K in FY 2000. Subsequent years would experience a growth of about \$10,000 K per year, divided equally between focussed intramural NSBRI research and complementary extramural investigator research. The NSBRI programs that will be funded with this NASA augmentation and the change in NASA support from FY 1999 to FY 2000 include the following: NSBRI Intramural Research Program (FY 1999: \$8,317 K; FY 2000: \$36,000 K); Cooperative National Research Initiatives (FY 1999: 0; FY 2000: \$5,000 K); Cooperative International Research Activity (no NASA contribution); Training, Education and Outreach (FY 1999: \$655 K; FY 2000: \$3,600 K); and Core Supporting Elements (FY 1999: \$1,183 K; FY 2000: \$3,400).

NSBRI Intramural Research Program

	<u>FY 1999</u>	<u>FY 2000</u>	<u>FY 2001</u>	<u>FY 2002</u>	<u>FY 2003</u>
	(Thousands of Dollars)				
NASA	8,317	36,000	40,000	45,000	50,000
Other Federal Agency	800	1,200	3,600	4,000	4,500
Private	982	3,850	4,350	5,100	5,850
Intramural Research Program (Total)	10,099	41,050	47,950	54,100	60,350

The Intramural Research Program augmentation for FY 2000 enables an expansion in the number of major research areas to allow full coverage of the critical research problems in space biomedical research. The 8 original research teams will be expanded to 12 with the addition of the following new teams:

- Integrated Human Function – This central team will focus on developing and carrying out a program of research to provide an overall integrated understanding of the response of the human body to space flight, covering all systems and integrated up from the molecular and biochemical level through cellular function to whole human function. This team will work at the cutting edge of mathematical and computer simulation to produce a digital human, integrating data from all of the other research teams.
- Neurobehavioral and Psychosocial Health – This team will focus on the critical area of psychosocial health, but will also include relevant aspects of human factors. The NSBRI’s *User Panel* of present and former astronauts and flight surgeons has strongly recommended the inclusion of this research area. In their July 1998 report to the NSBRI, they said “Psychosocial issues will take on paramount importance in long-duration space flight. A critical need exists to address these issues as an integral part of NSBRI research.”
- Nutrition, Physical Fitness and Rapid Rehabilitation – This team will be responsible for the ultimate development of a completely integrated approach to countermeasure testing, focussing on the whole body reaction to a unified countermeasure protocol and on the major issues of nutrition, fitness maintenance and on the speed of rehabilitation of astronauts following space flight.
- Smart Medical Care Systems – This team will focus on research directed at developing and testing new approaches to medical care for exploration missions (Mars type), integrating new and emergent technologies for non-invasive data gathering, automated medical assistance, and medical data systems with new individualized models of integrated human function.

In addition, the augmentation enables the number of tasks per research area to be expanded to the more appropriate level of 12 to 15 instead of 4 to 5. These tasks can now be distributed over all four of the countermeasure development phases:

- Molecular Mechanism Phase with an expected payoff in five or more years;
- Systems Concept Testing Phase with an expected payoff in three to five years;
- Ground/Flight Model Testing of Countermeasure with an expected payoff in one to two years; and
- Space Flight Validation of Countermeasure.

The augmentation will also allow the scope of research of the original teams to expand in significant ways. For example, the Human Performance team will be able to expand its program to include research focussed on the optimization of the relationship between humans and machines during long (Mars-type) exploration missions. The Technology Development team will be able to expand its activities to include the development of noninvasive and minimally invasive health-assessment hardware and on the design, development and use of virtual immersion tools. All teams will be able to include one or more projects focussing on the extremely important area of nutrition and the effects of diet on the functioning of each of the physiological systems within the body. Note that, in addition, nutrition and the integrated effects of diet on the overall health of astronauts are considered through the new team focussing on Nutrition, Physical Fitness and Rapid Rehabilitation.

Each of the 12 teams will receive \$3,000 K in NASA funding in FY 2000, leading to an intramural program of \$36,000 K in NASA funding. The increases of \$4,000 - \$5,000 K (total) in subsequent years will allow a small amount of growth to enable the NSBRI to include both space experiments and major integrated tests (e.g., of the new smart medical systems) as they become required elements of the program. The *Other Federal Agency* funding line in the budget is not a budget request; rather, it is a conservative estimate of the success that NSBRI investigators will have in obtaining competitive awards from other Federal agencies besides NASA. The *Private* funding line represents an estimate of the contribution of the consortium and participating institutions to the NSBRI programs (~10% contribution required), along with investments by the NSBRI's industrial partners.

	<u>FY 1999</u>	<u>FY 2000</u>	<u>FY 2001</u>	<u>FY 2002</u>	<u>FY 2003</u>
NASA	0	5,000	10,000	15,000	20,000
Other Federal Agency	800	5,800	10,800	15,800	21,000
Private	800	800	800	800	1,000
Cooperative National Research Initiatives (Total) ...	<u>1,600</u>	<u>11,600</u>	<u>21,600</u>	<u>31,600</u>	<u>42,000</u>

(Thousands of Dollars)

The Cooperative National Research Initiatives augmentation for FY 2000 allows the expansion of the demonstration program that the NSBRI has developed with the National Institute on Deafness and Other Communication Disorders and the National Science Foundation. The primary characteristics of these programs are: (1) the joint activity focuses on research that impacts both health on earth and health in space; (2) program announcements for the competition are issued from the partner Federal agency; (3) the peer reviews are carried out by the partner Federal agency using their standard review system; and (4) selection is done jointly.

Expansion of this cooperative program is vital to the long-term success of the NSBRI for a number of important reasons. This type of competitive, single investigator research activity is the backbone of the successful research management plan that both the NIH and the NSF have developed through years of experience. A stable program of this type, with an appropriate critical mass of investigators, will firmly establish space biomedical research in its proper niche within the National research agenda, and will enable new ideas and new investigators to cycle through the program. Questions related to health in space are direct analogues of questions related to health on earth and this type of joint program focuses on ways that such analogues can be synergistic.

Funding in FY 2000 of \$5,000 K by NASA and \$5,000 K by other Federal partners will enable a single competition for \$10,000 K to be held. Grants would usually be in the range of \$150-\$300 K/year each and would be for three to four years. Funding increases in subsequent years would enable an annual competition for \$10,000 K in new funds (divided equally between NASA funding and partner-agency funding). Assuming a four-year grant cycle (typical for the NIH) leads to a stable program costing \$40 M annually.

Cooperative International Research Activity

	<u>FY 1999</u>	<u>FY 2000</u>	<u>FY 2001</u>	<u>FY 2002</u>	<u>FY 2003</u>
NASA	0	0	0	0	0
Non-U.S. Agency	450	900	1,500	2,500	4,000
Private	50	150	250	300	350
Cooperative International Research Activity	<u>500</u>	<u>1,050</u>	<u>1,750</u>	<u>2,800</u>	<u>4,350</u>

(Thousands of Dollars)

No NASA augmentation is requested for this portion of the NSBRI's program. Funds for cooperative international research activity are expected to be provided by non-U.S. funding agencies. For example, in 1998 the NSBRI signed an agreement of affiliation with the Institute of Aerospace Medicine of the German Aerospace Center (Deutsches Zentrum für Luft- und Raumfahrt e.V., DLR) enabling German-funded projects to become part of the NSBRI's intramural program. Preliminary discussions concerning similar affiliation have been held with several other space agencies having a primary interest in space biomedical research.

Training, Education and Outreach

	<u>FY 1999</u>	<u>FY 2000</u>	<u>FY 2001</u>	<u>FY 2002</u>	<u>FY 2003</u>	
		(Thousands of Dollars)				
NASA	655	3,600	3,600	3,600	3,600	
Other Federal Agency	0	500	750	1,000	1,300	
Private	616	960	1,160	1,360	1,560	
Training, Education and Outreach (Total).....	1,271	5,060	5,510	5,960	6,460	

The Training, Education and Outreach Program augmentation for FY 2000 will enable the development of a dynamic training component of the NSBRI, missing from the FY 1999 program, and the expansion of the education and outreach component to include full participation of all consortium institutions. The training component will involve both graduate and postgraduate education. NASA funding of \$1,600 K will be devoted to training. This will support a nationally competitive NSBRI graduate training program of 36 students and a similar postgraduate program with 20 students. Subsequent NASA funding will remain at the FY 2000 level, but growth in the program is planned through industry support. The total projected funding for training, including industry support will be: FY 2000: \$2,000 K; FY 2001: \$2,100 K; FY 2002: \$2,200; FY 2003: \$2,300 K.

The education and outreach component of this program, with NASA funding of \$655 K in FY 1999 would expand to \$2,000 K in FY 2000. The current program only involves three major institutions; the FY 2000 program would expand to all consortium institutions and would represent a major force in providing the school and home with up-to-date information concerning space biomedical research and its impact on everyone's lives. Industry support of this activity has been particularly strong and growth in this component is expected. Finally, it is clear that the NSBRI's education and outreach activities are synergistic and complementary with those of other Federal agencies, particularly of the NSF and NIH, and joint programs with those agencies will be developed beginning in FY 2000.

Core Supporting Elements

	<u>FY 1999</u>	<u>FY 2000</u>	<u>FY 2001</u>	<u>FY 2002</u>	<u>FY 2003</u>
NASA	1,183	3,400	3,400	3,400	3,400
Private	200	465	490	540	590
Core Supporting Elements (Total)	<u>1,383</u>	<u>3,865</u>	<u>3,890</u>	<u>3,940</u>	<u>3,990</u>

(Thousands of Dollars)

The FY 2000 augmentation of the core supporting elements component of the NSBRI will enable the administrative component of the Institute to grow appropriately as the research activity expands. This component includes the costs of peer review, travel support, the cost of supporting meetings, workshops, retreats, and symposia, and headquarters staff expansion. In addition, included in this component, starting in FY 2000, will be a small, distributed staff of well-trained biostatisticians with the responsibility of working with all of the research teams to assure that all ground and space data collected by the NSBRI are appropriate to answer the research questions posed. The importance of providing this essential support was emphasized by the 1998 report of the Institute's Board of Scientific Counselors.

Summary

- NASA's Vision for Human Space Exploration: To Move Ahead from Today's Century of Air Travel to Tomorrow's Century of Space Travel and, Simultaneously, From the Century of Physics to the Century of Biology
- BUT, TO REALIZE THIS VISION
 - The Biomedical Risks of Space Flight to Health and Performance Must be Understood and Eliminated or Reduced to Minimal & Acceptable Levels
 - Thus, Focussed Biomedical Research
 - ❖ Is Critical to Future Human Space Exploration
 - ❖ Requires Long Lead Times to Address & Answer Key Questions
 - Optimum Low Cost/High Yield Management Approach
 - ❖ Should Involve the Leading Researchers of the Biomedical Community & the Latest, Strongest Weapons of Medical Science
 - ❖ Should Utilize the Well-Developed Infrastructure of the Nation's Leading Biomedical Research Institutions
 - ❖ Should Involve Strong Partnerships With the NIH Community
 - ❖ Should be Coordinated Through Solid Program/Project Management
- The National Space Biomedical Research Institute (NSBRI)
 - Has Clear Responsibility (Through Competitive Award) for the Leadership Role in Biomedical Research Supporting the Human Space Exploration Vision
 - Is Supported & Managed by Unique Consortium of Top Medical/Research Institutions in Country
 - Already Involves Some of the Strongest Researchers in the Biomedical Community
 - Has Developed a Strong, Peer-Reviewed Research Program in One Year
 - Has a Functioning Synergy with the NASA Intramural Research Community
 - Has Close Connections & Joint Demonstration Program with the NIH
 - Has Developed Strong Connections with Non-U.S. Space Agencies & International Science Community, Including Model Program with Germany
 - Has Infrastructure Already in Place to Rapidly Implement Full Program

- Current NSBRI Funding.(~\$10 M) is Inconsistent with Critical Space Biomedical Research Needs and the Full Scope of Institute Responsibility
 - Only 4-5 Tasks/Research Area are Funded – A Selective, Strong Initial Program
 - Only 8 Research Areas are Included: Important Areas (Psychosocial Aspects of Health and Performance, Nutrition, Rehabilitation, Development of Intelligent Medical Care Systems, etc.) Are Absent
 - Many Valuable and Interested Collaborators Cannot Now be Included
 - Joint Program with NIH involves Only One Institute (NIDCD)
 - Minimal Attention is Paid to Multidisciplinary, Integrative Issues
 - Insufficient Funds to Undertake Necessary Space Investigations Required for Countermeasure Evaluation

**This Augmentation Request Enables a
Comprehensive National Program to Prepare the Way to Mars (NSBRI's VISION 2005)**

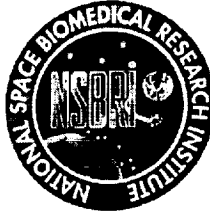
- **NEW THEME: The Whole Healthy Human on Earth and in Space**
 - Whole ⇒ Emphasis Shift to Integrated Physiology & Medicine
 - Healthy ⇒ Unique Focus on Environmental Challenge to Healthy People
 - Human ⇒ Clear Research Aim to Apply Molecular and Cellular Medicine to Human Beings
 - Earth & Space ⇒ Synergistic Approach to Promoting Astronaut Well Being and Improving Life on Earth
- **IMPLEMENTATION: Four New Integrated Core Research Teams**
 - Integrated Human Function – Integrating Molecular & Systems Approaches to Human Health
 - Neurobehavioral and Psychosocial Health – Integrating Physiological and Psychological Elements Critical to Sustained Health and Performance
 - Nutrition, Physical Fitness and Rapid Rehabilitation – Integrating Nutritional, Physical Fitness, and Pharmacological Approaches into a Unified Countermeasure Protocol that Maintains Mental and Physical Health During Flight and Speeds Up Recovery After Flight
 - Smart Medical Care Systems – Integrating New and Emergent Technologies for Non-Invasive Data Gathering, Evaluation, Robotic Medical Assistance, and Data Systems with Individualized Models of Human Function

• **IMPLEMENTATION: New Partnerships**

- Scientific Research Community – Development of Significant, Stable Extramural (to NSBRI) Competitive Research Program Tied Closely to the VISION 2005 THEME. Acts as Extramural Seed Program to Enable the Best Ideas of the Community to Enter the NSBRI. Annual Competition: At least \$10 M for new awards (4 year grants), i.e., ~ 50 awards annually
- Other Federal Agencies – Development of Full Partnerships, Primarily with the NIH and NSF, to Implement the “Earth and Space” Focus of the Vision – Should Reduce NASA Cost of Extramural Program by 50%. Peer Review of Extramural Grants Would Become the Responsibility of Partner Agency
- Academic Biomedical Research Community – Enlargement of NSBRI Consortium Base with Additional Prominent Medical and Scientific Research Institutions using an Open, Competitive Solicitation.
- Industry – Building a Stronger National Partnership with Industry
- International Research Community – Developing Additional International Partnerships to Enable World-Wide Resources to be Focused on Critical Biomedical Problems

• **IMPLEMENTATION: Building on the Strength of the Current NSBRI Program**

- Integration and Expansion of Discipline Research – Creation of Integrated Human Function Team Provides Central Focus for All Existing Research Teams
- Task Expansion – Growth in Number of Intramural Tasks per Research Area from Current Level of Only 4-5 to That of 12-15
- Rational Development Phases – Full Four-Phase Approach to Countermeasures:
 - Molecular Mechanism Phase (Payoff in 5 or more years)
 - Systems Concept Testing Phase (Payoff in 3-5 years)
 - Ground/Flight (Model) Testing of Countermeasure (Payoff in 1-2 years)
 - Flight Validation of Countermeasure and of Emergent Medically-Related Technologies
- Educating Future Leaders – Space Biomedical Research Graduate & Postgraduate Training Programs
- Outreach – Robust Outreach Program to Utilize Latest Technology to Bring Space Biomedical Research to the School, Home, and Hospital



NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

Special Announcement to Institutions

**An Opportunity to Become a
Member of the
National Space Biomedical Research Institute
Consortium**

**May 10, 1999
NSBRI 99-01**

Initial Letter of Application Due (Phase I):	July 2, 1999
Selection Announcement for Phase II:	July 16, 1999
Final Application Due (Phase II):	August 20, 1999
Selection Announcement:	September 27, 1999

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

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May 10, 1999

NSBRI 99-01

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NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE*Special Announcement to Institutions***An Opportunity to Become a Member of the
National Space Biomedical Research Institute Consortium**

**May 10, 1999
NSBRI 99-01**

1.0 OPPORTUNITY

The Board of Directors of the National Space Biomedical Research Institute (NSBRI), a private, non-profit organization, announces its intention to expand the consortium of educational institutions that govern the NSBRI from the present number of seven to twelve or more. Applications will be accepted from all categories of U.S. educational and research institutions satisfying the minimum requirements defined in Section 3.0 of this Announcement. This expansion will take place through a two-phase competitive process. The first phase involves a brief application describing the institution's strengths, interests, and current involvement with research related to the goals of NSBRI. The second phase involves the submission of more detailed information and a reverse site visit to speak with the review panel. A limited number of applicants will be invited to participate in phase two.

2.0 BACKGROUND

The National Space Biomedical Research Institute (NSBRI) sponsors and performs fundamental and applied space biomedical research with the mission of leading a world-class, national effort in integrated, critical path space biomedical research that supports NASA's Human Exploration and Development of Space (HEDS) Strategic Plan. It focuses on the enabling of long-term human presence in, development of, and exploration of space. This is accomplished by:

- designing, implementing, and validating effective countermeasures to address the biological and environmental impediments to long-term human space flight;
- defining the molecular, cellular, organ-level, integrated responses and mechanistic relationships that ultimately determine these impediments, where such activity fosters the development of novel countermeasures;
- establishing biomedical support technologies to maximize human performance in space, reduce biomedical hazards to an acceptable level, and deliver quality medical care;
- transferring and disseminating the biomedical advances in knowledge and technology acquired through living and working in space to the benefit of mankind in space and on Earth, including the treatment of patients suffering from gravity- and radiation-related conditions on Earth; and
- ensuring open involvement of the scientific community, industry, and the public at large in the Institute's activities and fostering a robust collaboration with NASA, particularly through Johnson Space Center.

The National Space Biomedical Research Institute is a private, non-profit corporation established in April 1997 following competitive selection by NASA to lead a national effort to carry out the research required to assure safe human exploration of space. Primary support for the activities of the NSBRI is furnished by NASA through Cooperative Agreement NCC 9-58 with the Lyndon B. Johnson Space Center, although funds to support Institute activities come from several sources, including the institutions involved in carrying out the NSBRI's programs. The Cooperative Agreement award is for a five and one-half year base period, lasting until September 30, 2002, and three five-year optional extensions. Current base funding has been set at approximately \$10,000,000 annually, although NASA has notified the Institute that it would like the NSBRI to expand its activities and will provide an additional \$4,000,000 during FY 2000 to develop the infrastructure to support the planned program growth beginning in FY 2001. This solicitation is being issued in anticipation of a substantial increase in the core research budget of the NSBRI beginning in October 2000. This substantial increase in the core research budget will require Congressional budgetary authorization and approval. The implementation of the planned augmentation described in this announcement is contingent upon favorable Congressional action.

2.1 Institute Infrastructure

The NSBRI is governed by a consortium of educational institutions that includes Baylor College of Medicine, Harvard Medical School, The Johns Hopkins University School of Medicine and the Applied Physics Laboratory, Massachusetts Institute of Technology, Morehouse School of Medicine, Rice University, and Texas A&M University. The Institute's headquarters are located in Houston at Baylor College of Medicine, the sole member of the corporation. The governance of the Institute is vested in the NSBRI's Board of Directors whose members are listed in Table 1. The Board of Directors includes two individuals from each of the consortium institutions, two members from industry, two distinguished members from outside of the consortium, and two senior medical statesmen. The Chairman of the Board and Chief Executive Officer is Bobby R. Alford, M.D. The Board of Directors of the Institute sets scientific, operational and technological priorities for the Institute, has ultimate authority and responsibility for the activities of the Institute, monitors progress and oversees the timely and cost-effective utilization of resources. The Board guides the Institute's efforts in specific science and technology areas; provides oversight to assure that the Institute accounts for its activities and utilizes its resources prudently; and reviews, documents, and reports Institute progress to NASA annually. The Board also ensures that the NSBRI-related resources of all participants, including resources available from NASA, are utilized effectively, that scientific and technological advances are encouraged, and that strong participation in Institute activities by the broader research community is developed.

Management of the NSBRI is carried out by a Director and Associate Director who have responsibility for all aspects of the Institute. The Director is the Chief Operating Officer of the Institute and is responsible to the Board for implementing the Institute's mission, goals, and objectives. The Director and Associate Director are responsible for coordination of the Institute's activities among the consortium members, affiliates, industrial partners, and NASA. The Director is Laurence R. Young, Sc.D., the Apollo Program Professor of Astronautics at MIT. The Associate Director is Professor Ronald J. White, Ph.D., of Baylor College of Medicine.

Because of the nature of the initial competitive process used by NASA to select the NSBRI, most of the Institute's research program is carried out at the consortium institutions. There are, however, no restrictions concerning institutional participation in Institute activity. In fact, the current program is carried out at twenty institutions and government laboratories in addition to the consortium. At these institutions, the NSBRI's research activities are built upon the considerable

infrastructure already developed through existing Federal programs. The management plan for the Institute is based on the model used by the National Institutes of Health. An independent Board of Scientific Counselors (Table 2) is responsible for assuring excellence in the Institute's intramural program through independent external peer review. An External Advisory Council (Table 3), consisting of leaders in the research fields central to the Institute's mission, is responsible for advising Institute management concerning programmatic effectiveness. The NSBRI has a User Panel (Table 4) of former and current astronauts and flight surgeons responsible for assuring that the research program is focussed squarely on astronaut health and safety. An Industry Forum (Table 5) of representatives of space and biomedically-related industries assists the Institute in developing industry participation in NSBRI and the timely transfer of technology.

In addition to its research program, the NSBRI has developed a vital program of education and outreach, translating cutting-edge research from the laboratory to the classroom and home. This important program provides for: development of several types of classroom materials; a summer teacher training program; and the preparation of public documentary radio and television programs on space biomedical research.

2.2 Current Research Program

The initial strategic research agenda of the NSBRI involves eight teams of research scientists focussed on:

- *Bone Loss* – Addressing the loss and weakening of bone during space flight with the inherent risks of fracture;
- *Cardiovascular Alterations* – Addressing the inflight increase of cardiac dysrhythmias and the postflight impairment of the cardiovascular response to orthostatic and exercise stress;
- *Human Performance* – Addressing maintenance of high cognitive performance and vigilance despite environmental or psychosocial stress and sleep disturbances;
- *Immunology, Infection and Hematology* – Addressing the potential for immune system impairment and altered susceptibility to infection, increased allergic response, decreased blood volume and postflight anemia;
- *Muscle Alterations and Atrophy* – Addressing the loss of skeletal muscle mass, strength and endurance that accompanies space flight;
- *Neurovestibular Adaptation* – Addressing the problems of space motion sickness and disorientation during flight and the postflight problems of balance and gaze disorders;
- *Radiation Effects* – Addressing the problem of increased cancer risk caused by the natural space radiation environment; and
- *Technology Development* – Developing instrumentation that will enhance the research of the other teams and transfer the technology to industry for the benefit of society.

Each team consists of individual complementary projects focussed on a common theme. Team management and coordination is the responsibility of a program director called a Team Leader. Table 6 lists the present group of Team Leaders. The total current intramural research program, including all eight research areas, involves 41 projects, with an average funding per project of approximately \$200,000 (Direct + Indirect Costs). Details concerning the current intramural projects are provided on the Institute's web page: www.nsbri.org.

