Sex, Space and Environmental Adaptation: A National Workshop on Research Priorities on Sex Differences in Human Responses to Challenging Environments

Sponsored by National Aeronautics and Space Administration and the National Center for Gender Physiology and Environmental Adaptation, University of Missouri

November 12-14, 2002
University of Missouri
Columbia, MO

QuickTime™ and a
Photo - JPEG decompressor
are needed to see this picture.

TABLE OF CONTENTS

Participants

Planning Committee

Meredith Hay, Ph.D., (co-chair), Director, National Center for Gender Physiology & Environmental Adaptation, University of Missouri-Columbia
Saralyn Mark, M.D., (co-chair), Senior Medical Advisor, NASA & U.S. Department of Health and Human Services, Office on Women's Health
Bette Siegel, Ph.D., (co-chair), Enterprise Scientist, NASA Headquarters

Ellen Baker, M.D., M.P.H., Astronaut and Medical Officer, NASA Johnson Space Center
Angela Bates, National Institutes of Health,Office on Research on Women's Health, U.S., Department of Health and Human Services
John B. Charles, Ph.D., Mission Scientist, STS-107, NASA Johnson Space Center
Susan Curley, Ph.D., OBPR Congressional Liaison, NASA Headquarters
Deborah Harm, Ph.D., Senior Scientist, NASA Johnson Space Center
Guy Fogleman, Ph.D., Acting Director Bioastronautics Research Division, NASA Headquarters
Charles Macri, M.D., Director, Division of Reproductive and Medical Genetics, Department of Obstetrics and Gynecology, Uniformed Services University of the Health Sciences
Sherry A. Marts, Ph.D., Scientific Director, Society for Women's Health Research, Washington, DC
Margaret Miller, Ph.D., Manager of Science Programs, Office of Women's Health, Food and Drug Administration, Rockville, MD
Louis Ostrach, Ph.D., Division of Fundamental Space Biology, NASA Headquarters
Marc Shepanek, Ph.D., Deputy Chief, Medicine of Extreme Environments, Office of the Chief Health and Medical Officer, NASA Headquarters
David L. Tomko, Ph.D., Enterprise Scientist, NASA Headquarters
Carol Van Hartesveldt, Ph.D., Associate Dean of Research, Florida State University College of Medicine, Tallahassee, FL (formerly representing National Science Foundation)
Susan Wood, Ph.D., Director, Office of Women's Health, Food and Drug Administration, Rockville, MD

Special Consultant to the University of Missouri

Joan Vernikos, Ph.D.

Workshop Participants

Group I

Bone Loss/Skeletal Muscle Atrophy

Saralyn Mark, M.D., (Steering Committee Contact), Senior Medical Advisor, NASA & U.S. Department of Health and Human Services, Office on Women's Health
Jay R. Shapiro, Ph.D., (co-chair), Director, Interdepartmental Center for Space Uniformed Services University of the Health Sciences, Bethesda, MD
Sherry Sherman, Ph.D., (co-chair), Director, Clinical Endocrinology and Osteoporosis Research, National Institute on Aging, Bethesda, MD
Susan Bloomfield, Ph.D., FACSM, Associate Professor, Dept. of Health & Kinesiology Texas A&M University, College Station, TX.
Marybeth Brown, Ph.D., Associate Professor of Physical Therapy, University of Missouri- Columbia,
Mary Anne Frey, Ph.D., Professor, Community Health, Wright State University School of Medicine, Dayton, OH
Lynn Gerber, M.D., Chief, Rehabilitation Medicine Department, Warren G. Magnuson Clinical Center National Institutes of Health, Bethesda, MD
Helen W. Lane, Ph.D., R.D., Chief Nutritionist, NASA Johnson Space Center

Adrian Leblanc, Ph.D., Director, Division of Life Sciences, Universities Space Research Association, Houston, TX
Keith Wear, Ph.D., Research Physicist, Food and Drug Administration, Rockville, MD

Group II
Cardiovascular Alterations
John B. Charles, Ph.D., (Steering Committee Contact), Mission Scientist, STS-107, NASA Johnson Space Center
Paula Johnson, MD, (co-chair), Executive Director, Connor's Center for Women's Health and Gender Biology, Brigham and Women's Hospital, Boston, MA
Janice Meck, Ph.D., (co-chair), Director, Cardiovascular Laboratories, NASA Johnson Space Center
Dominick D'Aunno, Ph.D., Assistant Professor, Baylor College of Medicine, National Space Biomedical Research Institute, Houston, TX
Eileen Hasser, Ph.D., Professor, Department of Biomedical Sciences, University of Missouri-Columbia
Virginia H. Huxley, Ph.D., Professor, Department of Physiology, University of Missouri-Columbia
Jane Reckelhoff, Ph.D., Professor, Department of Physiology and Biophysics, Univ. of Mississippi School of Medicine, Jackson, MS
Leona Rubin, Ph.D., Associate Professor, Department of Biomedical Sciences, University of Missouri-Columbia
Richard Summers, M.D., Associate Professor of Emergency Medicine, University of Mississippi, Jackson, MS
Mike Ziegler, Ph.D., Professor of Medicine, Director, General Clinical Research Center, University of California-San Diego

Group III
Immune Function
Bette Siegel, Ph.D., (Steering Committee Contact), Enterprise Scientist, NASA Headquarters
Denise Faustman, M.D. Ph.D., (co-chair), Associate Professor of Medicine Harvard Medical School, Charlestown, MA
Gerald Sonnenfeld, Ph.D., (co-chair), Department of Microbiology, Biochemistry & Immunology, Morehouse School of Medicine, Atlanta, GA
Margaret Conner, M.D., Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX
Craig Franklin, Ph.D., Department of Pathobiology, University of Missouri-Columbia
Michael **Lockshin**, M.D., Director of the Barbara Volker Center for Women, Professor of Medicine, New York, NY
Caroline Whitacre, Ph.D., Department of Immunology and Medical Genetics, The Ohio State University, Columbus, OH