In addition to this core intramural research program, the NSBRI has developed a special partnership with the National Institute on Deafness and Other Communication Disorders (NIDCD) to jointly fund competitive extramural research grants focussing simultaneously on health on Earth

and in space while complementing the NSBRI's intramural tasks. Proposals responding to a Program Announcement appearing in the NIH guide in June 1998 were submitted in October 1998. Selection announcements for this program are expected in June 1999. The NSBRI's funds for this model program presently come from private sources.

Finally, the NSBRI has begun to develop non-U.S. partnerships with the objective of enlarging the core research program by including projects carried out in other countries and supported by those countries. At this time, the Institute has signed an agreement of affiliation with the Institute of Aerospace Medicine of the German Aerospace Center in Cologne (Deutsches Zentrum für Luft- und Raumfahrt e.V., DLR) and a framework agreement with the Politecnico Di Milano. In addition, an agreement of cooperation with the Institute for Space Physiology and Medicine in Toulouse, France (Institut de Médecine et de Physiologie Spatiales, MEDES) has been approved by both parties and is awaiting signature.

2.3 Planned Augmentation

During 1998, it became clear that the NSBRI could fulfill NASA's vision of supporting human space exploration through focussed biomedical research by combining the basic research capabilities of leading academic research institutions with the operational capability of NASA and the applied research capability of industry. With this in mind, NASA and the Institute entered into serious discussions concerning the next logical steps that should be taken to realize the full potential that the NSBRI offered. A joint decision was made to develop an expansion plan that included: an increased number of research areas and intramural teams to allow for more complete coverage of the critical research problems of space biomedical research; increased funding levels for all of the research areas; and an augmented extramural grants program based on the model program developed by the Institute with the NIDCD, but funded with federal funds. In addition, it was decided to open the opportunity to participate in the intramural team research program to any member of the U.S. scientific community through the issuance of focussed research solicitations. Thus, the Institute intends to develop and release three announcements within the next year. The first one is this announcement to enlarge the NSBRI consortium. The second announcement will solicit research proposals to participate in four new research areas. The third announcement will solicit proposals to participate in the eight original research areas.

It is planned to expand the eight original research teams to twelve with the addition of the following new teams:

- *Neurobehavioral and Psychosocial Health* – This team will focus on the critical area of psychosocial health, but will also include relevant aspects of human factors. The NSBRI's *User Panel* of present and former astronauts and flight surgeons has strongly recommended the inclusion of this research area. In their July 1998 report to the NSBRI, they said, "Psychosocial issues will take on paramount importance in long-duration space flight. A critical need exists to address these issues as an integral part of NSBRI research."
- *Integrated Human Function* – This central team will focus on developing and carrying out a program of research to provide an overall integrated understanding of the response of the human body to space flight, covering all systems and integrated up from the molecular and biochemical level through cellular function to whole human function. This team will work at the cutting edge of mathematical and computer simulation to produce a digital human, integrating data from all of the other research teams.
- *Nutrition, Physical Fitness and Rapid Rehabilitation* – This team will be responsible for the ultimate development of a completely integrated approach to countermeasure testing,

focussing on the whole body reaction to a unified countermeasure protocol and on the major issues of nutrition, fitness maintenance and on the speed of rehabilitation of astronauts following space flight.

- *Smart Medical Care Systems* – This team will focus on research directed at developing and testing new approaches to medical care for exploration missions (Mars type), integrating new and emergent technologies for non-invasive data gathering, automated medical assistance, and medical data systems with new individualized models of integrated human function.

The augmentation plan also enables the number of tasks per research team to be expanded to the more appropriate average level of 12 to 15 instead of the 4 to 5 tasks/team in the current program. Thus, the research tasks will be able to be distributed appropriately over all four of the countermeasure development phases: the Molecular Mechanism Phase with an expected payoff in five or more years; the Systems Concept Testing Phase with an expected payoff in three to five years; the Ground/Flight Model Testing of the Countermeasure with an expected payoff in one to two years; and, finally, the Space Flight Validation of the Countermeasure.

This plan allows the scope of research of the original teams to expand in significant ways. For example, all teams will be expected to include at least one major task devoted to nutrition and the effects of diet on the system under study, one major task devoted to exercise and the effects of physical activity, and one major task devoted to artificial gravity and its use as a countermeasure (if appropriate to the research area). Each team will also be expected to include a modeling component designed to actively interface with the new Integrated Human Function team.

Another aspect of the Institute augmentation plan includes an expansion of the model demonstration program that the NSBRI has developed with the NIDCD. The primary characteristics of this model program are: (1) the joint activity focuses on research that impacts both health on earth and health in space; (2) program announcements for the competition are issued from the partner Federal agency, not the NSBRI; (3) the peer reviews are carried out by the partner Federal agency using their standard review system; and (4) selection is done jointly using the standard rules of the partner agency.

Expansion of this cooperative program is vital to the long-term success of the NSBRI's research strategy. Such competitively awarded, single investigator research activity is the backbone of the successful research management plan that both the NIH and the NSF have developed through years of experience. A stable program of this type, with an appropriate critical mass of investigators, will enable new ideas and new investigators to enter the program annually and will firmly establish space biomedical research in its proper niche within the national research agenda. Questions related to health in space are almost always directly analogous to questions related to health on earth and this type of joint program focuses on ways to make the research synergistic. It is planned to initiate discussions in late 1999 among the NSBRI, NASA, and other Federal agencies concerning the establishment of an annual competitive program of this type, with the first competitive announcements issued in late FY 2000 or early FY 2001.

Finally, the augmentation plan will include the development of a small (about 36 graduate students and 18 postdoctoral students) nationally competitive graduate and postgraduate training program in space-related biomedical research, and a significant enhancement to the current education and outreach program of the Institute. The current education and outreach program only involves three major institutions; the new program would expand to all consortium institutions and would represent a major force in providing the school and home with up-to-date

information concerning space biomedical research and its impact on everyone's lives. Industry support of this activity has been particularly strong and growth in this component is expected.

3.0 COMPETITIVE PROCESS

The competitive process for joining the consortium will consist of two phases. Phase I will involve a short application addressing the main points of the evaluation criteria, but without detail or back-up material. Phase I applicants will be evaluated on a qualified/not qualified basis. Those that are qualified will be invited to submit further details and back-up material for the Phase II competition. Phase II applicants will be invited to discuss their applications with the review panel in Houston, using the reverse site visit model, with travel costs borne by the applicant institutions.

3.1 Benefits of Consortium Membership

The major benefits of consortium membership are:

- Institutional participation in the development and management of a new model for a government/institutional/industrial partnership that can accomplish focussed research goals in a cost-effective manner;
- An opportunity to have one or more of the research team leaders (program directors) from that institution since every effort will be made to select all team leaders from consortium institutions;
- The opportunity to work closely with NASA and other Federal agencies to develop the research strategy and future directions of space biomedical research; and
- Institutional, faculty and student participation in developing special NSBRI graduate and postgraduate training programs

3.2 Responsibilities of Consortium Membership

The major responsibilities of consortium membership are to:

- Appoint upper administrative institutional representatives to serve on the NSBRI's Board of Directors and carry out all duties and responsibilities of the Board;
- Establish appropriate linkages between the NSBRI and the institution concerning public affairs, education, development, etc., as the need arises;
- Provide specific recommendations concerning research and supporting personnel of strength who would contribute significantly to the Institute's programs and who ought to be recruited to participate in those programs; and
- Participate in the cost-sharing program of the NSBRI that was proposed to NASA as part of the consortium budget plan: all institutions participating in the Institute's programs are asked to cost-share the funds received at the level of 10%. Institutions may specify how the cost sharing is to take place.

3.3 Review and Selection Process

All proposals will be reviewed and evaluated according to the defined criteria (Section 3.4) by a panel consisting of representatives of the present consortium institutions, the scientific community, and NASA. Those institutions whose proposals appear to be most promising will be identified and will be requested to submit revised and enlarged proposals for a second review. Other proposals will be declined.

The same review panel will examine the revised proposals and will interview up to three representatives of the submitting institution at a meeting to be held in Houston, Texas. All final proposals will be evaluated according to the defined criteria and the review panel will develop a selection recommendation to the NSBRI Board of Directors, who will make the final selection.

3.4 Evaluation Criteria

The principal elements, in relative order of importance, considered in the evaluation of proposals are: institutional contribution to NSBRI, complementary nature of the institutional contribution to NSBRI relative to the current consortium institutions, and potential NSBRI contribution to the proposing institution. Within each of these elements, the following factors are critical to the evaluation:

1. Institutional Contribution to NSBRI
 - Research and administrative personnel and infrastructure;
 - Current ongoing research programs and projects;
 - Existing education and training programs;
 - Special facilities; and
 - Other institutional strengths (specify).
2. Complementary Nature of the Institutional Contribution
 - Identification of specific institutional strength that complements the strengths of the current consortium institutions; and
 - Synergy between institutional strengths and strengths of the current consortium institutions, including specific research teams to which a major contribution would be made.
3. Potential NSBRI Contribution to the Proposing Institution
 - Special positive effects that NSBRI consortium membership may have on the proposing institution.

4.0 APPLICATION REQUIREMENTS

All categories of U.S. institutions are eligible to submit proposals in response to this announcement, including universities and medical schools, research institutions, and private sector laboratories. However, to be competitive, applying institutions should have substantial current research strengths in areas of interest to the NSBRI. Proposals from non-U.S. entities are not responsive to this announcement. Other methods exist to form appropriate relationships with these entities.

Initial (Phase I) proposals should consist of a letter from an institutional official summarizing the strengths of the application and addressing the evaluation criteria specified in Section 3.4. This letter must not exceed six pages in length. It should be typewritten and may be single spaced but should not contain more than 450 words per page. Proposals must include an original signature by the submitting official.

The proposal should be sent to:

Bobby R. Alford, M.D.
Chairman of the Board and CEO, NSBRI
Baylor College of Medicine
One Baylor Plaza, NA-102
Houston, TX 77030-2786.

The proposal should arrive before 5:00 p.m. CDT, Friday, July 2, 1999. FAXED proposals are not acceptable, neither are electronic mail (e-mail) responses.

Final (Phase II) proposals from the selected competitive group should include a similar second letter of application, but there is no page limit to this second application letter. In addition, the following set of attachments must be included with the application:

- Attachment 1. List and short CV's of key researchers who would be willing to contribute to NSBRI programs.
- Attachment 2. List of relevant ongoing research projects and programs, including principal investigator, title, funding level, funding period, and abstract, and citations of relevant publications.
- Attachment 3. List and description of graduate or postdoctoral education and training programs related to NSBRI's activities, including data on the number of students trained through these programs in the last five years and delineation of their present positions.
- Attachment 4. Description of other institutional strengths relevant to NSBRI.

Fifteen (15) copies of Phase II proposals, including at least one with an original signature from the submitting official, are to be submitted to the same address as Phase I proposals, namely:

Bobby R. Alford, M.D.
Chairman of the Board and CEO, NSBRI
Baylor College of Medicine
One Baylor Plaza, NA-102
Houston, TX 77030-2786.

The proposal should arrive before 5:00 p.m. CDT, Friday, August 20, 1999. At least one copy of the proposal must have original signatures. FAXED proposals are not acceptable, neither are electronic mail (e-mail) responses.

5.0 SCHEDULE

The following schedule is planned for the selection of additional members of the National Space Biomedical Research Institute consortium:

Initial (Phase I) Proposal Due:	July 2, 1999
Selection Announcement for Phase II:	July 16, 1999
Final (Phase II) Proposal Due:	August 20, 1999
Selection Announcement:	September 27, 1999

Original signed by _____ May 10, 1999
Bobby R. Alford, M.D. Date
Chairman of the Board and CEO
NSBRI

Table 1.
NSBRI BOARD OF DIRECTORS

Bobby R. Alford, M.D. (Chairman) Executive Vice President and Dean of Medicine Baylor College of Medicine	William L. Allen Editor National Geographic Magazine	Joseph V. Bonventre, M.D., Ph.D. Co-Director, Harvard-MIT Division of Health Sciences & Technology Harvard Medical School
James F. Buchli Space Station Program Manager United Space Alliance	Aaron Cohen Zachry Professor of Mechanical Engineering Texas A&M University	Bernard Cohen, M.D. (<i>ex officio</i>) Professor of Neurology Mount Sinai School of Medicine
Michael DeBakey, M.D. Chancellor Emeritus Baylor College of Medicine	E. Nigel Harris, M.D. Dean and Senior Vice President for Academic Affairs Morehouse School of Medicine	Richard J. Johns, M.D. Distinguished Service Professor of Biomedical Engineering Johns Hopkins University School of Medicine
Dennis Kasper, M.D. Executive Dean of Academic Programs Harvard Medical School	Robert A. Kennedy, Ph.D. Vice President for Research and Associate Provost for Graduate Studies Texas A&M University	Joseph P. Kerwin, M.D. Senior Vice President Wyle Laboratories
Jordan Konisky, Ph.D. Vice Provost for Research & Graduate Studies Rice University	J. David Litster, Ph.D. Vice President for Research & Dean of Graduate Education MIT	Larry McIntire, Ph.D. E.D. Butcher Professor of Chemical Engineering Rice University
Francis D. Moore, M.D. Moseley Professor of Surgery, Emeritus Harvard Medical School	James W. Patrick, Ph.D. Vice President and Dean of Research Baylor College of Medicine	Gary L. Smith, Ph.D. Director, Applied Physics Laboratory Johns Hopkins University
Walter Sullivan, Ph.D. Vice President of Operations and Planning Morehouse School of Medicine	W. Dalton Tomlin (Secretary/Treasurer) Senior Vice President & General Counsel Baylor College of Medicine	Arnold N. Weinberg, M.D. Medical Director MIT
Torsten N. Wiesel, M.D. President Emeritus Rockefeller University		Laurence R. Young, Sc.D. (<i>ex officio</i>) Institute Director

Table 2.
NSBRI BOARD OF SCIENTIFIC COUNSELORS

Hal E. Broxmeyer, Ph.D. (Chairman) Indiana University School of Medicine	H. Elliott Albers, Ph.D. Georgia State University	Joseph P. Allen National Technology Transfer Center
David J. Anderson, Ph.D. University of Michigan	James B. Bassingthwaight, Ph.D. University of Washington	Mary A. Carskadon, Ph.D. Emma P. Bradley Hospital East Providence, RI
Arthur A. Ciarkowski Food and Drug Administration	Priscilla M. Clarkson, Ph.D. School of Public Health and Health Sciences Amherst	Paul M. DeLuca, Jr., Ph.D. University of Wisconsin Madison
Paul A. DiZio, Ph.D. Brandeis University	William J. Evans, Ph.D., F.A.C.S.M. University of Arkansas for Medical Sciences	R. J. Michael Fry, M.D. Oak Ridge National Laboratory
Benjamin D. Levine, M.D. Presbyterian Hospital of Dallas	Peter Lipsky, M.D. University of Texas Southwestern Medical Center	Robert Marcus, M.D. Veterans Affairs Medical Center Palo Alto
	Connie Weaver, Ph.D. Purdue University	

TABLE 3.
NSBRI EXTERNAL ADVISORY COUNCIL

<p>Bernard Cohen, M.D. (Chairman) Professor of Neurology Mount Sinai School of Medicine</p>	<p>Martin J. Fettman, D.V.M., Ph.D. Professor of Pathology Colorado State University</p>	<p>Antonio Gotto, M.D. Provost for Medical Affairs and Dean Weill Medical College of Cornell University</p>
<p>Michael N. Gould, Ph.D. Professor of Human Oncology University of Wisconsin</p>	<p>Michael F. Holick, M.D., Ph.D. Professor of Medicine, Physiology & Dermatology Boston University Medical Center</p>	<p>Ann R. Kennedy, D.Sc. Professor of Research Oncology University of Pennsylvania School of Medicine</p>
<p>Martin J. Kushmerick, M.D., Ph.D. Professor of Radiology University of Washington Medical Center</p>	<p>Donald J. Marsh, M.D. Dean of Medicine and Biological Sciences Brown University School of Medicine</p>	<p>Robert Y. Moore, M.D., Ph.D. Professor and Chairman of Neurology University of Pittsburgh</p>
<p>Danny A. Riley, Ph.D. Professor of Cell Biology and Anatomy Medical College of Wisconsin</p>	<p>Richard M. Satava, M.D. Professor of Surgery Yale University School of Medicine</p>	<p>M. Rhea Seddon, M.D. Assistant Chief Medical Officer Vanderbilt University Medical Center</p>
<p>Warren K. Sinclair, Ph.D. President Emeritus National Council on Radiation Protection & Measurement</p>	<p>Ronald J. White, Ph.D. (<i>ex officio</i>) Institute Associate Director</p>	<p>Victor J. Wilson, Ph.D. Professor of Neurophysiology Rockefeller University</p>
<p>Thomas J. Wronski, Ph.D. Professor of Physiological Sciences University of Florida</p>	<p>Bill J. Yates, Ph.D. Assistant Professor of Otolaryngology and Neuroscience University of Pittsburgh</p>	<p>Laurence R. Young, Sc.D. (<i>ex officio</i>) Institute Director</p>

Table 4.
NSBRI USERS PANEL

<p>David C. Hilmers, M.D. (Chairman) Astronaut STS 51-J, STS 26, STS 36, STS 42</p>	<p>Joseph P. Allen, Ph.D. Astronaut STS 5, STS 51-A</p>	<p>Ellen S. Baker, M.D., M.P.H. Astronaut STS 34, STS 50, STS 71</p>
<p>Roger D. Billica, M.D. NASA Flight Physician</p>	<p>William Carpentier, M.D. Flight Physician 1965-1972</p>	<p>Laurel B. Clark, M.D. NASA Mission Specialist</p>
<p>John M. Fabian, Ph.D. Astronaut STS 7, STS 51-G</p>	<p>Owen K. Garriott, Ph.D. Astronaut Skylab 3, STS 9</p>	<p>Robert L. Gibson Astronaut STS 41-B, STS 61-C, STS 27, STS 47, STS 71</p>
<p>Joseph P. Kerwin, M.D. Astronaut Skylab 2</p>	<p>Byron K. Lichtenberg, Sc.D. Astronaut (Payload Specialist) STS 9, STS 45</p>	<p>Sam L. Pool, M.D. NASA Flight Physician</p>

Table 5.
Membership in the NSBRI *INDUSTRY FORUM*

Boeing Space and Communications Group
The Charles Stark Draper Laboratory
Information Dynamics, Inc.
Lockheed Martin Engineering & Science Services
Merck Research Laboratories
Michigan Biotechnology International (Application Pending)
Payload Systems Inc.
Raytheon Company
Silicon Graphics Inc.
Southwestern Bell
United Space Alliance (Application Pending)
Veridian
Wyle Laboratories (Application Pending)

Table 6.
NSBRI *RESEARCH TEAM LEADERS*

Bone Demineralization**J. R. Shapiro, M.D., USUHS****Cardiovascular Alterations****R. J. Cohen, M.D., Ph.D., MIT****Human Performance****C. A. Czeisler, M.D., Ph.D., Harvard****Immunology, Infection & Hematology****W. T. Shearer, M.D., Ph.D., Baylor****Muscle Atrophy****R. J. Schwartz, Ph.D., Baylor****Neurovestibular Adaptation****C. M. Oman, Ph.D., MIT****Radiation Effects****J. F. Dicello, Ph.D., Johns Hopkins****Technology Development****V. L. Pisacane, Ph.D., Johns Hopkins
Applied Physics Laboratory**

**NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE
NEW RESEARCH AREAS**

WORKSHOP RECOMMENDATIONS CONCERNING SCOPE

Neurobehavioral and Psychosocial Factors

This research area addresses individual neurobehavioral and psychosocial issues, group issues, and organizational and cultural issues related to the health, safety, and performance of crews involved in long-term space missions, particularly missions of exploration. The team formed in this area will carry out an integrated program of research focusing on the:

- Identification of the risks to crew health, safety, well being, performance, or productivity during long-duration space missions;
- Development of an array of tools to manage these risks and to enhance health, safety, and performance during such missions;
- Development of accurate, practical means to monitor human behavior and performance during missions; and
- Development and evaluation of countermeasures to improve human functioning during missions.

Within this research area, six interrelated themes define the range of factors critical for improving crew health and safety and optimizing human performance capability.

- **Biological mechanisms of neurobehavioral dysfunction.** Addresses adverse neurobehavioral events associated with alterations of nervous system function due to prolonged exposure to the conditions encountered during long-duration space missions (microgravity or altered gravity, loss of geophysical cues, isolation, and stress). The focus here is on the nervous system response at the cellular, molecular or organismic level to conditions likely to be encountered during long-duration missions.
- **Cognition and performance.** Concerns the assessment and enhancement of individual information processing, cognitive functioning, and operational performance during space missions.
- **Individual factors.** Addresses the individual factors involved in astronaut selection, training, and performance, individual issues related to crew monitoring and psychological support during and rehabilitation following a mission, and the impact of individual factors on strategies to deal with potential psychiatric problems and neurobehavioral dysfunction during a mission.
- **Team and interpersonal optimization.** Focuses on issues related to leadership, crew selection and composition for individual space missions, crew functioning during such missions (e.g., training, social interaction, time factors, decision making, and error management), and crew-ground interactions. In particular, the study of communication is of particular importance as multinational cooperation assumes a more prominent role in mission design and operation.
- **Organizational, cultural and management factors.** Examines the effects of cultures (organizational, professional and national), and management goals, policies and priorities on crew communication, performance, problem solving, and, ultimately, health and safety.

- **Pharmacology in space.** Addresses issues related to the utilization and efficacy of psychoactive and psychotherapeutic agents during space missions, including research into pharmacokinetics, changes in the blood-brain barrier, psychological and behavioral side effects of medications and their therapeutic effectiveness.

Research Questions

The following specific questions related to the preceding themes are provided only to illustrate the research scope appropriate to this area. For convenience, these questions have been placed in three categories: neurobehavioral and individual psychosocial issues, group level issues, and organizational and cultural issues. Many questions cut across the research themes and these categories. Individual project proposals should address relevant questions without concern for fitting them into specific themes or categories.

Neurobehavioral and individual psychosocial issues. What are the effects of stress and micro-gravity on central nervous system anatomy, physiology and neurobehavioral function? What are the relationships between stress and sleeping/waking neurobiology relevant to neurobehavioral functioning? What is the impact of long-duration space flight on drug pharmacokinetics? What pharmacological approaches are effective in improving performance? What are the durations of these effects? What are the secondary effects of countermeasure pharmacology (e.g., hypnotics and antinauseants) on performance? What are the effects of stress on neuroendocrine function relevant to healthy neurobehavioral functioning? What are the effects of stress on immune function and neuroimmune interactions? What are the most appropriate astronaut select-out and select-in criteria for long-duration space flight, given the likely heterogeneous make-up of crews (different genders, professional disciplines, and national cultures)? What are the threats posed to individual astronauts on long missions and what countermeasures are best for psychological support? What techniques and technologies can be developed to objectively evaluate human performance? What are the most effective means to monitor the psychological well being of astronauts, given that such monitoring should conserve critical resources such as crew time and spacecraft demands (e.g., power usage)? What is the level of astronaut cognitive performance during a mission (i.e., basic information processing such as working memory, focal attention, ability to retrieve information from long-term memory)? How can a measurement system provide a means of interpreting the performance information in a manner that indicates the likelihood that an astronaut can successfully perform a specific task? What are inter-subject and intra-subject factors that predict and affect performance? What factors predict individual vulnerability to performance failure? How can a measurement system be used to track and advise regarding the use of countermeasures to enhance performance? How can a measurement system be applied to individuals with different primary languages and cultures? What noninvasive measures can be developed to assess and predict the neurobehavioral, neurobiological, neuroendocrine, and/or neuroimmune consequences of stress? What training is required by the crew or ground personnel in order to recognize psychological difficulties experienced by crewmembers? What role can telemedicine effectively play in the management of such difficulties? What are the long-term sequelae of life-changes and other aspects of long-duration space missions? What countermeasures can help crewmembers deal with the stressors of the return? How can families best re-integrate astronauts after long missions?

Group level issues. In selecting flight crews for specific missions, what individual characteristics (exclusive of professional specialty and qualification) should be stressed and what *mix* of characteristics will lead to optimal performance and adjustment of the individuals and the crew? (A crew size of four to eight is anticipated.) What are the specific measures of crew behaviors that should be monitored during pre-flight periods and employed in determining crew composition? How might these measures be collected on board during missions? How can crews be trained to monitor their own behaviors and self-correct them? How do heterogeneous crews make group-level decisions and learn from their decision processes? How do crew decision-making behaviors change over time? How do crews reach consensus on issues with extreme consequences for individuals or for survival or success of the mission? What are the patterns of task behavior that unfold over time that are associated with low and high performance? What processes are employed by crews in error management and error prevention? How does human-machine interaction change over the course of a long-duration mission? What aspects of human performance ensure optimal human-machine interaction? How do crews successfully transition from nominal to off-nominal to nominal events over time? How do crews optimize mission leadership, recognizing the culturally heterogeneous composition of the group? How and when do systems of leadership break down? When are systems of leadership in crews emergent? How should crews structure and share meals and leisure activities? How should crews guard against engaging in dysfunctional social interactions apart from work-oriented activities?

Organizational and cultural issues. The behavior and performance of flight crews and ground support teams are influenced by culture at several levels – the national and professional cultures of crew members, the organizational culture of the lead organization and of the participating space agencies, and the organizational culture that emerges in the spacecraft during the course of a mission (i.e., the mission “micro-culture”). In addition, the organization of missions (i.e., goals and objectives, schedules, policies and procedures) will be a critical determinant of mission success. With these things in mind, what are the organizational requirements for support of human performance and the development and maintenance of an optimal behavioral ecosystem in space, including the level of crew autonomy and the distribution of authority, task scheduling, resource allocation and distribution, and implementation of behavioral countermeasures? How can crew-ground communication be optimized for long-duration missions with time-delayed communication? How will cultural factors influence the behavior and performance of multicultural crews? How is crew-error management affected by national culture? How do crew micro-cultures evolve in multicultural groups on long missions operating semi-autonomously in isolation, and how and when should organizations intervene if signs of conflict and stress emerge? How can crew culture overcome conflicts associated with differing national and professional cultures?

**National Space Biomedical Research Institute
NEUROBEHAVIORAL & PSYCHOSOCIAL HEALTH WORKSHOP**

July 19-20, 1999

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**NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE
NEW RESEARCH AREAS**

WORKSHOP RECOMMENDATIONS CONCERNING SCOPE

Nutrition, Physical Fitness and Rehabilitation

This research area involves the development of an integrative approach to the development of countermeasures to the potentially debilitating effects of long-duration space travel, focusing on the human responses to nutrition and exercise. In addition, such countermeasures should facilitate and enhance the rehabilitation of astronauts to an appropriate functional status following their transition from a microgravity environment to a gravitational one.

It is likely to be unrealistic to attempt to maintain pre-flight physical fitness and metabolic function throughout the course of prolonged space flight. Moreover, this may be contraindicated if certain physiological adaptations to space flight are, in fact, beneficial to the space traveler. The desired research outcome is to identify prudent countermeasures that achieve appropriate nutritional intake in combination with exercise and rehabilitation modalities necessary to maintain health and optimal performance of astronauts during and after an exploration-class mission. Some general research topics in this area are:

- development of mission phase-dependent nutrient requirements, avoiding single or multiple, concurrent nutrient deficiencies;
- nutritional/endocrine interactions and their influences on metabolic integrity;
- development of approaches to assess nutritional status that relate to functional outcome;
- quantification of baseline physiological and physical functions necessary for individuals to perform multiple operational tasks (extravehicular activity (EVA), emergency egress, piloting skills, etc.) involving one or more muscle groups;
- quantitative assessment of muscle strength and fatigability of specific muscle groups, maximal oxygen uptake, and autonomic vasomotor functions during and after space flight;
- identification of combined dietary and exercise prescriptions to optimize physical fitness of individuals for exploration-class missions;
- identification of the physical fitness requirements for operational tasks that may change during the course of a space mission and following transitions among different gravitational environments;
- development of context-specific rehabilitation interventions necessary to maintain performance during and following gravitational changes; and
- determination of how rehabilitation interventions must be adapted to the space environment for musculoskeletal and other injuries.

The following five interrelated themes characterize this research:

- **Interactions among nutrition, exercise and space flight environmental factors.** Addresses the way that adaptation to prolonged exposure to a space-flight environment, including changes in gravity-related forces, produces a reduction in physical fitness and changes in metabolic function.
- **Ground-based model development and evaluation.** Concerns the development and

quantitative, interdisciplinary evaluation of human, ground-based models of space flight to be used in countermeasure demonstration studies.

- **Assessment of task performance requirements for exploration missions.** Determines the functional and quantitative requirements of the operational demands made on the crew during an exploration mission in order to develop adequate prevention and rehabilitation strategies.
- **Criteria to evaluate countermeasure effectiveness.** Addresses the development of performance, physical fitness and motor performance assessments before, during and following space flight, and the development of a dynamic approach to increasing countermeasure effectiveness.
- **Rehabilitation following injury.** Focuses on the development of appropriate rehabilitation strategies following injuries that may occur during an exploration mission.

Research Questions

These questions are provided only as examples of the types of questions appropriate to this research area; they are not complete. Many are relevant to more than one theme. Individual project proposals should address the appropriate research questions that are pertinent to their project goals and objectives regardless of whether they appear on this list.

Does a countermeasure that attenuates the disorders of one physiological system simultaneously affect other physiological systems positively or negatively? Some investigations have demonstrated the effectiveness of individual countermeasures to ameliorate certain adverse physiological effects of short-term space flight, but these have generally targeted only one physiological system. What happens to the other systems? Can a resistance exercise training regimen designed to minimize muscle and bone loss during space flight favorably impact cardiovascular mechanisms associated with orthostatic tolerance? How much and what kind of periodic exercise patterns, dietary changes, or rehabilitation strategies should be used to maintain and restore normal motor function? What is the minimal volume or threshold of exercise necessary to maintain or to restore a specific function?

What is the optimal dietary composition (ratio of fat/carbohydrates, amount and type of protein or structured fats, role of specific amino acids and other nutrients) for phase-dependent differential activities of an exploration-class mission? What studies involving the interactions between exercise and nutrition are necessary to optimize functional benefit versus metabolic cost of exercise regimens? What is the impact of restricted caloric intake on countermeasure effectiveness? What is the practicality of oral hyperalimentation to enable adequate caloric intake and what are the effects on other physiological systems? What are the actual dietary requirements during space flight for macronutrients (calories, protein, etc.), micronutrients (vitamins, minerals, essential fatty acids, etc.), meal frequency, and meal volume? What is the appropriate role of therapeutic intervention to redress endocrine changes in space flight, including the use of exogenous anabolic hormones, hormone analogs, or modulators of hormonal release or sensitivity. What is the role for nutraceuticals, such as enriched foods and physiologic regulators, in the management of metabolic imbalances? What food safety issues are relevant to the achievement of nutritional goals? How should nutritional and physical status during space flight be addressed, including the measurement of body composition, the determination of surrogate metabolic

markers, and the development of biosensors and monitoring strategies to enable remote evaluation?

Food intake typically decreases during space flight. What are the potential impacts of appetite control, social/behavioral influences, gastrointestinal function, physical activity, and alterations in sleep/circadian cycles in causing this decrease? Experimental design of countermeasures may be flight-phase and task specific because countermeasures indicated for one time period or activity may be contraindicated for another. What are the appropriate performance-based evaluation criteria to determine optimum countermeasure structure? For example, astronauts who perform EVA under conditions of microgravity may require different dietary intake, motor skills, and coordination abilities than individuals who construct a planetary surface habitation module under conditions of hypogravity. Both groups must be properly prepared to do their assigned tasks in these environments.

What are the interactions of muscle-strengthening exercises with other systems, such as the cardiovascular and neurovestibular systems? How do these interactions depend on flight phase and individual adaptability? Can exercises intended to enhance musculoskeletal function also have a beneficial effect on visual-vestibular coordination? What are the combined effects of microgravity and restricted food intake or physical activity on acquiring motor skills? Can motor performance in altered gravitational environments be improved by instruction, simulation or practice? What are the contributions of isolation and confinement to the observed responses?

National Space Biomedical Research Institute
NUTRITION, PHYSICAL FITNESS & REHABILITATION WORKSHOP
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**NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE
NEW RESEARCH AREAS**

WORKSHOP RECOMMENDATIONS CONCERNING SCOPE

Smart Medical Systems

This research area focuses on health maintenance and acute and chronic medical care during exploration-class missions. It includes the development of new and advanced concepts of medical monitoring, diagnostic and therapeutic systems. Such systems could assist in training, decision making, and therapeutic intervention. The ultimate goal of this research is to develop a smart, integrated medical system that would assist in the delivery of quality health care on an exploration-class mission. This area includes the following topics:

- New or novel medical and surgical techniques;
- Novel sensor development;
- Automated medical data systems, including reliable patient data acquisition and analysis with minimal crew oversight and individualized models developed specifically for each astronaut;
- Automated decision support, training and diagnostic/therapeutic systems;
- Robotic medical assistance systems; and
- Novel drug synthesis and delivery systems.

The following five interrelated themes characterize the research in this area:

- **Patient monitoring and data management.** Concerns the development of methods and systems for minimally invasive and non-invasive individual patient monitoring and data capture, data communication, display and storage. This activity should be tightly coupled with the development of an individualized patient model.
- **Diagnosis.** Addresses the topic of assisted diagnosis and includes the development of methods to provide reliable diagnoses of off-nominal events during each phase of an exploration-class mission.
- **Treatment.** Focuses on development of novel approaches to treat acute and chronic medical and dental conditions, taking into account the constraints of exploration-class missions.
- **Medical system integration.** Addresses the development of an adaptable, easy to use, unobtrusive, and safe medical and decision support system with “intelligent” components that will include reliable patient monitoring.
- **Autonomous medical operations.** Concerns the development of: autonomous agents that serve as teacher, diagnostician and guide for medical and surgical therapy; systems and devices appropriate for ongoing medical training and augmentation of both knowledge and skill; and onsite manufacturing ability, allowing medical instruments, pharmaceuticals and biomaterials to be fashioned from primary materials.

Research Topics

The following topics are provided to illustrate the research scope of this area. They are not complete; project proposals may address these and other topics singly or in combination.

Novel sensor systems for monitoring and diagnosis. Sensors for medical use on exploration missions should have low noise/high specificity, low power requirements and minimal use of consumables. They should be modular, evolvable, adaptable, unobtrusive, comfortable, safe and easy to use. Non-invasive or minimally-invasive systems are of special interest, as are sensors that capture data relevant to a broad range of clinical and environmental parameters. Examples may include micro-array sensors for various metabolites and genomic expression.

Intelligent general-purpose reasoner. A valuable computer-based reasoning system (reasoner) would assist in the planning of optimal diagnostic and therapeutic courses of action, predict likely outcomes, and design realistic simulations and training scenarios individualized to a specific person. The reasoner would use comprehensive models to help integrate data, compute diagnostic consequences of the data, and provide real-time inference for emergency interventions and mentoring.

Decision support system for monitoring. Formalized approaches are needed to decide how changes in measured data should be brought to the attention of crew and/or ground support personnel. These approaches require domain-specific models of both short and long-term changes in physiological status and status of the crew's environment and life support systems. Computational techniques are required to direct monitoring systems, allocate monitoring resources across systems, and determine when, to whom, and how urgently to report monitoring results.

Decision support systems and knowledge bases for diagnosis and treatment. Medical care in a remote, isolated environment will depend on automated and semi-automated processes, alerts and reminders, and methods for aiding human decision makers. This, in turn, requires the ready availability of a corpus of medical knowledge resources, including textbooks, atlases, guidelines, formularies, diagnostic decision aids and other tools. Methods for organizing and retrieving knowledge relevant to a medical problem, inferring conclusions, developing and customizing diagnostic and treatment plans, and monitoring responses are needed.

Novel therapeutic modalities. Recognizing that facilities and specialty expertise for treating illness and injury will be limited, research is needed to identify alternative approaches that emphasize less invasive therapeutic interventions. Methods and devices that can be used by individuals with limited expertise under adverse conditions are required. The focus should be on approaches that minimize resource requirements and restore functionality, allowing mission completion.

Support for crew/ground collaborative decision making. Data, models, hypotheses, plans and decisions must be shared between decision makers on board the spacecraft and those supporting the mission on Earth. Communication latencies, dropouts, and limited bandwidth introduce unavoidable disturbances. All data must also be archived on the ground to support future scientific and problem-tracing investigations. System architectures and collaborative approaches need to be developed to support the requirement for shared decision making and data management.

Intelligent systems for mentoring and training. Supervision of crew-conducted procedures by automated processes can make them safer and more effective. For example, an intelligent mentor system (in the form of personalized avatars for each astronaut) could use personalized models

of a patient to guide surgical procedures and prevent errors. Similar capabilities could create personalized training scenarios that would allow a crewmember to practice emergency procedures and plan treatments or surgical procedures. Such a mentor would help prevent errors by providing guidance and feedback from the mentoring system.

Human-computer interaction techniques. New techniques are required to facilitate monitoring, alerting, mentoring and training. To make the content and procedures of a sophisticated health support system available to crewmembers, the system must be easy to use and employ innovative representations of the data and information. Research is needed to define and refine virtual reality visualization, including innovative user interface technologies for feedback and control.

Remote fabrication and pharmacologic production for space. Highly flexible ways to produce materials, tools and medications will be needed to supply exploration-class missions with equipment, drugs and prostheses, as they are required.

Novel three-dimensional imaging strategies. New devices and approaches are needed to provide improved anatomic definition both in routine monitoring and in acute, critical diagnostic circumstances. Three-dimensional data collected in flight should be readily comparable with ground-based data acquired prior to flight. Research is also needed to develop automatic measurement capabilities that routinely pass the data on to physiological modeling and decision support components of the medical care system.

Deep space telemedicine. Current interactive telemedicine applications require high bandwidth and zero latency communications, capabilities not available on deep space missions. Research is needed into data and image compression approaches that provide reliable transmission at relatively low bandwidth and maximize the ground's advice-giving capability when communications latency may be measured in minutes.

National Space Biomedical Research Institute
SMART MEDICAL CARE SYSTEMS WORKSHOP
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**NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE
NEW RESEARCH AREAS**

WORKSHOP RECOMMENDATIONS CONCERNING SCOPE

Integrated Human Function

This research area is concerned with the development of a comprehensive, computer-based approach to integrating general knowledge and information about human function with specific, individual functional characteristics and, ultimately, with producing an individual virtual human. Such a digital human will be dynamic. It will serve not only as an integrated repository of general knowledge and personalized medical and laboratory data but also as a simulation tool applicable to modeling changes in human function that may arise on exploration-class missions. Research in this area should focus on creating predictive models and simulations answering questions involving multiple human subsystems. All such models should treat human function in an integrated way. Research may contain both laboratory and computer-based modeling components, but the laboratory element must be fully justified by the proposed modeling project.

It is anticipated that the modeling of integrated human function will most likely involve both horizontal systems integration, synthesizing various organ or functional subsystems, and vertical systems integration, synthesizing molecular, biochemical, cellular, etc. subsystems. It may also involve integrating across certain thematic, fundamental physicochemical and biological processes that govern human function, including:

- biochemical and electrical signaling;
- biomechanics and movement;
- energetics and metabolism;
- fluid, electrolyte and acid-base balances;
- mass and energy transport and conservation;
- homeostatic regulation and multilevel control in hierarchical systems and the dependency of such regulation and control on functional state of the person; and
- adaptation to achieve steady states in continuously applied environmental stresses and the limits to that adaptation.

Research in this area may also include the development of strategies for creating federations of interoperable models and simulations of human function. Such software modules should be composable, extensible, reusable and retargetable. It should be possible to leverage and exploit existing standards and methods, including, among others, the High Level Architecture (HLA) for simulations developed by the Department of Defense, the Common Object Request Broker Architecture (CORBA) and the designs incorporated in the Physiome Project.

Research Topics

The following list of research topics is provided to illustrate the scope of this area. Models related to all of these topics should contain the appropriate ability to respond to changes in mission environmental parameters (e.g., gravity, radiation level, etc.). Whenever possible, consideration should be given to the ability of a model to be tailored to match a specific individual.

Multisystem models of function. Includes movement (vestibular and neuromuscular), adaptation (long-term changes in endocrine, immunologic, central nervous system (CNS), etc.), sensory and gravity perception (vestibular, visual, hearing, proprioceptive, kinesthetic, etc.), repair and remodeling (wound healing, skin, bone, immunologic and endocrine), etc.

Integrated sensorimotor performance model (1). Addresses the estimation or prediction of the physical ability of astronauts to perform a prototypical integrated physical task in a gravitational environment following a typical transit period in microgravity. The net effects on performance should be characterized by various appropriate combinations of deterioration or change in perception, sensorimotor control, musculoskeletal, cardiovascular and respiratory systems.

Integrated sensorimotor performance model (2). Concerns the prediction of the most likely sensorimotor and musculoskeletal capacity or performance failures that could occur during an exploration-class mission and determination of the appropriate strategies for preventing or correcting these problems.

Tissue repair and long-term function recovery. Involves the estimation or prediction, during different phases of a mission, of the functional integrity recovery curves of damaged organ systems following: crush wounds, simple fractures, burn/radiation/toxic substance skin exposure, toxic lung exposures, etc. What parameters affect the variability in these recovery curves?

Drug studies. Includes the estimation or prediction of drug absorption, metabolism, clearance and approximate efficacy over the course of an exploration-class mission. Determination of a minimal suite of agents that should be chosen to address short- and long-term analgesia, local and general anesthesia, seizure and arrhythmia suppression, antibiosis, gastrointestinal management, anti-vertigo, depression, etc.

Personalized human modeling. Addresses the development of individualized models for use in the smart medical systems described in Section 3. Comprehensive individual models of the anatomy, physiology, functional status, medical and environmental history of each astronaut will play a significant role in monitoring, diagnosis, treatment, outcomes prediction, training and simulation. Such models should combine data from all imaging modalities, physiological and environmental sensors, care providers and self-observation. A temporal component should represent changes in status or function of a body system over time. Models should include registered data from multiple modalities and dynamic mathematical system representations that support simulation and inference. The model should establish ground baselines for monitored parameters, and it should allow comparison of data with population norms, including those for mission-specific environments.

National Space Biomedical Research Institute
INTEGRATED HUMAN FUNCTION WORKSHOP
 July 13-14, 1999

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WORKSHOP ON
BIOMATHEMATICAL MODELS OF CIRCADIAN RHYTHMICITY, SLEEP
REGULATION AND NEUROBEHAVIORAL FUNCTION IN HUMANS
An NSBRI Human Performance Factors, Sleep and Chronobiology Team Initiative

Charles A. Czeisler, Ph.D., M.D. and Alexander Borbély, M.D., Co-Chairs

Megan E. Jewett, Ph.D., Organizer

MIT Endicott Conference Center, Dedham, MA

May 18 - 21, 1999.

Goals: To provide a cooperative working environment in which currently active mathematical modelers of circadian, sleep and human neurobehavioral systems can:

- Present their most recent models
- Discuss their model's limitations and advantages
- Compare the predictions of the available models and identify their areas of contradiction and agreement
- Integrate the current models as much as possible
- Identify gaps in currently existing data sets that must be filled in order to resolve remaining modeling questions
- Publish the results of the workshop in a special issue of the Journal of Biological Rhythms

In addition, this meeting is being held to honor the long and distinguished mathematical modeling career of Professor Richard E. Kronauer, Ph.D.

The workshop will begin with a welcoming reception on the evening of May 18. The next two days of the workshop will focus on familiarizing the participants with the detailed structure of the recently published models (since the last modeling workshop held in Zürich in 1991) of sleep regulation, circadian rhythms and neurobehavioral function. These two days will be divided into separate Discussion Sections of each of the four general types of models (molecular and cellular, circadian, sleep regulation, and neurobehavioral function). Two Co-Chairs will be appointed to each Discussion Section, and their duty will be to keep the presenters on time, to monitor the open discussion, and to provide a summary for that Discussion Section. Each Discussion Section will begin with descriptions of specific models in which the speakers present the details of their model (including its initial conditions, inputs, outputs and midcourse correction factors), simulation examples, and a summary of their model's limitations and advantages. After all of the models in that Discussion Section have been presented, the floor will be open to compare the models, determine areas of agreement and contradiction among the models' predictions, and list any features of currently available data that the models do not yet incorporate. The Discussion Section Co-Chairs will then lead a discussion identifying the open questions in their field which are needed to be answered before further modification of the models can take place. Specific experimental paradigms needed to provide these data will be discussed. At the end of the Discussion Section, the Co-Chairs will provide a summary of that Discussion Section. There will be poster sessions at the breaks and there will be a special after-dinner presentation by honoree Richard E. Kronauer on the evening of May 20th.

The morning of the third day of the workshop will focus on testing the models that were presented during the first two days. Speakers will discuss the best approaches to creating, refining and validating biomathematical models. This will be followed by an on-line comparison

of the models' predictions. Participants will be asked to provide their equations to the meeting organizers prior to the meeting so that they can all be programmed into one computer system. Participants will also be asked to suggest various test protocols to be input into the various models. The models' specific predictions for each of these protocols will be tested on-line so that areas in which further work is necessary can be identified. Computers will be available throughout the workshop so that participants may actively experiment with each other's models.

The afternoon of the third day of the workshop will focus on integrating the current models. The on-line versions of the models will be programmed in such a way that variables from one model can be easily linked to variables from another model. This will allow active modification and integration of the models during this portion of the workshop. The benefits and limitations of integrating the models will be discussed.

At the end of the workshop, the Co-Chairs of each Discussion Section will provide a summary of the workshop's conclusions for the models in their Discussion Section and the Co-Coordinator will put the overall findings of the workshop into a broader perspective for the field.

**WORKSHOP ON BIOMATHEMATICAL MODELS OF CIRCADIAN
RHYTHMICITY, SLEEP REGULATION AND NEUROBEHAVIORAL FUNCTION IN
HUMANS**

SCHEDULE

Day One

I. General Welcome: C. Czeisler, A. Borbély and M. Jewett

II. Molecular and Cellular Models of Circadian Systems

Co-Chairs: P. Lakin-Thomas and C. Johnson

Discussants: C. Weitz, M. Young, and D. Welsh

A. Model Descriptions and Simulations

1. A. Goldbeter and J. Leloup: Model for circadian rhythms in *Drosophila*
2. T. Roenneberg and M. Merrow: Circadian systems and metabolism
3. P. Ruoff: Modeling of temperature compensation in circadian rhythms
4. P. Achermann: Cellular Model of the SCN

**B. Model Agreements, Contradictions, and Missing Features
(Open Discussion)**

**C. Critical Experimental Data Needed for Model Refinement
(Open Discussion)**

D. Co-Chair Summary

Lunch

III. Models of the Effect of Light on the Human Circadian System

Chairs: C. Czeisler and E. Brown

Discussants: H. Illnerová and P. Lakin-Thomas

A. Model Descriptions and Simulations

1. M. Jewett : Effect of light on human circadian pacemaker
2. R. Kronauer: Dynamic Stimulus Processing model
3. A. Gundel and M. Spencer: Alternative model of human circadian system
4. D. Beersma: Entrainment model

**B. Model Agreements, Contradictions, and Missing Features
(Open Discussion)**

**C. Critical Experimental Data Needed for Model Refinement
(Open Discussion)**

D. Co-Chair Summary

Day Two

IV. Models of Human Sleep Regulation

Chair: D-J. Dijk and R. Kronauer

Discussants: T. Åkerstedt

A. Model Descriptions and Simulations

1. A. Borbély: Two Process Model: An historical perspective
2. P. Achermann: Two Process Model: Simulations
3. M. Nakao: Thermoregulatory model of sleep control: losing the heat memory

**B. Model Agreements, Contradictions, and Missing Features
(Open Discussion)**

**C. Critical Experimental Data Needed for Model Refinement
(Open Discussion)**

D. Co-Chair Summary

Lunch

V. Models of Human Neurobehavioral Function

Co-Chairs: D. Dinges and P. Achermann

Discussants: J. Horne and E. Brown

A. Model Descriptions and Simulations

1. S. Folkard and T. Åkerstedt: Three Process Model
2. M. Jewett and R. Kronauer: Interactive mathematical models of subjective alertness and cognitive throughput in humans

**B. Model Agreements, Contradictions, and Missing Features
(Open Discussion)**

**C. Critical Experimental Data Needed for Model Refinement
(Open Discussion)**

D. Co-Chair Summary

Dinner

After Dinner Speaker: R. E. Kronauer

Day Three

VI. Model Building and Quantitative Testing

Chair: M. Jewett and R. Kronauer

Discussant: D. Beersma

- A. E. Brown
- B. P. Achermann

VII. On-Line Comparison of Model Predictions

Co-Chairs: M. Jewett and E. Klerman

Discussant: V. Rajamani

- A. Entrainment Protocols
- B. Phase Shift Protocols
- C. Total Sleep Deprivation Protocols
- D. Cumulative Partial Sleep Deprivation Protocols
- E. Selective REM Sleep Deprivation Protocols
- F. Forced Desynchrony Protocols

Lunch

VIII. Discussion of Integration of Models

Chair: P. Achermann and M. Jewett

Discussants: D. Edgar and C. Johnson

- A. Integrating Molecular and Cellular Models into Human Circadian Models
- B. Integrating Human Circadian Models into Sleep Models
- C. Integrating Sleep and Circadian Models into Neurobehavioral Function Models

IX. Summary Statements

Co-Chairs: C. Czeisler and A. Borbély

- A. Molecular and Cellular Models: P. Lakin-Thomas and C. Johnson
- B. Human Circadian Models: C. Czeisler and E. Brown
- C. Human Sleep Models: D-J. Dijk, R. Kronauer and A. Borbély
- D. Neurobehavioral Function Models: D. Dinges and P. Achermann

X. Closing Remarks: C. Czeisler, A. Borbély and M. Jewett

Invited Participants

1. P. Achermann, Zürich, Switzerland
2. T. Åkerstedt, Stockholm, Sweden
3. D. Beersma, Groningen, Netherlands
4. A. Borbély, Zürich, Switzerland
5. E. Brown, Boston, MA, USA
6. C. Czeisler, Boston, MA, USA
7. D-J Dijk, Boston, MA, USA
8. D. Dinges, Philadelphia, PA, USA
9. D. Edgar, San Francisco, CA, USA
10. S. Folkard, Swansea, UK
11. A. Goldbeter, Brussels, Belgium
12. A. Gundel, Cologne, Germany
13. J. Horne, Leicestershire, UK
14. H. Illnerová, Prague, Czech Republic
15. M. Jewett, Boston, MA, USA
16. C. Johnson, Nashville, TN, USA
17. E. Klerman, Boston, MA, USA
18. R. Kronauer, Cambridge, MA, USA
19. P. Lakin-Thomas, Cambridge, UK
20. J. Leloup, Brussels, Belgium
21. R. Lewis, Auckland, New Zealand
22. M. Mero, Munich, Germany
23. M. Nakao, Sendai, Japan
24. Tjeerd olde Scheper, Oxford, UK
25. V. Rajamani, Boston, MA, USA
26. T. Roenneberg, Munich, Germany
27. P. Ruoff, Stavanger, Norway
28. M. Spencer, Cologne, Germany
29. C. Weitz, Boston, MA, USA
30. D. Welsh, Pittsburg, PA, USA
31. M. Young, New York, NY, USA

Additional Attendees

32. D. Forger, Cambridge, MA, USA
33. T. Graf, Zürich, Switzerland
34. R. Hughes, Boston, MA, USA
35. W. Larkin, Arlington, VA, USA
36. D. Neri, Moffett Field, CA, USA
37. C. Portin, Stockholm, Sweden
38. H. Van Dongen, Philadelphia, PA, USA
39. L. Young, Cambridge, MA, USA

Project Status Review
Comprehensive Medical Information System

Humans in Space – Information Management System

Site Visit: February 18-19, 1999

1. Nature of the Review

A project status review of Johnson Space Center's Humans in Space Information Management System initiative was conducted from February 18-19, 1999 at the Johnson Space Center (JSC). This review was conducted under the auspices of the National Space Biomedical Research Institute (NSBRI). The official visit lasted all day on Thursday, February 18, and the morning of Friday, February 19. A roster of site visitors and their affiliations is attached as Appendix A. The agenda is attached as Appendix B.

Two systems were reviewed during this site visit. The principal activity was a review of the Comprehensive Medical Information System (CMIS), a project in development to deploy an ambulatory Electronic Medical Record (EMR) system to the Flight Medicine Clinic and the Occupational Health Program at JSC. The second objective was to review the Life Sciences Data Archive (LSDA) Project, a repository of information from human life sciences research projects, and to consider the potential for integration of LSDA with CMIS to form a comprehensive information management system coded HIDS (Human Integrated Database System).

2. Presentations by JSC Staff

The documentation was clear, well organized, and very professional, and well presented by the team members, in spite of the fact that the issues were complex, and in some cases, controversial. The visit commenced with an executive session with the Space and Life Sciences Directorate, including Drs. Williams, Rummel, and Robinson. Dr. Judith Robinson stayed with the site visit for most of the sessions, and provided continuity between the executive issues and project team agenda.

Dr. Patrick McGinnis led the CMIS presentation. He is a flight surgeon responsible for astronauts' and their families' health care. Dr. Roger Billica presented an overview from his position in the Medical Operations Branch, which would have the clinical oversight of CMIS. Other presenters included Mary Wear and Martha Thomas from the Longitudinal Study of Astronaut Health (LSAH), an epidemiological research program, who have been seconded to CMIS, and by Phyllis McCulley, a critical care nursing specialist who also specializes in medical records. Byron Smith, a network engineer, presented technical details, while Tony Laudin from Insource Management Group (IMG), a healthcare information technology consulting firm, reviewed their role in system selection and project management.

David Bell, director of the LSDA Project, led its presentation, which was deferred to the morning of the second day. This review did not focus on the implementation of the LSDA, but on its potential for integration with CMIS during this project phase.

3. Principal Findings

The CMIS project team was thoroughly prepared for the site visit and appears to have progressed well thus far:

- a. Overall long-term objectives and scope are clear and appropriate,
- b. The selected software product, MedicaLogic's Logician, appears to fit the requirements well,
- c. The overall plan is thorough and comprehensive, and
- d. The project team members seem competent, dedicated, and focused.

The site team unanimously recommends that CMIS proceed to deployment of the Logician software.

However, NASA and the assigned project team can further increase the likelihood of success of CMIS by taking a number of steps. NASA needs to rethink the management structure, both of the project(s) and the subsequent routine operation and administration of the information system that they are developing. The CMIS team must add tasks that have as their objectives the definition of clear and formal data access policies and procedures to govern access to this sensitive and valuable data, plus adding tasks to design methods of enforcing those policies and procedures.

JSC must carefully design details of the technological and data management infrastructure that will allow access to patient-specific data according to the protocols of medicine and the well-defined policies, procedures, and enforcement activities mentioned just above. Furthermore, they should reconsider the step-by-step phasing of the objectives of the project for two reasons. The team must avoid dependencies on tasks that may delay the project, such as dependencies on a laboratory information system that is not yet year-2000 ready, and the project team must be permitted to define and make measurable progress and maintain and improve its credibility.

Specific Recommendations are listed here:

1) *Project Manager for CMIS.*

Dr. Pat McGinnis is an enthusiastic flight surgeon who works very closely with the NASA staff. He is donating time to this project and serves as the de facto project manager. JSC needs to assign a full-time leader to this project, who has information technology project management experience and, ideally, some background with clinical systems. Dr. Billica requested a list of qualifications for such a position, and a consensus would include:

- a) Background either in clinical care or clinical system deployment.
- b) Prior project management experience and training.
- c) Optimally, an advanced management degree.
- d) If not clinical system deployment experience, familiarity and ease with EMR systems.

Further advice on this issue can be obtained from IMG, the systems consultant on the CMIS project.

It is worth noting that Byron Smith, who works for JSC's principal life sciences consultant Wyle Laboratories, is the sole Technical Support person, performing a vital function to the project. Mr. Smith provided a substantial amount of the technical detail to the site visitors. He stated at the site visit that he is currently studying to be a Microsoft Certified Network Engineer, which would develop skills not directly a part of CMIS. If his career direction is toward network support, then a replacement technical lead needs to be recruited for CMIS.

2) *Scope to be limited to two clinics.*

The CMIS project scope includes establishing the Logician system in the Occupational Medicine and Flight Medicine clinics, as well as integration of data from the Longitudinal Study of Astronaut Health and the Life Sciences Data Archive. Also, integration of other medical systems is contemplated. To maximize the chance of success with CMIS itself, this first project's scope needs to be limited to establishing a successful electronic medical record in the original two clinics. This project will prove sufficiently challenging, inasmuch as this type of deployment has challenged every institution that has faced it. As part of even this reduced scope, Crew/Mission Medical Officers (M.D. and Non-M.D.) will be required to participate as members of various teams, particularly the Project Charter Team.

The scope must also address the requirement for constant (that is, 24 hours x 7 days) functionality of the system in the Flight Medicine Clinic, including a back-up plan for system failure or shutdown. The availability of a new information system will in effect change the standard of care at JSC, and astronauts and their families will have an expectation that their new EMR will be available at all times in an emergency. This is a reasonable, tested expectation and should be met with the project.

To ensure reliability of the data, a consistent vocabulary of clinical terminology needs to be established for the EMR. This is a challenge and will require a near half-time commitment from an experienced physician (presumably Dr. McGinnis), who cannot also serve as project manager. To accelerate the process JSC may wish to work with Memorial-Hermann or Baylor College of Medicine, both of which have active Logician deployments at this time. It may be possible to adapt the clinical data base from one of these installations rather than having to redevelop it at NASA.

The initial phase of the project should be redefined so that it can proceed parallel to other activities on which it now depends and which may delay it. This will allow the project team to define and achieve fairly formal measures of success for this phase, thus demonstrating the value of the project and reinforcing the credibility of the project team. For example, the site visit team concluded that the initial phase should be free of back-loading of historical data, as that data can be partially or fully entered manually or semi-automatically in the future as time permits and the need arises.

Moreover, the initial phase should focus just on the clinical side, since that project is very similar to the state-of-the-art projects of mainstream healthcare institutions, which offer roadmaps that may help expedite this part of the project. Additionally, the automated interface with the Antrim lab system might also be left out of this first phase, partly because of a yet incomplete Y2K-dependent upgrade. Furthermore, NASA has never

before done an interface with this lab system here, so that there are no existing software routines and procedures to emulate, requiring considerable startup effort.

3) *Objective measures of success.*

Detailed success criteria were not presented during the site visit. Many clinical system implementations fail due to the inexact nature of their deployment, and the lack of a set of goals for clinical or operational benefits. The current Logician implementation at Baylor and the Cerner implementation at the University of Texas Health Sciences Center have teams working on defining these success criteria. The site team recommends that an explicit set of criteria be developed and ratified by executive management.

4) *Operations plan and detailed budget.*

The budget that was provided to the site team is very general and "high-level." A detailed operational budget with program planning tools is required. This budget needs to outline the implementation in detail, but also requires:

- a) 24 x 7 functionality of FMC, including back-up plan for system failure or shut down.
- b) The same people cannot implement Phase 2 while maintaining and operating Phase 1. The team needs to generate a personnel count for the internal and external workload.

There was not sufficient justification for the creation of the electronic medical record (EMR) system. Given an unlimited source of money and time, there is no doubt that an EMR would be "nice to have." However, the site team was expecting a more formal justification (e.g. cost-benefit or cost-effectiveness analysis) for why the information system must go online and what *value* the EMR brings to NASA's decision-makers and their patients. The demand for the EMR is there, and would probably increase if the EMR were created.

The budget justification is quite lacking in detail. The contributions of NASA employees also need to be included in the budget because their involvement with this MIS project will distract from their other responsibilities. In addition, a budget for the continued operation and maintenance of the information system must also be developed. Although the project staff thought the data base created by the EMR would be easily accessible, other experience with Logician suggests that the programming required will involve a substantial amount of work.

The operations and maintenance of the system needs to be included as a part of the overall plan. In addition, once the system goes online, additional epidemiological or programming personnel will need to be hired to create standardized as well as ad hoc reports.

In order to implement effective data access control procedures, the implementation should partition the data base into two separate data bases, separately administered and controlled, but with common structure, codes, and other conventions that would allow them to be accessed as one virtual data base. Additionally, the site visit team agrees that the project team should evaluate the fairly new technology known as Virtual Private

Networks (VPN), which makes use of sophisticated encryption technology to maintain confidentiality of data both in a data base and while it is being transmitted. This fairly new technology may be more cost effective than the complete separation of networks that had been previously planned and budgeted.

5) *Consolidation of system management for CMIS and all clinical systems.*

Once the system becomes operational, and a staff is identified to manage it, CMIS should be integrated with other clinical information systems for operational issues. The clinical laboratory's Antrim system should be placed within this management framework, as well as any departmental systems. Operations should be vested in a group experienced with clinical information management, and the JSC CIO office should have some role either in oversight or consultation. It is not clear that the CIO has been involved with any of the decision-making concerning this project. Given the personnel and financial size of the project, it seems that his involvement is appropriate and necessary.

6) *Formal information/patient confidentiality policies.*

Much of the discussion during the site visit centered on data management policies. This included the complexity of access control procedures to meet the expectations of the physicians directly serving their patients, as well as the normal data privacy expectations of the patients themselves. The issue is complicated by the potential use of data aggregated from CMIS and LSDA for research inside NASA by authorized researchers, data access by other interested researchers outside of NASA, and data access for quality assurance management, as occurs in hospitals. Further complicating is the fact that astronauts are a small celebrity population, whose clinical data may impact their fitness to fly. These and other potential categories of access must be well defined, and policies and procedures for each defined. Once defined, detailed measures for enforcement must be planned and ultimately implemented.

NASA needs to strike a formal, written, and premeditated deal with its astronauts with respect to these issues of data release. In this context, a contract regarding internal safety and health use of all data is an excellent suggestion. A second suggestion considered the role of an elite team of researchers and clinicians arbitrating confidentiality issues. Two concerns with both approaches are that (a) the choice of the people on such a team may well be political, and (b) that there will still be loud complaints to Congress and other sponsors about limitations of access to NASA research data.

The issues regarding privacy, security and the release of medical information need to be worked out by the various constituencies (administrators, clinicians, astronauts, employees, etc.). The analogy of astronauts as similar to "patients in clinical trials" is one that cannot be resolved by the site visit team, but one that will have to be addressed in discussions within JSC as the pilot phase of CMIS is concluded.

Similarly, the tension between clinical versus research data needs to be addressed. This situation is analogous to the situation of academic versus administrative health services research or the publishing of detailed variations in physician practice. The earlier stages of the project, which involve incorporating only data from the clinics, is less problematic than the later stages which involve the incorporation of research data. For the earlier stages, the crucial points are creating a good security system to limit inappropriate access

to the electronic medical record and a good record of who obtains access to what information.

The incorporation of research data raises further issues about the integration of medical and research information that have been much discussed by the JSC Institutional Review Board (IRB), the astronaut office, and the NASA Bioethics Policy Task Force. The major policies that have emerged are:

- a) Researchers needing data from the medical record to help in the interpretation of the research data should incorporate that need into their protocol and secure the approval of the IRB and the consent of the astronaut subject before the data is released;
- b) More generally, data which is attributable to subjects should not be released without subject consent; non-attributable data (especially about sufficiently large groups of subjects) can be released without that consent;
- c) Research data obtained during a mission should be shared with flight surgeons when it indicates serious risks to the subject or to others on the flight or to the flight mission, but it should never by itself be the basis for disqualification from future flights.

It is important that any policies for the CMIS project be based on these earlier discussions. The best way to do that is to insure that representatives of the JSC IRB (e.g., Drs. Dietlein and Sawin) and of the astronaut office (e.g., Dr. Baker) be involved in the CMIS policy development process.

Related problems with clinical data include: No single patient I.D. number is available (i.e., Medical data from either flight-mission protocols or from additional elective research should be identified by protocol-specific patient identifier).

JSC should review the National Institutes of Health guidelines for patient confidentiality while conducting research. These form the basis for most clinical research in academic medical centers. Both Baylor and the University of Texas are interested in assisting JSC in developing their own specific guidelines. Also, these institutions have experienced IRBs who frequently review health services research and clinical projects, as do other members of the NSBRI. JSC may wish to consult with these IRBs to assist with data release policies and procedures.

JSC may wish to explore contractual arrangement whereby astronauts agree that medical data from flight-mission protocols on which they agree to fly (as opposed to additional elective research for which they may agree to participate) is to be reviewed by NASA for the advancement of the understanding of space flight. Such a contract should specifically outline:

- i) confidentiality;
- ii) "life-threatening" or "mission-threatening" policies;
- iii) peer-review activity before publication (web or medical literature).

The concept of data mining to ensure safety of astronaut missions is reasonable. This procedure is similar to the use of quality assurance in hospitals. In both cases, the activity is necessary in that such data needs to be analyzed; however, it is in the

institution's self-interest to never be published. Explicit policy should be made regarding the need to do this activity, even though it may be contrary to the needs of individuals.

7) *Human Integrated Database System issues.*

HIDS is an ambitious, albeit laudable goal for JSC. However, at the current state of the art this should be a concept, not a deliverable of the system. LSDA and LSAH data should be separate from the live clinical information in CMIS, which itself should be rigorously protected using the most stringent protocols for clinical data.

As HIDS evolves, extramural peer review will be necessary to give credibility to results and conclusions published on the World Wide Web. Without this review, there is an inherent risk that selection of data publication will be accused of being self-serving. Also, the Web is a notoriously insecure communications medium at the present time; any NASA data should be vigorously monitored before archiving on the Web.

Peer review (combined effort of both extramural and NASA) will also be necessary for applications to review or utilize data sets. JSC's IRB could be useful in this regard.

In the summary discussions the site team raised the prospect of a Health Services Research Office at JSC. The LSDA and LSAH projects are typical health services research projects, and data mining from the EMR will engender more projects. The team recommends the establishment of a focus for Health Services Research, in conjunction with the HIDS initiative.

8) *Further Applications Envisioned.*

With respect to the proposed EMR and phase 2 and 3 uses such as telemedicine, NASA cannot meaningfully relate the choice and use of EMR technology to these uses unless the goals of the uses are better defined. It does relatively little good to say that the EMR will or even should "support" these clinical applications if (1) the specific clinical applications are uncertain, (2) the technologies used to deliver the services are unspecified, and (3) the desired sites of delivery have not been adequately considered. For example, it seems as if telemedicine would have a large number of useful applications in helping manage the care of the roughly 200 NASA personnel and dependents in Russia. Installation of an image-capable (and preferably video-capable) EMR in this location could make case management much easier-especially when continuity of care is desired. (Note: the explanation that "telemedicine was used before and didn't work" without specifics requires explication)

4. Summary

The CMIS project is important and necessary for JSC at this time. The choice of product is appropriate, and the clinic sites selected are ready for implementation. An enthusiastic staff is available to conduct the project. The review panel strongly recommends the deployment of CMIS at this time.

In order for the project to succeed, a specific detailed budget and a timeline need to be developed. Objective measures of success need to be defined in advance. A full-time project manager must be assigned to CMIS. Issues of patient confidentiality must be addressed in the deployment, and a plan for operation and maintenance must be developed. Other research-oriented systems that will ultimately comprise HIDS should not be integrated into CMIS until a later phase, once the core two clinics have been successfully converted to the EMR milieu.

The site team and the local academic medical centers stand ready to support NSBRI and JSC in their efforts to deploy a state-of-the-art EMR system.

National Space Biomedical Research Institute
HUMANS IN SPACE - INFORMATION MANAGEMENT SYSTEM
Site Visit Review Panel
February 18-19, 1999

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National Space Biomedical Research Institute

Humans in Space - Information Management System (HISIMS) Site Visit

February 18-19, 1999

**National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Space and Life Sciences (SLS) Directorate**

AGENDA

Thursday, February 18

8:00 a.m.	Welcome Executive Session with SLS Directorate and NSBRI Management (Drs. Williams, Rummel, Robinson, White)	Dr. Dave Williams
9:00	CMIS Presentation	Dr. Patrick McGinnis
12:00 p.m.	Lunch Site Team Executive Session in Conference Room	Dr. Bob Beck
1:00	Brief by Integration Contractor, IMG	Mr. Tony Laudin
2:00	CMIS Wrap-up, Privacy Concerns, and Budget	Dr. Patrick McGinnis
3:00	Life Sciences Data Archive Project	Mr. David Bell
5:00	Adjourn	
6:30	Executive Session Dinner at Churrasco's	Dr. Bob Beck

Friday, February 19

8:00 a.m.	Meeting with Integration Contractor and Vendor	IMG
10:00	Site Team Executive Session	Dr. Bob Beck
11:00	Adjourn	

1999

ARTIFICIAL GRAVITY

WORKSHOP

Proceedings & Recommendations

**League City, Texas
January 14 – 15, 1999**

Edited by

William H. Paloski, Ph.D.

Laurence R. Young, Sc.D.

Executive Summary

NASA's vision for space exploration includes missions of unprecedented distance and duration, and relies upon new, advanced countermeasures such as artificial gravity (AG). To explore the utility of AG as a multi-system countermeasure during long-duration, exploration-class spaceflight, eighty-three members of the international space life sciences and spaceflight community convened in League City, Texas, on January 14-15, 1999. During this inaugural workshop, we also considered a number of other pertinent topics related to implementation of an AG countermeasure, including biomedical research, technology development, and mission requirements.

We began with a series of plenary lectures that addressed the knowledge and assumptions fundamental to this workshop: the current American and Russian countermeasure programs, a historical overview of AG research studies, the engineering possibilities for and constraints upon AG, and the existing ground-based facilities appropriate for AG research. We then debated the physiological requirements for AG, reviewed results from current AG-related research, and identified the next logical steps for developing an AG countermeasure.

At the end of the workshop, we formulated a series of recommendations to NASA. We concluded unanimously that the potential of AG as a multi-system countermeasure is indeed worth pursuing, and that the requisite AG research needs to be supported more systematically by NASA. More than 30 years of sporadic activity in AG research has not elucidated the fundamental operating parameters for an AG countermeasure; for this reason, we do not advise NASA to discontinue support of countermeasures currently under development. Instead, we recommend that NASA appropriate the resources—primarily, deploying and funding a peer-review research program—necessary to initiate AG parametric studies on the ground and in flight. Such rudimentary studies would serve as the basis for exploring an AG countermeasure, and must precede prescriptions for the application of AG during long-duration spaceflight.

In view of this workshop's success and potential, our final recommendation is that NASA establish a standing AG working group. The group would meet annually for the purpose of continuing and advancing our progress.

William H. Paloski, Ph.D.
NASA/JSC

Laurence R. Young, Sc.D.
NSBRI

14 March 1999

Recommendations to NASA Headquarters

The participants of the AG Workshop conclude that NASA Headquarters should commit now to a rigorous, peer-reviewed research program to systematically investigate rotational AG as multidisciplinary countermeasure during long-duration, exploration-class missions. To that end, we offer the following specific recommendations and timeline.

FUNDAMENTAL GOALS

1. Implement a rigorous, coordinated, and peer-reviewed research and development project to investigate rotational AG. The desired outcome should be a multi-system countermeasure against the detrimental health and performance effects of long-duration, exploration-class spaceflight.
2. Determine the optimal design characteristics for an AG countermeasure facility that will best promote human health and performance. Advocate multidisciplinary investigator teams.
3. Support the upgrade of existing ground and flight research sites and facilities as needed to perform fundamental research and development activities.
4. Promote the participation of and communication among all concerned, including experts from bone, muscle, cardiovascular, and neurovestibular fields, human factors, international space agencies, mission and vehicle design, crew representation and training, and rehabilitation.

IMPLEMENTATION OBJECTIVES

Immediate (0–6 months)

1. Establish a cross-disciplinary, international working/advisory group on Artificial Gravity to sustain the work started at the League City Workshop.
2. Provide scientific guidance and support to existing human-rated, inflight centrifuge projects, because some elements of the human response to AG can only be investigated in the microgravity environment.
 - a. Incorporate the following preliminary specifications into the design of a long-arm orbital testbed (e.g., TransHab) suitable for use on the ISS:
 - i. the largest possible diameter to yield a minimal rotation rate and allow for a wide range of activities
 - ii. an adjustable angular velocity with constant radius that yields between 0 and 3 g
 - iii. the space for two or more crewmembers to move about easily, ambulate, and perform upright exercise using the ISS treadmill and/or resistive exercise device
 - b. Encourage the Ukrainian and Russian efforts to develop a human centrifuge, as these could provide a unique, short-arm centrifuge facility for space research.
3. Identify potential flight opportunities for deploying a short-arm human centrifuge aboard the Space Shuttle, including a human-powered centrifuge or the Neurolab centrifuge. Concurrently, initiate a process to design, develop, and peer-review pilot studies. These flight studies will characterize the physiological effects of g transitions encountered during intermittent rotation.
4. Implement a peer-review process and/or peer-review guidelines for “parametric” research and development activities. Prescriptions for both intermittent and continuous AG should maintain the

bone, muscle, cardiovascular, and neuromotor function required during exploration-class missions. Call for ground-based research proposals¹ to:

- a. Establish fractional g amplitude requirements for continuous AG.
- b. Establish radius-rotation rate requirements for continuous AG, with a specific sensitivity to neuromotor function.
- c. Establish the optimal AG characteristics (duty cycle, amplitude, radius, and rotation rate) for intermittent AG. These characteristics should necessarily include prescriptions for promoting dual-adaptation to the AG and non-AG environments.

Near-Term (6–24 months)

1. Begin funding of ground-based research activities solicited in the initial call for proposals.
2. Establish a joint NASA/NIH research initiative to investigate the use of centrifuge devices in treating clinical populations (e.g., osteoporotic patients). Solicit research proposals against these objectives.
3. Evaluate the degree to which critical AG questions can be addressed using the ISS animal centrifuge. Modify and/or expand the planned program to include specific AG research objectives and then solicit relevant research proposals.
4. Begin flying AG pilot studies on the Space Shuttle using the human-powered centrifuge or possibly the Neurolab centrifuge. Establish peer-review process and solicit proposals for subsequent shuttle studies.
5. Provide AG recommendations/requirements to Mars vehicle designers.

Long-Term (2–7 years)

1. Solicit, develop, and perform ISS animal centrifuge AG experiments.
2. Solicit, develop, and perform ISS AG experiments with human-rated centrifuges.
3. Solicit, develop, and perform ISS short-arm human centrifuge AG experiments.
4. Discontinue Shuttle short-arm centrifuge experiments as ISS venues become available.
5. Answer the critical questions necessary to make a go/no-go decision for a 2014 Mars mission, based upon ground-based and flight studies already initiated.
6. Focus funding on AG countermeasure development activities, as warranted by research findings.

Sustaining

1. Provide funding for the upgrade and support of key ground-based AG facilities.
2. Strive for a peer-reviewed research program that balances basic and applied research. This approach will continue to attract promising young scientists to the space life sciences community.

¹ Note that concerns were raised regarding our ability to extrapolate from animal models to humans. While animal experiments should be considered, caution must be exercised in this regard.

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“Artificial gravity is an idea whose time has come around... and around... and around...”

*Dr. Larry Young
AG Workshop Co-chair*

Introduction

Historically, artificial gravity (AG)—rotating a spacecraft to maintain a 1 g-equivalent environment for crewmembers—was designed to overcome the adverse effects of long-duration spaceflight and to simplify in part the complications of living in a free-fall environment. Until recently, artificial gravity for humans meant one of two unsatisfactory alternatives: the 50m diameter torus, popularized by Willie Ley, Werner von Braun, and Arthur C. Clarke, and seen by much of the world in Stanley Kubrick’s popular 1967 movie "2001: A Space Odyssey," or small short-arm centrifuges. Each approach has its own shortcomings. The torus is too large and too expensive for a practical maneuvering station, while the short-arm centrifuges would require astronauts to crouch immobile in a tiny restraint and would need considerable improvements to allow even intermittent exposure. While of limited practical use, these early concepts provide an important historical perspective to our discussions of AG, present and future.

Despite a manifest need for new countermeasure approaches, concepts for applying AG as a countermeasure have not developed apace. During 30 years of human spaceflight experience, including numerous long-duration missions, research has not produced any single countermeasure or combination of countermeasures that is completely effective. Current countermeasures do not fully protect crews in low-Earth orbit, and certainly will not be appropriate for crews journeying to Mars and back over a three-year period. The urgency for exploration-class countermeasures is compounded by continued technical and scientific successes that make the exploration of Mars increasingly attractive. If we can assure the viability of human crews, then we are markedly closer to the long-sought goal of planetary exploration. Although the rotation of a Mars-bound spacecraft will not be a panacea, and cannot solve the critical problems of radiation exposure, isolation, confinement, and environmental homeostasis, it does offer significant promise as a multidisciplinary countermeasure. The critical and possibly fatal problems of bone loss, cardiovascular deconditioning, muscle weakening, neurovestibular disturbance, space anemia, and immune compromise may be alleviated by the appropriate application of AG.

From this perspective of limited practical capability and a distinct need for improved countermeasures, we examined several attractive and realistic near-term opportunities for exploring AG. Ground-based venues and models for AG research were accorded much discussion; numerous ground-based venues currently exist and may require only minimal augmentation to support AG research. The theoretical and experimental models that make use of animal and human subjects are valuable tools as well.

Opportunities for conducting animal and human research in space and on Earth are needed to further direct the evolution of an AG countermeasure. Research must first elucidate basic AG parameters (how much g is needed, how often it should be applied, and what are the minimum acceptable radius and the maximum rotation rate) and later progress to investigate AG countermeasure approaches. Some realistic, practical, and affordable AG opportunities are in the offing and should catalyze progress in AG research. From these discussions on research, facilities, countermeasures, and parameters, we formulated the rational and scientifically justified steps that will guide us in the development of a practical multi-system countermeasure.

Purpose of the Workshop

The NASA and NSBRI Artificial Gravity Workshop was convened at the request of NASA Headquarters/Code U (Office of Life and Microgravity Sciences and Applications). Participants were charged with determining whether and how an AG research project should be incorporated into the human space exploration objectives of the coming decades.

GOALS

The goals of the AG Workshop were to:

1. Debate the merits of pursuing AG as a multi-system countermeasure during long-duration, exploration-class spaceflight.
2. Develop an AG research and development plan that:
 - a. articulates a set of long-term, fundamental goals
 - b. defines near-term objectives, focusing on biomedical research, technology development, and spaceflight mission activities
 - c. identifies critical roles played by current programs and/or facilities in accomplishing these tasks
 - d. proposes a strategy for implementing research and technology development to enable a go/no-go decision for Mars expeditions by 2005.

PARTICIPANTS

Eighty-three participants (Appendix 1) represented the full spectrum of interest groups. These included scientific experts in the bone, muscle, cardiovascular, and neurovestibular disciplines; operational experts in space medicine, space operations (astronauts and mission scientists), centrifuge facilities, and flight simulators; engineering experts in AG device design, space vehicle design, and propulsion systems; and program managers. Participants crossed multiple boundaries: researchers working on both human and animal projects, representing NASA centers (Johnson Space Center, Glenn Research Center, and Ames Research Center), NASA extramural partners, NSBRI members, NASA international partners (including Russia, Japan, France, Germany, and the Ukraine), the Department of Defense, and NIH organizations. A leading movie director who is preparing a feature film on Mars exploration capably represented public interest.

GUIDELINES

At this workshop, we concentrated on intermittent and continuous rotational AG. The technology permitting linear AG—accelerating halfway to Mars and decelerating the rest of the way—would not be available to support our working assumptions, namely the 2014 Mars Design Reference Mission described in Appendix 4.

Summary of Workshop Proceedings

The workshop began with a series of plenary lectures designed to present a diverse gathering of people with a common basis for discussion. These lectures were comprised of the following tutorials and served as the genesis for the three subsequent discussion sessions. The substance of these lectures is summarized in Appendix 2.

PLENARY SESSION TUTORIAL LECTURES

Artificial Gravity Overview

Space Medicine Perspective

Sam L. Pool, M.D.

Scientific Perspective

William H. Paloski, Ph.D.

Current Countermeasures Status

U.S. Countermeasures

Kenneth M. Baldwin, Ph.D.

Russian Countermeasures

Inessa B. Kozlovskaya, M.D., D.Sc.

What do we already know about AG?

Overview of Previous AG Studies

Laurence R. Young, Sc.D.

The Pensacola Rotating Room Experience

Fred Guedry, Ph.D.

The Russian Short-Radius Centrifuge Experience

Inna Vil-Viliams, Ph.D.

AG Target: Exploration-Class Missions

Mars Design Reference Mission

John B. Charles, Ph.D.

Engineering Considerations

Lawrence G. Lemke, Ph.D.

TransHab Considerations

William C. Schneider, Ph.D.

Near-Term AG Research Venues

Station Accommodations–Human Research Facility

Suzanne M. Schneider, Ph.D.

Station Accommodations–Animal Centrifuge

Charles E. Wade, Ph.D.

Ground-Based AG Research Facilities

David M. Warmflash, M.D.

ARC Centrifuge Facilities

Emily M. Holton, Ph.D.

DISCUSSION SESSION I: What are the physiological requirements for AG?

SESSION CHAIRS: John B. Charles, Ph.D. and John Greenleaf, Ph.D.

QUESTION 1.1: *How much AG is required to maintain operational performance during exploration-class missions?*

RESPONSE: *Due to lack of systematic, appropriate research, no overall prescription for AG could be reached. The ensuing discussion centered on system-specific concerns, adaptive states in different g environments, and physiologic changes induced by a continuously rotated environment. Intermittent AG was accorded limited attention only because no experimental data are available for consideration.*

QUESTION 1.1.A: *Should AG be applied continuously or intermittently?*

- ◆ **No consensus** Opinions were mixed with respect to whether AG should be applied continuously or intermittently. More detailed discussion of some of these issues occurred during Question 2a.
- ◆ **Skeletal system** While some felt that continuous AG supplemented with exercise would be essential to maintaining bone integrity, others suggested that intermittent AG might be sufficient. The latter group pointed out that in normal humans confined to bed rest, 4 hours or less of standing daily has been shown to prevent calcium loss.
- ◆ **Cardiovascular system** Concerns were raised about adverse cardiovascular affects associated with transitions between g environments: the frequent transitions from microgravity to AG associated with intermittent centrifugation might lead to reduced crew efficiency and/or reduced compliance with the countermeasure. Some participants cautioned that the cardiovascular system might be incapable of dual-adaptation, such that every g transition might produce untoward cardiovascular effects. For example, the effects of intermittent AG on the cardiovascular system might be analogous to the effects of lower body negative pressure (LBNP) countermeasures studied previously. In these studies, flight crews exposed to LBNP testing frequently experienced malaise, facial edema, and other symptoms that resembled post-flight orthostatic hypotension.
- ◆ **Neurovestibular system** The neurovestibular system and the CNS itself are presumably capable of simultaneously maintaining adapted states to multiple different sensory environments. Nonetheless, some concern was expressed regarding the ability of the CNS to adapt to the continuously varying sensory stimuli created by the complex force environment of continuous rotating AG (see Question 2a). Furthermore, assuming that such adaptation would be possible, additional concern was expressed about the time required to readapt to the Martian, Earth, or microgravity environments following long-term exposure to continuous rotating AG.
- ◆ **Crew compliance** In her tutorial lecture, Dr. Kozlovskaya presented data demonstrating that Russian long-duration spaceflight countermeasure effectiveness is unrelated to mission duration, but is strongly dependent upon crew compliance. To the extent that an intermittent AG countermeasure would require periodic crew time allocations, many factors would be expected to affect crew compliance (work load, off-nominal operations, personal motivation, psychosocial adaptation, etc.). One advantage of a continuous AG countermeasure is that it would be passive; thus, compliance would not be an issue.

QUESTION 1.1.B: What are the physiological thresholds for effective gravito-inertial force (GIF)?

- ◆ **Caveat** Some participants noted, quite emphatically, that this question is overly simplistic. The answer depends on the physiological system in question, the orientation(s) of the AG vector with respect to the crewmember's body, the duration and duty cycle of the AG exposure, and the types and levels of physical activity to be performed while exposed to AG.
- ◆ **No overall consensus** Participants were unable to answer this question, even when discussion was limited to the simple case of a continuously rotating space vehicle with the AG vector orientation similar to the gravity vector orientation on Earth ($-g_z$ throughout most waking activities and a combination of g_x and g_y while sleeping).
- ◆ **Dearth of research** Participants unanimously voiced the need for definitive data regarding the human—even mammalian—responses to GIFs within the 0 g to 1 g range. Concern was expressed that despite more than 30 years of AG discussion, and dozens of theoretical and/or position papers (see bibliography), even the simplest low-g threshold studies have not yet been performed.
- ◆ **Call for peer-review research program** One explanation for the dearth of low-g data is a failure of the scientific peer review system to recognize the importance of parametric and/or operational studies. Participants agreed that NASA needs a program to support this type of research.
- ◆ **Call for performance standards** Acceptable levels for operational performance—for instance, at what point bone mineral loss increases the risk of bone fracture—have not yet been defined. Participants agreed that the goal of spaceflight countermeasures should be less than maintenance of pre-launch fitness levels. Rather, the goal should be two-fold: to maintain the level of operational performance required during and after flight, and to minimize irreversible changes likely to compromise the long-term health and safety of the crewmember. While some physiological function and performance information relevant to activities of daily living may be available in the clinical, aging, and/or rehabilitation research literature, no systematic attempt has yet been made to apply these data to astronaut operational duties. Furthermore, the Mars Design Reference Mission provides little information on the types and frequencies of tasks expected of astronauts during any phases of the mission. Strength, agility, and aerobic performance requirements for certain EVA tasks may be much greater than for most IVA tasks.
- ◆ **Minimum g amplitude** In the absence of experimental data, many participants advanced opinions regarding the minimum continuous AG amplitude necessary to maintain operational performance. To determine whether a consensus could be reached, the session chairs took a poll in which no consensus was reached, but over 50% of participants felt that 0.5 g was a minimum threshold (breakdown of votes: 0 g = 6 votes, 0.25 g = 0 votes, 0.5 g = 18 votes, and 1 g = 9 votes). Equally important, most participants agreed that some form of AG would be necessary during the course of the Mars Design Reference Mission, which would require crews to function in 0 g or 0.38 g for up to 900 days even in an abort scenario.

QUESTION 1.1.C: What minimum GIF should be used during flights to and from Mars?

- ◆ **No overall consensus** Because the physiological thresholds for effective GIF are not known, participants could not answer this question definitively.
- ◆ **Continuous AG** The best AG strategy would be to adapt crews to Martian gravity during the flight to Mars and to Earth gravity during the return trip.
 - This approach could be achieved via a fixed AG amplitude of 0.38 g en route to Mars and 1 g during return to Earth. As-yet-undetermined threshold or adaptation constraints might dictate that the AG amplitude be varied during the trip. For instance, if 0.38 g were too low to maintain physiological function and performance, the outbound trip would start at a higher AG amplitude

(perhaps 1 g) and then taper or step down to lower AG amplitudes during the trip. Alternately, if humans could not easily adapt to the angular velocity required for 1 g, the return trip would start at a lower AG amplitude (perhaps 0.38 g) and then taper or step up to higher AG amplitudes during the trip.

- Negative physiologic impacts may arise as result of this AG strategy. For example, “spinning-down” a rotating vehicle is necessary in order to initiate the propulsive capture or aerobraking maneuvers required for landing on Mars or Earth. Engineering estimates suggest that spin-down would require approximately 3–5 days, during which the AG amplitude would be reduced gradually to zero. Although propulsive capture and aerobraking would subject crews to different g environments (0.25 g and 3-5 g, respectively), both maneuvers are expected to be of relatively short duration. For this reason, participants expressed little concern about the adverse physiological effects of capture and aerobraking.
- ◆ **Intermittent AG** For intermittent AG, adaptation and/or protection may be a function of amplitude and duty cycle. So little is known about this paradigm, however, that no specific proposals could be made.

QUESTION 1.1.D: Would AG be required for extended stays on the Martian surface?

- ◆ **No consensus** Because the physiological thresholds for effective GIF are not known, this question could not be answered. Significant concerns were raised regarding the impact of living in a 0.38 g field for 18 months. Specific attention was directed to the skeletal system because it adapts much more slowly than the cardiovascular, sensorimotor/neurovestibular, or muscular systems. The need for AG and/or other countermeasures on the Martian surface must be further evaluated as new physiological threshold findings become available.

QUESTION 1.2: What are the acceptable and/or optimal ranges for radius and angular velocity of a rotating space vehicle?

RESPONSE: Slow rotating room studies suggest that humans can adapt to 6 rpm angular velocities with minimal difficulty. While no other specific values were offered for discussion, much attention was focused on the challenge of g gradients and g transitioning processes. Participants agreed the most effective approach is likely to involve AG in combination with exercise or other countermeasure.

QUESTION 1.2.A: What are the adverse physiological consequences of rotational AG?

- ◆ **G transition** Transition from one GIF environment to another causes adaptive responses in the bone, muscle, cardiovascular, and neurovestibular systems, which may be appropriate for the new environment. The detrimental physiologic changes associated with spaceflight and transitions back to earth have already been well documented. For example, orthostatic intolerance or balance control disturbances occur immediately following return to Earth from orbital spaceflight because the microgravity-adapted state is inappropriate for the Earth environment. Likewise, increased incidence of renal stone formation is a deleterious side effect of the hypercalcuria and bone resorption that are initiated upon exposure to microgravity.
- ◆ **System-dependent transition** The development of adverse physiologic adaptations is a dynamic process that occurs on different time scales. While all of the physiologic adaptations presumably begin during or soon after transitions between GIF environments, the time constants associated with functional neurovestibular and cardiovascular consequences are quite short compared to those of the bone and muscle systems. For example, while calcium excretion is known to increase early after insertion into orbit, bone loss after short-duration Space Shuttle missions is negligible. In contrast, bone loss after long-duration *Mir* station missions is substantial and requires many months to recover

after return to Earth. On the other hand, orthostatic hypotension is manifest after both short- and long-duration missions, but persists longer after extended duration missions.

- ◆ **Adverse effects of rotation** Rotational environments introduce peculiar physical characteristics that may lead to negative physiological consequences. One such peculiarity occurs with movements made out of the plane of rotation of the vehicle or centrifuge and results in “cross-coupling” and Coriolis forces (Appendix 2, Dr. Paloski’s lecture), which have both biomechanical (human factors) and vestibular effects. In his tutorial lecture (Appendix 2), Dr. Guedry described how the vestibular sensations experienced by astronauts in a rotating spacecraft would differ from those experienced by subjects working in a rotating room on Earth. In a rotating room, subjects usually stand on the floor such that the angular velocity vector of the room is aligned with their bodies. When subjects make head movements that are out of the plane of rotation, they experience nauseogenic cross-coupled vestibular stimulation in a consistent and predictable direction. Similarly, when subjects make linear head, trunk, or limb movements out of the plane of rotation, they encounter Coriolis forces—a deflection of the limbs or body dependent upon the direction of room rotation and the movement itself—that are consistent and predictable. In a rotating space habitat, however, the crewmembers effectively live on the outside wall of the rotating environment and are usually perpendicular to the spacecraft angular velocity vector. This orientation has an important consequence: the magnitude of nauseogenic effects depends on the crewmember’s orientation when making a given head movement. The central nervous system (CNS) can adapt to sensory rearrangements in which the relationship between motor commands and sensory inflow remains consistent. Consequently, rotating room subjects who experience 1 g at low rotation rates eventually adapt to the predictable Coriolis stimuli and are no longer sick. For intermittent 0 g AG applications, a strategy of orienting subjects in the appropriate direction should limit nauseogenic effects. This theory is based upon current interpretation of the Skylab M131 experiments, in which astronauts experienced no space motion sickness for Coriolis head movements initially conducted during the fifth flight day. In order to validate the continuous short-/medium-radius AG approach as a countermeasure, we must first determine how fully humans can adapt to the complex vestibular sensations induced by living perpendicular to the angular velocity vector of their habitat.
 - **Transitioning** While CNS adaptive responses are expected to eventually optimize sensorimotor system performance to the prevailing force environment, concern was expressed about the effects of transitioning from one gravito-inertial environment to another. Specifically, the critical issues were determined to be the time required for readapting to any novel gravity environment following long-term adaptation to continuous rotating AG, and the side effects associated with neurovestibular adaptation (motion sickness, perceptual illusions, discoordination).
 - Experience from the Pensacola Slow Rotating Room (Appendix 2, Dr. Guedry’s lecture) and more recent context-specific adaptation experiments (Discussion Section II, Dr. Shelhamer’s presentation), suggest that following sufficient g transition training, the CNS will dual-adapt. The transition times and concomitant side effects would then be negligible during subsequent transitions. Nonetheless, mechanisms, characteristics, and prescriptions for dual-adaptation to different GIF environments are not well understood.
 - The impacts of cross-coupled Coriolis forces on the bone, muscle, and cardiovascular systems are unknown, but if extant, are not expected to be important.
- ◆ **AG field gradients** Another characteristic of rotational environments is that the AG force amplitude varies directly with the radial distance from the center of rotation. For some orientations or motions of a crewmember within the AG field, this might elicit adverse physiological consequences. For example, a crewmember exposed to a $-g_z$ AG vector in a 4m radius centrifuge could experience 1 g at the feet but only approximately 0.5 g at the head. This z-axis g gradient would result in a novel hydrostatic load on the cardiovascular system unlike that experienced on Earth or during spaceflight, and uneven loading on the bone and muscle systems. It would also provide a unique center of gravity location,

which could result in inappropriate adaptation of the balance control system. If the crewmember were to raise her/his arms, they would become lighter. Likewise, if the crewmember were to climb "up" a radially oriented ladder, s/he would lose weight with each step. While little data exist on these potential consequences, the consensus was that the g gradient effects would probably be of minimal concern.

QUESTION 1.2.B: *What are the physiological limits for angular velocity, g gradient, etc.?*

- ◆ **Theoretical limits** While few experimental data are available, some guidance on these limits can be obtained from the many theoretical analyses that have been performed (cf. Stone, Shipov, Diamandis, and Young in Bibliography). For a fixed rotational force amplitude (F_c), an inverse relationship between radius (r) and angular velocity (ω) exists: $F_c = \omega^2 r$. Designers generally rely upon existing physiological and/or human factors data, coupled with reasonable assumptions, to identify optimal design regions in the ω versus r plane.
- ◆ **Additional considerations** The adverse physiological consequences of cross-coupling and Coriolis forces (see Question 2a) can be limited by minimizing the angular velocity. For a fixed AG amplitude, this can be achieved by maximizing the radius. Maximizing the radius would also minimize the g gradient and its potential physiological consequences. Practically, the size and cost of the vehicle will increase sharply with increasing radius.
- ◆ **Existing data** Data from slow rotating room studies in the United States (Appendix 2, Dr. Guedry's lecture) and Russia (Appendix 2, Dr. Vil-Viliams' lecture) show that humans have little problem adapting to angular velocities below 1 rpm, some difficulty adapting to angular velocities between 1 rpm and 6 rpm, and more difficulty adapting to angular velocities between 6 rpm and 10 rpm. No adaptation data are available for higher angular velocities.

QUESTION 1.3: *What additional countermeasures would be required to supplement AG?*

RESPONSE: *An AG countermeasure supplemented by exercise may be the most effective approach, although a combination of dietary, pharmacologic or other measures may provide additional benefit.*

- ◆ **Exercise** Based on the consensus response, resistive and aerobic exercise devices would likely be required to supplement any form of AG. Even on Earth, most astronauts require resistive and/or aerobic training to maintain their fitness levels.
- ◆ **Combination** The combination of multiple countermeasures is likely to improve effectiveness. For example, AG and exercise combined with dietary control and/or pharmacologic supplements could prove the most beneficial countermeasure for long-duration, exploration-class missions.

Discussion Session II: What research are we currently doing?

SESSION CHAIRS: PAUL DI ZIO, PH.D. AND VICTOR CONVERTINO, M.D.

The second session of the Workshop was a forum for brief, informal presentations of ongoing research and development efforts in AG. A brief summary of each presentation follows.

1. Sickness Induced by Centrifugation (W. Bles)

- ◆ Long-duration centrifugation studies have revealed a potential ground-based model for understanding space adaptation syndrome (SAS): sickness induced by centrifugation (SIC) strongly correlates with susceptibility to SAS in flight. This paradigm suggests the existence of some ubiquitous vestibular adaptation mechanism, which may generate valuable training approaches, for both desensitization to SAS and adaptation to continuous AG.
- ◆ Of the eight astronauts and cosmonauts tested with this paradigm, the five who experienced SIC also experienced SAS in flight. SIC is elicited by 1 hour of 3 g centrifugation but not by 2 g. Both SAS and SIC may result when a change in head orientation produces a new gravitational field.
- ◆ Because short duration centrifugation at higher g levels would lead to long-term after-effects, intermittent stimulation is not recommended for a Mars exploration mission.

2. Context-Specific Adaptation of the AVOR (M. Shelhamer)

- ◆ Saccadic eye movements adapt to different context cues, supporting the possibility of dual adaptation for AG and microgravity.

3. Heart Size and Heart Rate in Apollo 1/6 g Astronauts (J. Charles)

- ◆ Apollo biomedical data suggest that time spent on the Moon had a small protective effect on heart size.
- ◆ Relevant data **must** be collected for Mars mission.
- ◆ Shuttle pilots or those with a jet-flying background have more orthostatic tolerance post-flight than other crewmembers. Does high g exposure provide some degree of protection?

4. Are GEP-Peptides Altered by Motion Sickness? (G. Wolfram)

- ◆ Experiments have demonstrated that motion sickness alters the levels of gastroenteropancreatic (GEP) peptides in animals.

5. Three-Dimensional Eye Movements on Mir (A. Clarke)

- ◆ Data on voluntary head movements were collected preflight, inflight, 12 hours post landing, and 9 days postflight. Inflight data revealed that the horizontal component of head movement disappeared, but that the torsion component remained. Immediately postflight, the horizontal component was still reduced and was only recovered during the next 9 days.

6. Linear Acceleration Using the Neurolab Rotator: Inflight AG Testbed? (G. Clement)

- ◆ The ESA Off-Axis Rotator (Neurolab, 1998) provided centripetal acceleration of 0.5 g or 1.0 g for human subjects several minutes during spaceflight. Previous linear acceleration devices, the Linear Sled flown in 1985 and the NASA MVI Rotator flown during mission IML-1 in 1992, delivered only 0.2 g of alternated linear or short-duration centripetal acceleration, respectively.

- ◆ Linear acceleration in the Neurolab Rotator was perceived as artificial gravity in microgravity, since all 4 subjects tested had a sense of tilting to their side when the centripetal acceleration was along their interaural axis (G_y), or being upside-down when the centripetal acceleration was along their body axis ($-G_z$).
- ◆ The tilt sensation (somatogravic illusion) and eye counter-rolling was two-fold less at 0.5 g than at 1.0 g. Since no tilt or counter-rolling was observed during centrifugation at 0.2 g (in the NASA MVI Rotator), the threshold for perceiving artificial gravity during centrifugation in microgravity is presumably between 0.2 and 0.5 g.

7. *Device for Exercise and LBNP (A. Hargens)*

- ◆ The response of heart rate at 55 mm Hg LBNP (supine) is similar to exercising erect for 40 min per day at 1.4x body weight.
- ◆ Eventually, a variable stress leotard should be combined with LBNP to produce normal blood pressure distribution.

8. *Human-Powered Centrifuge (J. Greenleaf)*

- ◆ The human-powered centrifuge (HPC) at NASA Ames is designed to collect physiologic, psychologic, and performance data while the subject pedals to generate a maximum of 5 g at subject's feet. The HPC can be powered by an off-board generator, or by other manual devices including a stair stepper, rowing device, or other exercise equipment.
- ◆ Monitored parameters include electrocardiogram, heart rate, blood pressure, oxygen uptake, and temporal arterial blood flow.

9. *Ukrainian AG Exerciser on the Russian Module of the ISS (V. Shkapa)*

- ◆ Plans are being developed for a human rotator facility to be flown on the ISS.

10. *AG Mars Transfer Vehicle Concept Using "Bimodal" Nuclear Thermal Rocket Propulsion (S. Borowski)*

- ◆ The nuclear thermal rocket (NTR) is one of the leading propulsion technologies for crewed exploration-class missions. Twenty NTR systems were designed, built, and ground-tested during the NERVA program of 1961-1973.
- ◆ In addition to providing propulsive thrust during Earth departure, Mars orbit capture, and departure for Earth, current "bimodal" NTR also supplies abundant electrical power (up to 50kW_e) to the crew transfer vehicle (CTV) during the entire mission.
- ◆ On the CRV, the bimodal NTR propulsion stage is connected to the TransHab crew module by a 20m long saddle truss design.
- ◆ CTV rotation at $\omega \leq 4$ rpm about the vehicle center of mass provides Mars gravity (0.38 g) at the TransHab location during transit to and from Mars.
- ◆ In the current Mars Design Reference Mission, crew exposure to the 0 g environment could reach approximately 900 days in the event of a Mars lander or surface habitat failure. This would necessitate a crew abort-to-orbit in the CRV.
- ◆ Bimodal NTR CTV design is naturally configured to provide AG in the range of 0.38 g to 0.75 g for the TransHab crew during the mission duration as necessary.

11. Sensorimotor Adaptation to AG (G. Kaufman)

- ◆ Eye movements and balance data were compared between static tilt test and centrifuge subject groups.

12. Mathematical Models of Canal-Otolith Interaction (D. Merfeld)

- ◆ The g prediction theory was described as it relates to canal-otolith interaction. The g environment prior to a Mars landing should be at Martian g in order to avoid disorientation.

13. Long-duration Centrifugation of Animals (C. Wade)

- ◆ Long-duration centrifugation of animals in ground-based facilities reveals several important trends. Body weight decreases with increased g level. Although body weight does increase during centrifugation at 0 g, food intake is unchanged. Daily energy expenditure is slightly elevated as AG is increased from 1.5 g to 2 g. Animals show significantly less activity at higher g levels.

14. Russian Space Flight Experiments on AG (A. Shipov)

- ◆ Russian researchers have employed animal studies to determine the minimum g and maximum angular velocity.
 - Data collected from rodents exposed to flight centrifuges produced an interesting threshold. Above 0.28 g, animals responded as if exposed to 1 g. Conditions below 0.28 g were less like the Earth's gravity and animals showed a different response. From these data, it appears that 0.28-0.3 g is the minimal threshold that will emulate the benefits of an Earth environment.
 - Rodents subjected to 18 days of 1 g centrifugation in flight do not manifest signs of deterioration.
 - Although Biocosmos flight facilities permit AG levels to be varied, animal subjects were not affected by variable magnitude AG.
- ◆ The response of the cardiovascular and musculoskeletal systems should be used to determine minimum g thresholds.
- ◆ Tsiolkovsky selected 0.28 g as the minimum g level, which was in agreement with 0.28 g established by Yurganov with parabolic flight

15. Short-Arm Centrifuge Experiments on Humans in Japan (K. Yajima)

- ◆ NASDA is not pursuing AG research at this time, so the 1.8m human centrifuge at Nihon University is the only one in Japan. Cumulative experience suggests that 1 hour of a maximum 1 g load, combined with leg exercise, could serve as an intermittent countermeasure during flight.
- ◆ Human subjects exposed to a 2 g load for 1 hour during each of 7 days exhibit increased baroreceptor sensitivity, a trend that exactly opposes what occurs in space.
- ◆ Another study protocol exposed humans to 6-degree head-down tilt and a 30 minute 2 g load twice daily. This periodic g_z exposure eliminates hematocrit change for 5 days.

DISCUSSION SESSION III: What further research is required?

SESSION CHAIRS: RONALD WHITE, PH.D. AND ALAN HARGENS, PH.D.

QUESTION 3.1: *Should an AG countermeasure be pursued for exploration-class missions?*

RESPONSE: *Participants agreed unanimously that an AG countermeasure should be pursued for preventing multi-system physiologic adaptations. AG has the potential to bring significant benefit to space-faring crews, although its limitations are easily identified. Research and development activities should be implemented in parallel with extant countermeasure work.*

- ◆ **Unanimous affirmative** By unanimous opinion, Workshop participants agreed that AG should be pursued as a multi-system countermeasure during long-duration, exploration-class missions.
- ◆ **Need for comprehensive countermeasures** Current data suggest that the existing long-duration countermeasures do not sufficiently prevent physiologic degradation (particularly bone loss), and consequently require long-term postflight readaptation/rehabilitation. AG may act as a comprehensive countermeasure and may therefore alleviate many of the present rehabilitation issues.

QUESTION 3.1.A: *What biomedical problems would be mitigated by an AG countermeasure?*

- ◆ **Significant benefits** The consensus was that an AG countermeasure could potentially reduce or eliminate any of the physiological changes associated exclusively with microgravity. These changes include loss of bone mineral density and the associated increase in renal stone risk; muscle atrophy; cardiovascular system deconditioning including fluid shift regulation; orthostatic hypotension and loss of myocardial wall thickness; and sensorimotor/neurovestibular alterations including balance and oculomotor disturbances, and perceptual illusions. Some forms of AG would also reduce the levels of floating particulate matter in the habitable areas, thereby reducing the risk of potential microbiological and/or toxicological hazards. These forms would also have positive ergonomic effects, particularly for materials handling, surgery, sleeping, and excretory function.
- ◆ **Limitations** Like comparable 0 g alternatives, an AG countermeasure would not mitigate radiation exposure, failure of environmental control systems, behavioral and psychosocial consequences of isolation and confinement, or circadian rhythm disruption.
- ◆ **Potential** Because knowledge of the adaptive process continues to evolve, some suggested that an AG countermeasure may also limit or mitigate as-yet-undiscovered physiological changes.

QUESTION 3.1.B: *What other countermeasure research, if any, would be obviated by a vigorous AG research program?*

- ◆ **Continue all countermeasure research** While AG shows significant theoretical and intuitive potential as a multi-system countermeasure, research and development efforts should be continued for other countermeasure concepts currently under consideration. Once fundamental questions regarding potential side effects, implementation/engineering costs, and mission requirements have been addressed, funding may be increasingly focused on an AG countermeasure.

QUESTION 3.2: *How should we pursue AG countermeasure research?*

RESPONSE: *Priorities include understanding g transition processes, g thresholds, and AG engineering parameters. While numerous ground-based models and animal subjects may be of use, many participants voiced the need for flight studies with human subjects. A majority of the existing ground-based facilities would*

require only limited augmentation; in contrast, very few venues for flight-based research currently exist. Overall, the consensus was for immediate implementation of a comprehensive ground research program to serve as the foundation for a parallel flight program.

QUESTION 3.2.A: What remains to be learned about the physiological constraints and/or implementation requirements for AG?

- ◆ **Dearth of research** One consensus was that data regarding the human physiological responses to g environments between 1 g and 0 g must be obtained before we can determine threshold requirements for AG. Such studies must also address the question of whether countermeasures would be required during an eighteen-month human sojourn to the Martian surface. Note that much of the discussion during Discussion Session I also centered on this question.
- ◆ **G transitions** Another consensus was that the most critical physiological constraint on AG may be the full or partial inability of humans to transition without symptoms from one GIF environment to another. Even without AG, multiple such transitions will be required in a Mars mission: Earth to space, space to Mars, Mars to space, and space to Earth. Continuous AG would introduce at least four new transitions, while intermittent AG would require an even greater number of transitions. The neurovestibular/sensorimotor and cardiovascular systems were judged to manifest the most significant g transition symptoms.
- ◆ **Dual adaptation** The capability for and implications of dual adaptation were accorded much discussion. Clearly, the discussion of intermittent versus constant AG could be significantly influenced by better understanding of adaptive plasticity and the ability to dual-adapt. Ground-based research with the slow rotating room paradigm should be pursued, based on the concept that findings can be directly applied to the implementation of rotating orbital stations or spacecraft.
- ◆ **Parametric studies** Data regarding the human response to varying characteristics of rotating AG environments (e.g., radius, angular velocity) must be obtained before optimal designs can be achieved.
- ◆ **Performance standards** Acceptable standards must be defined to maintain the level of operational performance required during and after flight, and to minimize irreversible changes likely to compromise the long-term health and safety of the crewmember.

QUESTION 3.2.B: What can be learned from animal studies? What must be studied in humans?

- ◆ **No overall consensus** No consensus was reached in this area—there seemed to be no clear agreement between what could be learned using animal versus human models. Several participants voiced uncertainty about the extent to which results from animal models could be extrapolated to humans.
- ◆ **Model limitations** Most participants thought that valuable data could be obtained from animal models, but a number of questions were raised regarding the animal models most appropriate for extrapolation to humans. Some suggested that rat models might be appropriate for bone and muscle studies, but that monkey models were necessary for cardiovascular and neurovestibular/sensorimotor studies. Others suggested that rat models might be appropriate for short duration studies, but that monkey models should be used for long-duration studies. The current prohibition on primate experiments in space was noted and lamented as a limitation to comprehensive research. In addition, Russian experimenters noted that initial conclusions formed from research with rat models had to be modified when monkey models were used: monkeys developed maladaptations that were never observed in rats.

- ◆ **Continued model studies** Many lamented the discontinuation of Bion/Biocosmos flight experiments using rats and monkeys. A consensus of participants voiced the opinion that an AG experiment plan, as described by Dr. Shipov in his Session II presentation, could have been performed as part of this program and would have added significantly to our understanding of the physiological responses to fractional g in space.
- ◆ **Clinical populations** It was suggested that we might not be taking full advantage of the “human models” here on Earth. Rather than just deconditioning normal human subjects, we should also consider using clinical populations suffering from pathological changes similar to those observed in long-duration crewmembers. For example, to learn more about the protective effects of AG on the bone system we might examine the responses of osteoporotic patients to centrifugation. NASA may be able to team with NIH in support of such studies.

QUESTION 3.2.C: What can be learned from ground-based studies? What must be studied in space?

- ◆ **No substitute for flight studies** The Earth's gravity vector is a confounding factor that precludes full study and exploration of AG on the ground; we need to begin our studies in space as soon as possible.
- ◆ **Ground-based models** Ground-based experiments could provide some important background and/or precursor data that would help guide the design of space-based centrifuges or rotating spacecraft. “Teflon bed” studies, for example, could serve as a basic model for determining continuous and intermittent g thresholds for the bone, muscle, and cardiovascular systems. In this model, subjects can limit the longitudinal g gradient they experience during centrifugation. By lying on a radially oriented platform, which glides on Teflon bearings, subjects push from away from the centrifuge wall and lessen the GIF at their feet. Additional ground-based models include the slow rotating rooms for examining multi-environment adaptation, and short-arm centrifuges for investigating characteristics of dual adaptation.

QUESTION 3.2.D: What facilities, existing or planned, should be used for this research? What new facilities are required/desired?

- ◆ **Existing ground facilities** Because several ground-based venues already exist (Appendix 3), participants did not recognize the need to build new AG facilities at this time. Instead, several existing facilities can be minimally augmented to accommodate new equipment and procedures.
- ◆ **ISS animal centrifuge** Participants agreed that the planned ISS animal centrifuge could be an invaluable tool for investigating the effects of fractional g on system-specific function and performance. Questions were raised regarding the potential effects of periodic stops required to service the device. More importantly, some concern was focused on whether the current program plan could be altered to investigate AG designs for exploration-class missions. For example, the experiment described by Shipov starts at 0.5 g and then systematically increases or decreases to the g level that best maintains physiological function in the target system.
- ◆ **Flight test facilities** AG flight experiment facilities that can accommodate human subjects are imperative, and should be provided as soon as possible. To that end, participants voiced enthusiastic, widespread support for participating in the design and development of any testbed facility, such as the proposed 8-meter diameter TransHab centrifuge described by Dr. Schneider in his plenary talk (Appendix 2). The TransHab alternative, a low cost, inflatable crew module, could also be designed to link to a second module, and the pair rotated about their common center of mass to yield a longer diameter, variable gravity rotating facility. Similarly, tethering two TransHab-class vehicles could result in a very long diameter centrifuge. The planned Ukrainian short-arm centrifuge, as described by Dr. Shkapa, received support as well. Finally, some discussion centered on examining the possibility of rotating the Shuttle about its center of mass, at a maximum of 6 rpm, to generate AG

environments. Subsequent assessments of the Orbiter's structural tolerance and its "controllability" while rotating at a maximum of 4rpm reveal that this concept is not feasible.

- ◆ **Mars vehicle design** No unanimous consensus was reached about including AG in the design requirements for an interplanetary Mars transfer vehicle. Some of the engineering, management, and scientific participants expressed concern about the drawbacks of delaying such a recommendation—most notably, the relative increases in cost and the decreased probability of implementation. Despite this admonition, many participants felt that a specific recommendation could not be made at this time given the number of unknown parameters. Nonetheless, participants did recognize the increasing need for preliminary design assessments to examine how basic AG requirements would impact a Mars transfer vehicle.

QUESTION 3.2E: Assuming that a go/no go decision for Mars expeditions must be made in the middle of the next decade, how should AG research activities be implemented and prioritized?

- ◆ **Comprehensive parallel programs** One consensus centered around the need to begin a comprehensive AG ground research program immediately, and a parallel flight research program as soon as possible. To the extent possible, the ground-based results should be used to define the goals and/or strategies of the flight experiments.
- ◆ **Priority: g transition states** Another consensus was that the highest AG research priority should be given to studies addressing means to minimize the physiological effects (primarily cardiovascular and/or neurovestibular/sensorimotor) of g transitions. These should include studies that define optimal prescriptions for intermittent AG.
- ◆ **Priority: g thresholds** Another consensus was that the next highest AG research priority should be accorded to studies addressing the physiological and engineering parameters for implementing AG. These studies would define g threshold requirements for maintaining physiological function and performance, with particular emphasis placed on long-duration performance in the Martian 0.38 g environment, and the optimal specifications for rotational AG environments.

Conclusions of the Workshop

1. Rotational AG has the potential to serve as a multi-system countermeasure, and may be significantly more effective if combined with supplemental exercise or other existing countermeasures. In addition to mitigating bone loss, muscle atrophy, cardiovascular deconditioning, and sensorimotor/neurovestibular adaptations, some AG countermeasure protocols could also reduce potential microbiological and toxicological hazards and introduce positive ergonomic effects. Given that our understanding of the adaptation process continues to evolve, AG may also protect against adverse effects not yet identified.
2. NASA Headquarters should commit now to a rigorous, peer-reviewed research program that investigates rotational AG as multi-system countermeasure to be used during long-duration, exploration-class spaceflight. Fundamental ground- and flight-based research must first define operational parameters and then sustain development of an appropriate countermeasure.
3. Current knowledge and understanding suggests that the capacity to transition between different g environments will be a critical factor in developing an AG countermeasure.
4. AG research should not preclude research or development of other promising countermeasure concepts presently under consideration; AG countermeasure research should be accorded highest funding priority only when potential side effects, design impacts, costs, and operational considerations have been sufficiently addressed.
5. While theoretical and animal models are valuable in any research process, they cannot substitute for systematic ground- and flight-based studies of the human response to AG.
6. Standards for operational performance during spaceflight should be established. Such metrics would not only direct studies of an AG countermeasure, but would also refine the analysis of existing countermeasure approaches.

Critical Questions

1. What relationships exist between operational performance and *continuously* applied AG (between 0 g and 1 g)? How does supplemental exercise affect these relationships?
 - a. What minimum continuous GIF would be required to maintain operational performance during interplanetary travel to Mars?
 - b. What type and level of AG, if any, would be required during an eighteen-month stay on the Martian surface?
2. What relationships exist between operational performance and *intermittently* applied AG?
 - a. What optimal duty cycle would be required to maintain operational performance during interplanetary travel to Mars?
 - b. How do different duty cycles affect these relationships?
3. What are the acceptable ranges of radius and angular velocity required to maintain operational performance in a rotating spacecraft? What are the optimal ranges for these same parameters?
4. What is the human capacity for dual adaptation, and how can the transition process between different GIF environments be investigated systematically?
 - a. Can the cardiovascular system dual-adapt to different GIF environments?
 - b. Can the central nervous system dual-adapt to different GIF environments? Can it adapt to/from the complex force environment within a rotating spacecraft?
 - c. What restrictions on orientation and/or movement within the rotating vehicle would simplify the adaptive processes of the central nervous system?
5. What are quantifiable standards for operational performance during a mission? What are the limits for degradation of the specific systems during various phases of a mission to Mars?

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Each of the Session Chairs stepped forward on short notice, and with little direction, to guide our Workshop discussions. Each of the Plenary Speakers contributed a different dimension of the quest for artificial gravity—as a group they expertly and succinctly summarized an enormous body of multidisciplinary knowledge. All participants dedicated time from their busy schedules to travel to League City (in some cases from great distances) and contribute to the success of this Workshop.

Special thanks go to Captain John Young, the celebrated NASA astronaut, who shared with us his experiences in space and on the Moon, and reminded us that that our work is fundamental to the future of human exploration. Special mention also goes to Mr. James Cameron, the award-winning Hollywood producer, who reminded us of the world-wide interest in a Mars exploration mission.

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APPENDIX 2: Highlights from Tutorial Lectures

ARTIFICIAL GRAVITY OVERVIEW

Space Medicine Perspective (Sam L. Pool, M.D.)

- Based on our joint US/Russian Phase 1 experience, the currently available countermeasures are certainly not adequate!
- A combination of AG and exercise may be an effective countermeasure, such that a 1 g level of AG is not necessary.
- The human-powered centrifuge concept, currently under development, will provide a combination of aerobic exercise and $-g_z$ centrifugal force. The subject's head is located at or near the center of rotation, while the subject is seated on a "bicycle" and pedals around the axis of rotation at up to 35-40 rpm.
- Two concerns about the use of AG:
 1. Numerous transitions between AG and 0 g may keep crew members in an uncomfortable adaptive state (full head, stuffy nose, etc.).
 2. Sensorimotor adaptations may also present problems, as observed in slow rotating room experiences in US and Russia, even with 50 ft diameters. The Russians found that subjects could adapt rapidly up to about 6rpm, but then had to stabilize at that rate for a while before proceeding on to 10 rpm—subjects could not immediately tolerate 10 rpm.
- We must define the dose response curve of humans subjected to continuous rotation and then identify thresholds and operating characteristics for a rotating crew module. Because engineers are currently developing lightweight low cost space vehicles for a Mars mission, the time to make recommendations is now. The potential rotation of the TransHab module is one salient example.

Scientific Perspective (William H. Paloski, Ph.D.)

- We face numerous practical and operational obstacles to validation of AG and other countermeasures on the ISS. A primary concern is that only about 60 astronauts will inhabit it before the go/no-go decision must be made.
- Subjects moving about in rotational AG experience a complex force environment that includes velocity cross-coupling, Coriolis forces, and g-gradients, all of which may have profound effects on the efficacy of an AG countermeasure.
- Theoretical approaches may be used to guide selection of the operating parameters for rotational AG (cf. Stone, 1970); these parameters, however, must be validated with human subjects and must be ultimately tested in space.

CURRENT COUNTERMEASURES STATUS

U.S. Countermeasures Status (Kenneth M. Baldwin, Ph.D.)

- The 1997 Countermeasures Task Force Report (available electronically at http://peer1.idi.usra.edu/peer_review/prog/countermeasures/countermeasures.html) provides a useful overview of the current program and areas for future focus. In particular, the report examines the shortcomings of current countermeasures by discipline. The average healthy astronaut has neither the strength nor the stamina to perform an emergency egress after a short-duration spaceflight (data

presented by Mike Greenisen of JSC at the First Biennial Space Biomedical Investigators' Workshop).

- One novel approach is the UC-Irvine Human Powered space cycle being developed by Dr. Arthur Kreitenberg. This device includes an intermittent cam in the cycling device, providing impact loading that may be necessary to protect bone.

Russian Countermeasures Status (Inessa B. Kozlovskaya, M.D., D.Sc.)

- In the Russian space program, cosmonauts are considered to be patients.
- A compilation of Russian human spaceflight experience reveals that 87 cosmonauts have performed 171 person-flights. Of these 171 flights, 57 are considered long-duration; without a program of countermeasures, none of these flights would have been possible.
- Of 57 long-duration missions completed, a majority (44) have lasted six months or less and one has lasted 14 months (Polyakov).
- In-flight countermeasure testing and validation consists of "natural experimentation". Although cosmonauts are normally willing to perform a countermeasure protocol, they frequently try to improve upon it during the course of a mission.
- Each countermeasure added to the *Mir* program is permanently retained and will remain available for use, like a component of a clinical program. Current countermeasures include:
 - the "Penguin suit", a system of bungees aligned with the longitudinal axis of the body that simulates the terrestrial loading of antigravity muscles.
 - the "Chibis"/LBNP system, which partially simulates terrestrial blood circulation. It may reproduce appropriate terrestrial patterns of intra-thoracic blood distribution, but does not reproduce normal head or abdominal circulation.
- Physical exercise is the core of the Russian countermeasure program. Treadmill locomotion coupled with bungees for resistive training serves as the primary element of the program, although cosmonauts also use a bicycle ergometer.
- During the first 10-20 flight days, cosmonauts must adapt to the microgravity environment, and therefore are not encouraged to begin exercising. Most start by flight day 10.
- The standard Russian exercise countermeasure prescription follows a four-day exercise cycle in which Day 1 is low load at high intensity; Day 2 is moderate load at moderate intensity; Day 3 is high load at low intensity; and Day 4 is active rest or low load performed *ad lib*.
- Anaerobic activity with the in-flight treadmill is encouraged, since IBMP studies reveal that in-flight aerobic exercise results in postflight orthostatic intolerance. Short duration intervals of high intensity (anaerobic) running are interspersed with walking to prevent lactate build-up.
- A minimal amount of running may provide loading sufficient to limit musculoskeletal attenuation. Skylab exercise data supports this: during Skylab 2 and 3, crew members experienced significant losses in leg volume, leg strength, and weight despite the use of the bicycle ergometer, and the MK I and II exercisers. During Skylab 4, these losses were eliminated by the addition of only 10 min/day of treadmill running. Similar conclusions have been reached by Dr. Bill Thornton, whose data show that impact loading during running yields a 10-fold increase on leg muscle load, and Dr. Rob Whelan, who has published work on musculoskeletal adaptation to varying mechanical forces.
- Exercise performance is not monitored daily, but is instead evaluated during monthly performance sessions on a high load treadmill test. Test results, including blood lactate, heart rate, and resistive load, are used to prescribe the next month's exercise regimens.

- Salient postflight findings include:
 1. muscular atonia and atrophy, decreased force velocity properties, and alteration of muscle fiber composition (slow to fast twitch transformation)
 2. altered sensorimotor control and suppression of proprioceptive activity
 3. sensory and motor ataxia.
- An “expert system” is used to rate individual performance postflight. While performance is not at all correlated with flight duration, it is highly correlated with compliance with in-flight exercise countermeasure prescriptions.
- The exercise countermeasure protocol currently in use is not satisfactory, and investigations are in progress to improve upon it. A main concern is the physical and psychological toll of 2-hour diurnal exercise sessions.

WHAT DO WE ALREADY KNOW ABOUT AG?

Previous AG Studies Overview (Laurence R. Young, Sc.D.)

- The article “Artificial Gravity Considerations for a Mars Exploration Mission” is reproduced in Appendix 5.

The Pensacola Slow Rotating Room Experience (Fred Guedry, Ph.D.)

- The Slow Rotation Room (SRR) paradigm was initiated in 1958 by Ashton Graybiel to study human adaptation in an enclosed rotating room. In these early studies, rotation rates ranged from 1-10 rpm and continuous rotation experiments ranged from as short as a few hours to as long as three weeks. While many responses were measured, motion sickness, self-movement perception, reflexive eye movements (VOR), and postural control are the most relevant parameters.
- In the SRR, subjects experience novel feedback from arm, leg, and head movements. Because head movements are unpleasant and nauseogenic, subjects quickly learn to restrict them; the magnitude of discomfort during a head movement is related to SRR angular velocity.
- Head tilts in a SRR provoke motion sickness that results primarily from canal-otolith mismatch. During a head tilt, the canals perceive rotation about an axis that is orthogonal to the axis indicated by otolith input. The canals are responding to cross-couple stimulus (CC), an angular acceleration vector produced by head tilt angular velocity cross-coupled with SRR angular velocity.
- A related consequence of the CC stimulus is an inappropriate vestibular-ocular reflex (VOR) that gradually attenuates until only functionally essential VOR components remain. By performing visual tasks during repeated head tilts (100), subjects had a substantially reduced VOR response and diminished nausea.
- When SRR rotation was momentarily stopped, head movements revealed direction-specific adaptation vectors. That is, head pitch in an upright position produced a roll perception exactly opposite the perception produced during rotation.
- On-board experimenters moved about when SRR rotation was halted and showed the capacity to dual-adapt to SRR and Earth-normal conditions. Subjects remained stationary during these stops and were maladapted. Subjects adapted to SRR rotation in one direction are maladapted to rotation in the opposite direction. Since aviators are able to dual-adapt to CC canal stimulation during clockwise and counter-clockwise rotation, the capacity for dual adaptation and reduced nauseogenic effect is likely and requires further investigation.
- On Earth and in space, the vector of the CC canal stimulus is dependent upon the position of head relative to the plane of rotation. In a rotating spacecraft, however, the environment is complicated by

centripetal acceleration (the gravito-inertial factor) in the plane of rotation. Thus, a 30° head movement (yaw right) in space and in the SRR yields different, yet still inappropriate, VOR responses that are dependent upon the direction a subject is facing (Figure A). In the SRR, however, subjects can rely upon otolith and postural input (see table below) to predict initial position, while

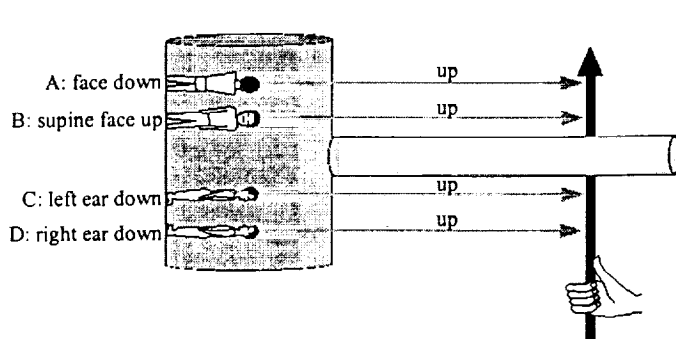


Figure A. An individual lying in the plane of rotation of the SRR relies upon postural and otolith input, as well as information from cross-couple canal components (see table below), to determine position.

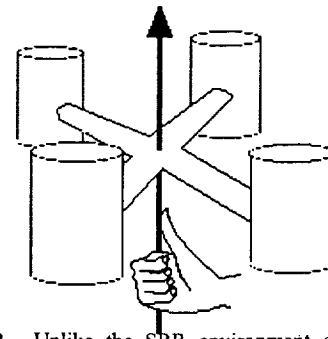


Figure B. Unlike the SRR environment on Earth, a rotating space station, configured like the one above, does not provide subjects with sufficient postural or otolith input to determine position.

individuals in the spacecraft cannot (Figure B).

Head movement YAW RIGHT	Cross-Couple Effect on Canals	Head Movement PITCH DOWN	Cross-Couple Effect on Canals
Position A	roll left	Position A	none
Position B	roll right	Position B	none
Position C	pitch up	Position C	yaw right
Position D	pitch down	Position D	yaw left

- The SRR paradigm is more complex than the prism shift and other optical distortion paradigms. To maintain appropriate locomotor and balance function, SRR subjects must employ visual-vestibular and postural adjustments to adapt to linear Coriolis acceleration and cross-coupled angular velocities. The SRR is a rich source of clinical relevance for rehabilitation patients as well.

The Russian Short-Radius Centrifuge Experience (Inna Vil-Villiams, Ph.D.)

- Russian experience with short- and long-arm centrifuges encompasses the past 20 years.
- Subjects tolerate large g-gradients no worse than small g-gradients.
- Short-arm centrifuges (SACs) have been used to examine human tolerance to gravity gradients. Subjects can tolerate a 2m radius, high gradient, SAC at 0.8 and 1.2 g, but not at 1.6 g. One subject, who also used a salt-loading protocol, experienced multiple dysrhythmias in the SAC at 1.6 g.
- SACs have been used to examine combinations of AG and other countermeasures. SAC use is recommended in conjunction with, but not instead of, other countermeasures.
- The combination of SAC and bicycle ergometer exercise was no better than SAC alone.
- After deconditioning induced by long-duration bed rest, 60-90 minutes/day of g_z at 0.6–1.2 g was an effective countermeasure.
- After deconditioning induced by 3 days of dry immersion, AG tolerance to 3 g_z was decreased. Use of combined salt loading and SAC at 0.8 g or 1.6 g helped prevent AG intolerance.
- SAC countermeasure prescriptions should be developed from the results of bedrest studies, and then validated during short-term space missions. The effects of SAC and standard countermeasures on g-tolerance of humans should be examined on crewmembers after return to Earth.

AG TARGET: EXPLORATION-CLASS MISSIONS

Mars Design Reference Mission (John B. Charles, Ph.D.)

- Key human health and performance aspects of a crewed mission to Mars are detailed in Appendix 4.

Engineering Considerations for AG (Lawrence G. Lemke, Ph.D.)

- Institutional interest in AG rises and falls concomitant with interest in Mars exploration, mainly because AG may solve all biological problems simultaneously.
- There are three different approaches to designing AG capacity into spacecraft:
 1. Continuous AG of about 1 g with a slow spin rate of 2 rpm or less, requiring a vehicle radius of 225m or greater. Although this approach will involve implementation tradeoffs between two- and three-body tethered or trussed vehicles, the complete von Braun-style torus is too voluminous to be a useful alternative. A tethered design developed at The Case for Mars Conference would allow a 150–770m separation of two identical vehicles.
 2. Continuous AG of about 1 g with a high spin rate, sufficient to stimulate the neurovestibular system. One such design was developed at the Role of Life Sciences in the Variable Gravity Research Facility workshop (NASA/ARC, March 27-30, 1988).
 3. Intermittent application of AG above 1 g with a very high spin rate. One such design, originally intended for Space Station Freedom, provided 1 g at 10 rpm for 4 hrs/day/occupant. As an attachment to the station, it would have housed two occupants and been accessible by experimenters during rotation.

TransHab Considerations (William C. Schneider, Ph.D.)

- A new, inflatable habitat module is being designed at JSC; the Shuttle could transport the module to orbit, where it would be inflated to a cylinder of 9m diameter and 9m long. Because it is under consideration as a habitation module for ISS, it could be outfitted with a 4 m radius human centrifuge designed (within limits) to our specifications.
- The current Mars Lander-TransHab AG design for a Mars mission would allow for a rotation radius of approximately 15-20m.
- A short-radius human centrifuge is being designed to fit within the Spacehab module for Shuttle experiments. It also houses a cycle ergometer, but is powered by a DC electric motor (designed by Chris Hansen). The subject rotates about the interaural axis and will experience 2 g at the feet.
- The workshop was counseled to submit a mandatory requirement now for AG on a Mars mission. Because these vehicle have not yet been designed, AG requirements are relatively inexpensive to consider and perhaps incorporate; if the vehicle designs proceed without consideration, then AG requirements will necessitate expensive augmentations. We must not postpone the formulation of such requirements because detailed physiological studies are incomplete. Instead, we should submit our best-guess requirements now and refine them later as appropriate.

NEAR-TERM AG RESEARCH VENUES

Station Accommodations—Human Research Facility (Suzanne M. Schneider, Ph.D.)

- Hardware and experiment plans for the ISS Human Research Facility are currently in development. Its first rack goes up early—March 2000—and does not provide any human-rated AG capacity.

Station Accommodations–Animal Centrifuge (Charles E. Wade, Ph.D.)

- Hardware and experiment plans for the ISS animal centrifuge are in development. Details are available in the NASA HEDS-02 NRA (http://peer1.idi.usra.edu/peer_review/nra/98_HEDS_02.html).

Ground-Based AG Research Facilities (David M. Warmflash, M.D.)

- Ground-based venues currently available for AG research are summarized in Appendix 3.

ARC Centrifuge Facilities (Emily M. Holton, Ph.D.)

- The workshop should not eliminate any of the current treadmills or other countermeasures under development in favor of AG.
- Ground-based venues currently available for AG research at Ames Research Center are summarized in Appendix 3.

APPENDIX 3: Artificial Gravity Ground Test Facilities (as presented by Dr. David Warmflash)**AMES RESEARCH CENTER (ARC)**

DEVICE	RADIUS (m)	MAXIMUM G LEVEL	MAXIMUM RPM	PASSENGERS	DURATION	DESIGNING SECTION	CONTACT
20 G CENTRIFUGE	8.9	20.0	47	humans & other animals	hours	n	Emily Holton cholton@mail.arc.nasa.gov
♂-CARRYING ROTATIONAL DEVICE (MCRD)	2.0 variable	4.5	48	humans, monkeys & rodents	weeks	n	
VESTIBULAR RESEARCH FACILITY	0.79	1.4	42	small monkeys & rodents		n	
24-FOOT DIAMETER CENTRIFUGE	3.7 variable	4.15	33	monkeys & rodents	months	n	
52-FOOT DIAMETER CENTRIFUGE (2 ROTATING ROOMS)	8.0	3.0	20	humans, monkeys & rodents	months	y	
8-FOOT DIAMETER CENTRIFUGE	1.25	10.0	89	rodents	months	n	

NASA KC-135 AIRCRAFT

DEVICE	RADIUS (m)	MAXIMUM G LEVEL	MAXIMUM RPM	PASSENGERS	DURATION	DESPINNING SECTION	CONTACT
KC-135	-	1-2		maximum 19-20 humans; pigs, rats, mice, pigeons, & fish have flown on other types of flights	4-5 minutes	n	John Yaniek (281) 244-9809

JOHNSON SPACE CENTER (JSC)

DEVICE	RADIUS (m)	MAXIMUM G LEVEL	MAXIMUM RPM	PASSENGERS	DURATION	DESPINNING SECTION	CONTACT
SHORT-ARM CENTRIFUGE	0.8	1.4	~33	1 human	hours	n	Bill Paloski wpaloski@ems.jsc.nasa.gov
ARTIFICIAL GRAVITY SIMULATOR (AGS)	~2.55	2.0?	~28	4 humans	hours	n	Edgar Benavides ebenavid@ems.jsc.nasa.gov

UNITED STATES AIR FORCE SCHOOL OF AEROSPACE MEDICINE
BROOKS AIR FORCE BASE

DEVICE	RADIUS (m)	MAXIMUM G LEVEL	MAXIMUM RPM	PASSENGERS	DURATION	DESPINNING SECTION	CONTACT
CENTRIFUGE GONDOLA	6.15	35	75	1-2 humans	hours	n	Lt. Col. James Dooley jdooley@alcf.brooks.af.mil
CENTRIFUGE EQUIPMENT/ EXPERIMENT FIXTURE	3.9	22	75	pigs, small primates, & other animals	days	n	

OTHER U.S. AIR FORCE CENTRIFUGES

DEVICE	RADIUS (m)	MAXIMUM G LEVEL	MAXIMUM RPM	PASSENGERS	DURATION	DESPINNING SECTION	CONTACT
AEROMEDICAL RESEARCH LABORATORY (WRIGHT-PATTERSON AIR FORCE BASE)	5.8 (6.3 for experiment at platform)	12-20	56	1-2 humans	hours	n	
HOLLIMAN AIR FORCE BASE	6.1	15	48	1-2 humans	hours	n	

NAVAL AEROMEDICAL RESEARCH LABORATORY - CORIOLIS ACCELERATION PLATFORM
PENSACOLA, FLORIDA

DEVICE	RADIUS (m)	MAXIMUM G LEVEL	MAXIMUM RPM	PASSENGERS	DURATION	DESPINNING SECTION	CONTACT
ROTATING ROOM	~3.0	12-32*	20-33	5-15 humans	chronic (several weeks)	n	A.H. Rupert arupert@namrl.navy.mil
TRACK PLATFORM	~6.8	7.45	33	humans or other animals	hours	n	Paul DiZio dizio@brandeis.edu

* Dependent on installation of kitchen, storage, and shower facilities.

CHRONIC ACCELERATION RESEARCH UNIT (CARU)
UNIVERSITY OF CALIFORNIA-DAVIS

DEVICE	RADIUS (m)	MAXIMUM G LEVEL	MAXIMUM RPM	PASSENGERS	DURATION	DESPINNING SECTION	CONTACT
I, II	3.0	~4.5	~40	animals, ranging from chickens to rhesus monkeys (10K)	chronic	n	Charles Fuller cafuller@ucdavis.edu

DEVICE	RADIUS (m)	MAXIMUM G LEVEL	MAXIMUM RPM	PASSENGERS	DURATION	DESPINNING SECTION	CONTACT
III MOST SIMILAR TO ISS CENTRIFUGE	1.3	~3.5-4.0	~55	animals as large as squirrel monkeys	chronic	n	
				animals as large as squirrel monkeys	short	n	
IV for profiles	~5	20.0	~62				

**JOHNSVILLE CENTRIFUGE AT NAVAL AIR WARFARE CENTER (not in operation due to funding constraints)
WARMINSTER, PENNSYLVANIA**

DEVICE	RADIUS (m)	MAXIMUM G LEVEL	MAXIMUM RPM	PASSENGERS	DURATION	DESPINNING SECTION	CONTACT
CENTRIFUGE	15.4	40	50	humans	hours*	n	Dave Bischoff dbischoff.wam@veda.com Dennis Keifer

* Studies have been conducted for up to 24 hours.

**ASHTON GRAYBIEL LABORATORY
BRANDEIS UNIVERSITY**

DEVICE	RADIUS (m)	MAXIMUM G LEVEL	MAXIMUM RPM	PASSENGERS	DURATION	DESPINNING SECTION	CONTACT
SLOW ROTATION ROOM	3.4	4+	35	1-5 humans & other animals	weekst	n	J. Lackner lackner@binah.cc.brandeis.edu
CENTRIFUGE	1.0	2.5	50	humans	short	n	Paul DiZio dizio@brandeis.edu

† If such long runs are desired, facilities for cooking, sleeping, and sanitation can be installed with additional funding.

OTHER NORTH AMERICAN ROTATORS

DEVICE	RADIUS (m)	MAXIMUM G LEVEL	MAXIMUM RPM	PASSENGERS	DURATION	DESPINNING SECTION	CONTACT
MIT SHORT-ARM ROTATOR	2.0	2.0	~31.0	1 human	10 hours	n	Larry Young lry@mit.edu
DEFENSE & CIVIL INSTITUTE OF ENVIRONMENTAL MEDICINE (TORONTO, ONTARIO)	6.1	15	48	1 human	hours	n	
MULTI-AXIS SHORT-ARM CENTRIFUGE (LEGACY HOLLADAY PARK MEDICAL CENTER, PORTLAND, OREGON)	≤0.65 variable or 1 if fixed	1*	58.3	1 human	1 hour†	n	Owen Black fob@lhs.org (503) 413-5353

* dependent upon seat orientation.

† dependent upon seat orientation and protocol.

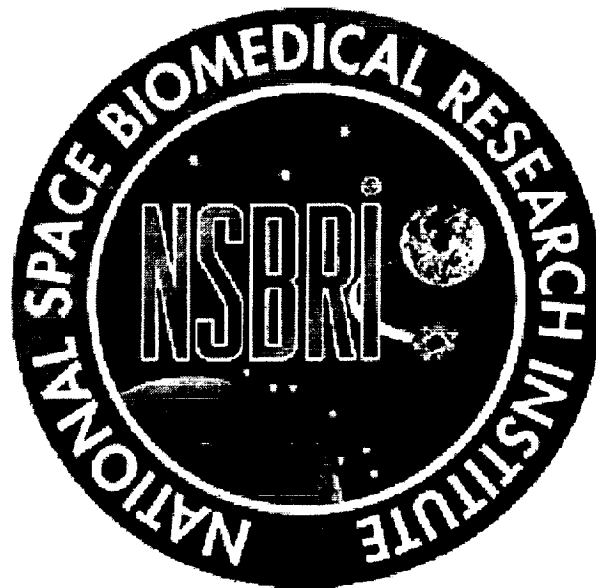
EUROPEAN UNION

DEVICE	RADIUS (m)	MAXIMUM G LEVEL	MAXIMUM RPM	PASSENGERS	DURATION	DESPINNING SECTION	CONTACT
RAF INSTITUTE OF AVIATION MEDICINE, (FARNBOROUGH, UK)	9.14	5-10	30	2 humans & other animals	hours	n	
LABORATOIRE DE MEDICINE AEROSPATIALE (BRETAGNE, FRANCE)	6	15-40	80	1-2 humans & other animals	hours	n	
TNO INSTITUTE FOR PERCEPTION (NETHERLANDS)	~6.8	7.45	33	humans or other animals	hours	n	Willem Bles bles@tm.tno.nl

**NATIONAL SPACE BIOMEDICAL RESEARCH
INSTITUTE**

Workshop Report

Gender-Related Issues in Space Flight Research and Health Care



**An Element of NSBRI Project 99-4 (Cooperative Agreement NCC 9-58):
Enabling a Broader Segment of the Population to Explore, Live and Work in
Space in the 21st Century**

Submitted to

**National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas**

September 30, 1999

Workshop Report

Gender-Related Issues in Space Flight Research and Health Care

A workshop on Gender-Related Issues in Space Flight Research and Health Care was convened on August 24 – 25, 1999 in Houston under the sponsorship of the National Space Biomedical Research Institute. Members of the workshop panel included: Rhea Seddon, M.D. (Chair, Vanderbilt University Medical Center), Kenneth Baldwin, Ph.D. (University of California, Irvine), Jennifer Hays, Ph.D. (Center for Women's Health, Baylor College of Medicine), Adrian LeBlanc, Ph.D. (Baylor College of Medicine), Ellen Baker, M.D. (Astronaut Office, Lyndon B. Johnson Space Center), Baruch Brody, Ph.D. (Center for Medical Ethics and Health Policy, Baylor College of Medicine), Richard Jennings, M.D. (The University of Texas Medical Branch at Galveston), Saralyn Mark, M.D. (U.S. Public Health Service's Office on Women's Health), Gerald Sonnenfeld, Ph.D. (Morehouse School of Medicine), Robert Weller, Ph.D. (National Institutes of Health, Center for Scientific Review).

The charge to the panel was as follows:

WORKSHOP CHARGE

This workshop is focussed on gender-related issues in space flight research and crew health care. Panelists will review the following, with an emphasis on gender-related issues: the knowledge base of human space flight; the status of current investigated or proposed medical countermeasures for maintaining crew health in flight and post-flight rehabilitation; and, existing and proposed human-machine interface standards and requirements, addressing aspects of training and space operations relevant to crew members health, well-being and safety.

The panel will develop a report with recommendations that address the following: the adequacy of existing demographic and epidemiological information; the areas which need further research; the best means to accelerate the research on the ground and in space to ensure health and maintain performance of space crews and to provide the best medical care to diverse space crews; specific additional measurements that should be included on upcoming missions; and, specific additional clinical or scientific measurements or data that should be included in the Integrated Test Regimen (ITR) under development.

Over the course of the two-day meeting the group was briefed by NASA scientists and managers on the relevant data, issues, policies and plans. A copy of the agenda is attached.

Women were first admitted to the Astronaut Corps in 1978. Thirty-two have flown as part of the US Space Program since 1983. They have served as subjects in all flight research programs. Study results have been published in numerous peer-reviewed scientific journals. It is NASA's goal to have research data archived in the Life Sciences Data Archive (LSDA) which is in development. Selected portions of all astronauts' medical data are part of the Longitudinal Study of Astronaut Health (LSAH). With over 20 years of data collection, a significant body of information has been collected. As the Space Program plans for longer duration stays in low Earth orbit and future exploration missions, a look at the existence and significance of any

possible gender differences and the need for future studies and policy changes is appropriate. This report will address issues and make recommendations in three areas: research and countermeasures, health care and the human-machine interface.

Research and Countermeasures

From the data presented to the group, there are a few areas that show definite measurable gender differences, such as post-flight orthostatic hypotension susceptibility. No spaceflight data exists but differences could be predicted for several systems (post-menopausal bone loss, iron intake requirements, muscle strength and endurance). In still other areas, spaceflight data has not been collected and prediction of gender differences is not possible but studying them is important for long term health, safety and performance (decompression sickness susceptibility, pharmacokinetics, immune function, radiation sensitivity, and psychosocial adaptation). Priority in research funding should be given to those areas where differences are apparent or predictable and in which differences are highly relevant for health and performance

Since few opportunities for extensive in-flight research will be available, the panel felt it important that ground based research be strengthened. Women should not be excluded from studies for reasons of cost or convenience. Only by including a sufficient number of women in all future protocols will it become clear whether gender differences exist. In those ground-based studies where there are trends indicating gender differences, the number of females should be increased to ensure findings achieve statistical significance. In a number of the areas of interest, good ground analogs to spaceflight (bed rest studies for example) exist and will give needed insight into female physiology.

Additionally, there should be improvements in the ability to retrieve data from both the LSAH and LSDA data bases. Researchers should be made aware that data exists and what the requirements are to access this important data. Prior to developing a plan for future studies, previously collected data should be reexamined in all disciplines for gender differences. The LSAH project should make sure that appropriate gender-specific parameters are being collected. NASA's partners on the International Space Station should be made aware of the gender-related issues and encouraged to collaborate in this research.

An extremely important reason for performing NASA life science research is to understand those changes that may adversely impact health and performance in-flight and upon return to earth so that appropriate countermeasures can be designed to prevent or partially counteract these changes. Research plans should be designed not only to identify problems but also to provide information specific enough to lead to the development of feasible countermeasures. Gender differences in physiology may lead to different approaches to ameliorating problems.

Health Care

Several areas of concern for female astronaut health care were identified. All women are accepted into the astronaut program during their childbearing years. Many of these women have postponed childbearing in order to establish themselves in their careers. The uncertainty in the Shuttle and International Space Station (ISS) manifests makes it difficult to plan pregnancies. Once assigned to a flight crew, a woman must not become pregnant if she wishes to fly with her crew. Delays in her flight will mean her attempts at pregnancy will be delayed, for months or perhaps years. Should a woman not yet assigned to a crew wish to try to become pregnant, she will be removed from consideration for assignment while attempting to conceive or until she

returns from maternity leave. If she has difficulty becoming pregnant, her career as a flight crewmember will be negatively impacted and NASA will lose a valuable asset for a time. For the well being of these women and to return them to flight crew status as quickly as possible, the provision of assisted reproductive technologies should be part of the medical care that is the responsibility of the Flight Medicine Clinic.

On the other hand, the prevention of pregnancy deserves special consideration. Individualized counseling regarding the best methods of birth control should always be available. The unknown risk to mother and fetus if conception occurs just prior to or in-flight should be stressed. No data exists on the pharmacodynamics of birth control pills in zero gravity and this should be studied to insure efficacy. This is also important data since these medications may also be used by flight crewmembers for noncontraceptive benefits including maintenance of bone density, reduction in the risk of ovarian cysts, ovarian cancer, anemia and benign breast disease and for the prevention of menstruation or controlling its timing.

Another issue that is not entirely a female problem may impact women's health and well being disproportionately. Career women are more likely to be in dual career families and, at least in the general population, women are more likely to be single parents. While a family support plan currently exists in the Astronaut Office, the capabilities and responsibilities of this office should be expanded, with inputs from the astronauts and their families. Additionally, the design of "family friendly" training schedules, travel responsibilities and deployment to remote sites should be taken seriously by the leadership of the Astronaut Office and the Johnson Space Center for the benefit of both genders. Astronauts assigned to long deployments away from home should receive support at the deployment site. Their families should be fully supported both psychologically and practically whether deployed or at home. Investments in the above programs can be expected to have positive effects on the retention of flight crews and on their willingness to volunteer for further flights.

Human-Machine Interface

The performance of a given task depends on the person performing the task, the design of the task and on the equipment provided. It should be the goal that all people selected to be astronauts be able to perform all tasks associated with the astronaut job regardless of size or gender. A study is underway at NASA to identify "gaps" in existing equipment and task design that prevent achieving this goal. The work group supports this approach. It also applauds the plan to better document anthropometric measurements of the Astronaut Corps. These stature and strength measures should be available in a reference document.

NASA should commit itself in the future to monitoring the development of all new equipment and assessing all new programs to assure that they are in keeping with the anthropometric measures in the reference document. It should not accept designs that restrict crew assignment to tasks, flights or vehicles or compromise safety. If individuals are selected to the Astronaut Corps based on NASA requirements, they should be assured that all aspects of the job are open to them. A space "glass ceiling" should not exist based on size or gender.

In particular, the EVA suits and Shuttle egress suits that will be used by all astronauts in the future should be carefully assessed for operability. Poor design in current suits or lack of appropriately sized off-the-shelf suits in the future should not be used as an excuse to exclude women from certain jobs or to provide them with equipment that is less than optimal for their

own performance. The feasibility of custom-designed suits should be evaluated if the “generic” suit design cannot be made to work.

Conclusion

In conclusion, there are a number of areas of research that that should focus on the study of female subjects, both on the ground and in flight. There are several health care issues unique to the female astronaut population that NASA must address. A firm commitment to equipment and task design to optimize job performance and safety is required. None of these recommendations require that all-female crews be flown. NASA is developing a strategic plan for prioritization of studies for the Space Station era. There should be a well thought out integrated research plan to systematically study these issues over the next several years. Countermeasures, training, task and equipment design and health care need not take a “one size fits all” approach. The capabilities and talents of both genders will be needed for the monumental task of exploring our universe in the next millenium.

National Space Biomedical Research Institute

Project Proposal

Tactical Planning and Integration, Part I

Project 99-5

Presented to:

Space and Life Sciences Directorate

NASA Johnson Space Center

By:

The National Space Biomedical Research Institute

Houston, Texas

July 9, 1999

**National Space Biomedical Research Institute
Tactical Planning and Integration, Part I**

1.0 Title

This project proposal is entitled "Tactical Planning and Integration, Part I." This proposal is a partial response to NASA's Request for Project Proposal (RPP) entitled "Tactical Planning and Integration," issued March 11, 1999. It includes initial plans and cost estimates in the following areas, each of which will be treated in turn in all of the proposal sections that follow:

- 1.1 Initiation of new Integrated Research Teams.**
This topic refers to items 2.1.1 and 2.3.1 in NASA's RPP.
- 1.2 Consortium Expansion.**
This topic refers to item 2.4.1 in NASA's RPP.
- 1.3 Growth of NSBRI Core Research Program.**
This topic refers to item 2.4.3 in NASA's RPP.
- 1.4 Space Asset Coordination.**
This topic refers to item 2.1.5 in NASA's RPP.

Other areas specified in NASA's RPP will be treated in a separate, but coordinated project proposal entitled "Tactical Planning and Integration, Part II." Examination of the interconnections among the various other areas contained within the RPP made it clear that the most effective approach for dealing with the substantial issues facing both the NSBRI and NASA would involve a major realignment of responsibility within our partnership. Such an action, though radical, would greatly enhance our joint ability to assure the safety and health of space flight crews. With this in mind, we will develop a new integrated approach to coordinating the various other areas in the RPP and include that response as Part II of our overall project proposal.

2.0 Goals and Objectives

- 2.1 Initiation of new Integrated Research Teams.**
The goal of this activity is to expand the core research program of the Institute to include those essential new research areas critical to the mission of the NSBRI, but outside the Institute's original capability to support. The objectives include instituting new teams in: Integrated Human Function; Neurobehavioral and Psychosocial Factors; Nutrition, Physical Fitness and Rapid Rehabilitation; and Smart Medical Care Systems.

2.2 Consortium Expansion.

This activity's goal is to expand the number of institutions in the NSBRI consortium from the present level to one more representative of the Institute's national mission. The objective is to accomplish this goal through a competitive process by the start of FY 2000.

2.3 Growth of NSBRI Core Research Program.

This activity is designed to develop new research programs in each of the eight current research areas for initiation in Year 4 of NSBRI, after completion of the original three-year program. Constraints are as follows:

- Program must be open to community and competitive – Research will be solicited through an NSBRI Announcement. Prior participation in the research team will not be sufficient to guarantee future selection.
- Level of Funding per Team will increase – All funding will be competitively awarded and research areas will not be kept at the same level. For planning purposes, it is assumed that approximately \$24 M will be available for award in FY 2001. The funding will include both ground and flight research (but will exclude flight hardware development). The division between ground and flight funding will be made on a case-by-case basis for each research area.
- New activities within each team – Each science discipline team should include at least one major task devoted to nutrition and the effects of diet on the system under study, one major task devoted to exercise and the effects of physical activity on the system under study, and one major task devoted to artificial gravity and its use as a countermeasure (if appropriate to the research area). Each team should also include a modeling component designed to actively interface with the new Integrated Human Function team.

2.4 Space Asset Coordination.

This activity is designed to enable the NSBRI to develop the capability to define, evaluate and coordinate the utilization of the various space-related assets available to the space biomedical research community. The ultimate objective of this activity is to develop the infrastructure to support an international tactical planning group focussed on the optimum utilization of available space resources to carry out biomedical research.

3.0 Background

3.1 Initiation of new Integrated Research Teams.

Although the NSBRI has made considerable progress in developing and implementing its research program with the current annual NASA funding level of approximately \$10 million, its research program and other activities are hampered by this limited support. In fact, the current level of funding is inconsistent with both the critical research needs of space biomedical research and the full scope of the Institute's responsibility. This was clear at the NSBRI's outset; in development of the initial research plan, the NSBRI devoted itself to eight of the most critical research areas and delayed research on other important issues. The result is that the current program has specific inadequacies because insufficient funds exist to pursue research in all of the research areas vital to

human exploration. No NSBRI activity is currently devoted to the psychosocial and behavioral aspects of long-duration space flight, or to the importance and effects of nutrition on the body's adaptation to space flight, or to the development of intelligent medical care systems appropriate to a remote mission. Because of funding limitations, only minimal attention is currently focussed on the multidisciplinary, integrative physiologic aspects of the research questions. These aspects are of paramount importance in the development of a strategy to deal effectively with the complex reactions of the whole body to space flight.

3.2 Consortium Expansion.

During 1998, it became clear that the NSBRI could fulfill NASA's vision of supporting human space exploration through focussed biomedical research by combining the basic research capabilities of leading academic research institutions with the operational capability of NASA and the applied research capability of industry. With this in mind, NASA and the Institute entered into serious discussions concerning the next logical steps that should be taken to realize the full potential that the NSBRI offered. A joint decision was made to develop an expansion plan that included an increase in the number of institutions within the NSBRI consortium.

3.3 Growth of NSBRI Core Research Program.

The initial core research program begun in FY 1998 involves 41 ground projects, with an average funding per project of approximately \$200,000 (Direct + Indirect Costs). This level of funding is inconsistent with both the critical research needs of space biomedical research and the full scope of the Institute's responsibility, a fact that has been clear since the NSBRI began. In development of the initial research plan, NSBRI devoted itself to eight of the most critical research areas involved in human space exploration and delayed research on other important issues, resulting in a research program that has specific inadequacies. Some of these inadequacies involve the lack of programmatic breadth, and others involve the lack of programmatic depth. Within each research area, current funding will support only four-to-five tasks. This small number of tasks cannot cover the full range of activity necessary to develop and test ideas for countermeasures designed to reduce the biomedical risks of exploration.

3.4 Space Asset Coordination.

The National Space Biomedical Research Institute (NSBRI) is a mission-driven research entity, dedicated and committed to sponsoring, integrating and promoting fundamental and applied advances in space biomedical research. The mission of the NSBRI is to lead a world-class, national effort in integrated, critical path space biomedical research that supports NASA's Human Exploration and Development of Space (HEDS) Strategic Plan by focusing on the enabling of safe, long-term human presence in, development of, and exploration of space. This is accomplished by:

- designing, implementing, and validating effective countermeasures to address the biological and environmental impediments to safe, long-term human space flight;
- defining the molecular, cellular, organ-level, integrated responses and mechanistic relationships that are responsible for these impediments, where such activity fosters the development of novel countermeasures;

- establishing biomedical support technologies to maximize human performance in space, to eliminate biomedical hazards or reduce them to an acceptable level, and to deliver quality medical care;
- transferring and disseminating the biomedical advances in knowledge and technology acquired through living and working in space to the benefit of mankind in space and on earth, including the treatment of patients suffering from gravity- and radiation-related conditions on earth; and
- ensuring open involvement in the Institute's activities by the scientific community, industry, and the public at large, and a robust exchange with NASA, particularly through Johnson Space Center.

The Institute began its life as a ground-based research organization, but it has reached the stage where the next logical step in the development of some of the countermeasures requires a vigorous space-flight program. The main space platform which will provide some of the resources required in the proper development and testing of countermeasures is the International Space Station (ISS). However, the current ISS approach to distributing and managing scarce resources appears to be fundamentally flawed, particularly in the arena of human subject research. The number of people that can be accommodated on the ISS at one time and the distribution of the crew across the international partners are likely to frustrate even the most optimistic scientist intending to carry out countermeasure development, testing and evaluation using human subjects.

For these reasons, a new approach is needed to deal effectively with this problem. That approach should forge a strong alliance among the international partners expecting to use the ISS for human subject research and should support the common goal of coordination of available space assets. Since future ISS human research is essential to the success of the Institute, the NSBRI intends to play a leadership role in the development of that alliance.

4.0 Approach

4.1 Initiation of new Integrated Research Teams.

During FY 1999, following four formal workshops with the scientific community to craft its language, a competitive research announcement will be released inviting proposals in each of the four new research areas. Near the end of the first quarter of FY 2000, proposals would be submitted by the scientific community in response to the research announcement. Later in FY 2000, following peer review, team leaders would be selected and funded in each of the four areas. Following a special meeting of prospective investigators, individual projects and investigators would be identified for selection. Selection and funding would begin in FY 2001.

4.2 Consortium Expansion.

The competitive process to select institutions to add to the consortium will consist of two phases. Phase I will involve a short application addressing the main points of the evaluation criteria, but without detail or back-up material. Phase I applicants will be evaluated on a qualified/not qualified basis. Those that are qualified will be invited to submit further details and back-up material for the Phase II competition. Phase II applicants will be invited to discuss their applications with the review panel in

Houston, using the reverse site visit model, with travel costs borne by the applicant institutions.

4.3 Growth of NSBRI Core Research Program.

The planned growth enables the number of tasks per research area to be expanded to the more appropriate average level of 12 to 15 instead of the current level of 4 to 5. With this growth, the tasks can be distributed appropriately over all four of the countermeasure development phases:

- Molecular Mechanism Phase with an expected payoff in five or more years;
- Systems Concept Testing Phase with an expected payoff in three to five years;
- Ground/Flight Model Testing of Countermeasure with an expected payoff in one to two years; and
- Space Flight Validation of Countermeasure.

The growth plan also allows the scope of research of the initial discipline teams to expand in significant ways. For example, the Human Performance team will be able to expand its program to include research focussed on the optimization of the relationship between humans and machines during long (Mars-type) exploration missions. The Technology Development team will be able to expand its activities to include the development of noninvasive and minimally invasive health-assessment hardware and on the design, development and use of virtual immersion tools. All teams will be able to include one or more projects focussing on the extremely important area of nutrition and the effects of diet on the functioning of each of the physiological systems within the body, and on the corresponding effects of exercise and artificial gravity.

Growth of the core research program will be accomplished in the following way. During the early part of FY 2000, workshops involving the current investigators and the academic community will be held in each of the original eight research areas of the Institute. These workshops will be designed to recommend the language that should be contained in a call for proposals from the scientific community. Near the beginning of the second quarter of FY 2000, the NSBRI will prepare and release that call. Following peer review of the proposals, a meeting of the eligible investigator groups will be held and a program plan will be developed in each area. In the last quarter of FY 2000, projects and investigators will be identified for selection. Selection and funding will take place in FY 2001.

4.4 Space Asset Coordination.

The following steps will be taken to develop the infrastructure to support the necessary space asset coordination. First, at the invitation of NASA, we will hire a small number of experienced space-flight engineers who are familiar with the issues and problems of implementing human subject research in space and assign them to a joint NSBRI-NASA team dealing with the current problems of human experiment implementation in space. Second, this team will inventory and evaluate the scarce resources from all of the international partners. Third, in parallel with this activity, the NSBRI will form an ISS/Shuttle Tactical Planning Group, with membership from the international partners interested in human subject research. Preliminary discussions indicate that the partners will support this activity. This Tactical Planning Group will be supported by an NSBRI Space

Planning Group led by the experienced space-flight engineers hired earlier. These two groups, working together, will develop coordinated plans for appropriate space asset coordination across international boundaries and will provide the ISS/Shuttle personnel with an optimum utilization plan for human subject experimentation in space.

5.0 Expected Results

5.1 Initiation of new Integrated Research Teams.

This activity should lead to four new Institute core research teams. Each team should consist of 12 to 15 projects.

5.2 Consortium Expansion.

The outcome of this activity should be a consortium base for the Institute of from 10 to 15 institutional members.

5.3 Growth of NSBRI Core Research Program.

It is expected that growth will be from about 40 tasks in FY 1999 and FY 2000 to about 120 tasks in FY 2001, a net growth of 80 tasks.

5.4 Space Asset Coordination.

This activity should lead to the formation of an ISS/Shuttle Tactical Planning Group, with participation of all the international space partners interested in human experimentation in space. This group will be supported by an NSBRI Space Planning Group, consisting of a core group of experienced space-flight engineers.

6.0 Schedule

6.1 Initiation of new Integrated Research Teams.

The following schedule is planned for the initiation of the new Integrated Research Teams:

- (a) June – July 1999: Workshops Held in each new area.
- (b) September 1999: Release of competitive Announcement.
- (c) December 1999: Proposal due date.
- (d) January 2000: Peer Review.
- (e) March 2000: Selection & Board approval of Team Leaders.
- (f) April 2000: Funding of Team Leaders' tasks.
- (g) June - July 2000: Prospective Investigators Meetings.
- (h) August 2000: Selection of Projects and Investigators
- (i) October 2000: Initiation of funding for new programs.

6.2 Consortium Expansion.

The following schedule is planned for the selection of additional members of the National Space Biomedical Research Institute consortium:

- (a) May 10, 1999: Institute Competitive Announcement Released.
- (b) July 2, 1999: Initial (Phase I) Proposal Due.
- (c) July 16, 1999: Selection Announcement for Phase II.
- (d) August 20, 1999: Final (Phase II) Proposal Due.

- (e) September 27, 1999: Selection Announcement.

6.3 Growth of NSBRI Core Research Program.

The following schedule is planned for the growth of the NSBRI Core Research Program:

- (a) October – December 1999: Workshops in each Research Area.
- (b) January 10 – 14, 2000: NSBRI Retreat: Final discussion of research solicitation.
- (c) February 2000: Release of Announcement.
- (d) May 2000: Proposal due date.
- (e) June – July 2000: Peer Review.
- (f) September 2000: Selection & Board approval of research program.
- (g) October 2000: Funding of program.

6.4 Space Asset Coordination.

The following schedule is planned for the development of a detailed plan for space asset coordination:

- (a) July - December 1999: Formation of NSBRI Space Planning Group.
- (b) September 1999: Introductory Discussions of Tactical Planning Group - Space Planning Group Concept with international space life sciences community.
- (c) April 2000: Formation of ISS/Shuttle Tactical Planning Group.
- (d) September 2000: Development of Detailed Plan for Space Asset Coordination.

7.0 Resources/Budget

	FY1999	FY2000
7.1 New Teams		
Salaries & Fringe – Management, Scientific Coordination, and additional Staff Support	\$100,000	\$200,000
Travel – National Announcement Preparation, Workshops & Organizational Meetings	\$120,000	\$180,000
Subcontracts – Peer Review and Initial Team Leader Awards	\$ --	\$800,000
Supplies & Services – Database System	\$ 8,000	\$ --
Indirect Cost	\$ 32,000	\$ 60,000
Subtotal	\$260,000	\$1,240,000
7.2 Consortium Expansion		
Salaries & Fringe – Management	\$ 30,000	\$ 60,000
Travel – Review Panel, Management Meetings with New Consortium Members, and Additional Travel for Board of Director and External Advisory Council Meetings.	\$ 30,000	\$ 63,000
Indirect Cost	\$ 9,000	\$ 17,000
Subtotal	\$ 69,000	\$140,000

	FY1999	FY2000
7.3 Research Core Growth		
Salaries & Fringe – Existing and Additional Scientific Management and Corresponding Staff Support	\$ 40,000	\$265,000
Travel – National Announcement Preparation Workshops & Organizational Meetings	\$ 60,000	\$380,000
Subcontracts – Peer Review	\$ --	\$400,000
Supplies & Services – Database System	\$ 18,000	\$ --
Indirect Cost	\$ 17,000	\$ 75,000
Subtotal	\$135,000	\$1,120,000
7.4 Space Asset Coordination		
Salaries & Fringe – Flight Engineers (6), and Staff Support	\$ 80,000	\$640,000
Supplies – Renovations, Furniture, and Computers	\$ 25,000	\$ 40,000
Indirect Cost	\$ 31,000	\$200,000
Subtotal	\$136,000	\$880,000
Grand Total	\$600,000	\$3,380,000