Group IV
Neurovestibular/Neuroscience
Meredith Hay, Ph.D., (Steering Committee Contact), Director, National Center for Gender Physiology & Environmental Adaptation, University of Missouri-Columbia
F. Owen Black, M.D., (co-chair), Director, Neurotology Research, Legacy Holladay Park Medical Center, Portland, OR
Daniel Sklare, Ph.D., (co-chair), Program Administrator, Hearing and Balance
Vestibular Sciences Branch, Division of Human Communication, National Institute of Health/ National Institute on Deafness and Other Communication Disorders

Susan Herdman, Ph.D., P.T., FAPTA, Emory University School of Medicine
Dizziness and Balance Center, Department of Rehabilitation Medicine, Atlanta, GA
Sheri Jones, Ph.D. Associate Professor, Department of Surgery, University of Missouri-Columbia
Tim Jones, Ph.D. Professor, Dept. of Physiology, University of Missouri-Columbia
Kathleen S. Matt, Ph.D., Associate Director, Arizona Biomedical Institute,
Arizona State University, Tempe, AZ
Carol Van Hartesveldt, Ph.D., Associate Dean of Research, College of Medicine Florida State University, Tallahassee, FL

Group V
Reproductive Biology

Sherry A. Marts, Ph.D., (Steering Committee Contact), Scientific Director, Society for Women's Health Research, Washington, DC
Florence Haseltine, M.D., Ph.D., (co-chair), Director, Center for Population Research, National Institute of Child Health and Human Development, Rockville, MD
Richard Jennings, M.D., (co-chair), Director, Aviation Medicine Center University of Texas Medical Branch, Galveston, TX
Jean Fourcroy, MD, Ph.D., MPH, Assistant Professor, Uniformed Services University Health Sciences, Bethesda, MD
William Gibbons, M.D., Director, The Jones Institute for Reproductive Medicine
Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA
John Rock, M.D., Chancellor of the LSU Health Sciences Center, New Orleans, LA
Joseph Tash, Director, Cell Imaging Core of the Center for Reproductive Sciences, University of Kansas Medical Center, Kansas City, KS
Michelle P. Warren M.D., Director, Center for Menopause, Hormonal Disorders, and Women's Health, New York, NY.
Elizabeth Whelan, Ph.D., National Institute for Occupational Safety and Health, Cincinnati, OH
Steve Young, M.D., Associate Professor, Dept. of Ob/Gyn., University of Missouri-Columbia

Group VI
Human Behavior/ Performance

Marc Shepanek, Ph.D., (Steering Committee Contact), Deputy Chief, Medicine of Extreme Environments, Office of the Chief Health and Medical Officer, NASA Headquarters
Virginia Cain, Ph.D., (co-chair), Deputy Director, Office of Behavioral and Social Sciences Research, National Institute of Mental Health, Bethesda, MD
Edna Fiedler, Ph.D., (co-chair), Manager AAM-520, Selection, Training and Organizational Assessment Branch, Civil Aerospace Medical Institute, Federal Aviation Administration, Norman, OK
Ellen Baker, M.D., Ph.D., Astronaut and Medical Officer, NASA Johnson Space Center
Gloria Leon, Ph.D., Professor of Psychology, University of Minnesota, Minneapolis, MN
Des Lugg, MD, Chief of Medicine of Extreme Environments, NASA Headquarters
Carol Otis, MD, Physician, Director, Women's Sports Medicine, Kerlan Jobe Orthopaedic Clinic, Los Angeles, CA.
Larry Palinkas, M.D., Professor, Department of Family and Preventative Medicine, University of CA at San Diego
Naomi Rogers, Ph.D., Unit for Experimental Psychiatry, Division of Sleep and Chronobiology, University of Pennsylvania School of Medicine, Philadelphia, PA
Peter Suedfeld, Ph.D., Professor Emeritus of Psychology, University of British Columbia, Vancouver, BC

Keynote Speakers

Kathie Olsen, Ph.D., Associate Director, Office of Science and Technology Policy, Executive Office of the President, White House
Ellen Baker, M.D., M.P.H., Astronaut and Medical Officer, NASA Johnson Space Center
Des Lugg, M.D., Chief of Medicine of Extreme Environments, NASA Headquarters
Vivian Pinn, M.D., Associate Director for Research on Women's Health, Director of Office of Research on Women's Health, National Institute of Health
Carol Otis, M.D., Director, Women's Sports Medicine, Kerlan Jobe Orthopaedic Clinic, Los Angeles, CA

PREFACE

In April 2001, the Institute of Medicine published a landmark document entitled, "Exploring the Biological Contributions to Human Health, Does Sex Matter?" This report charted the current state of knowledge on the impact on sex and gender on health and disease outcomes in women and men. Additionally, it outlined opportunities for future research, which would explore how disease processes and health are often impacted by sex and gender. The message was clear, namely, that sex and gender do matter to our understanding of diseases related to nearly every major organ system.

With the dawn of the new millennium, the scientific community has completed a tremendous feat in the cloning of the human genome. With this wealth of information, however, there remains yet only limited understanding regarding how many of these genes may be differentially regulated in males and females. Understanding sex differences in gene regulation is critical to our ability to ultimately translate this information for the improvement of the health and quality of life for men and women everywhere.

The existing critical gaps in our basic understanding of sex differences in human health and disease create not only concerns regarding the status of our medical research and health care but also mark a more general social shortcoming in our nation. From the microcosm of space, sex-based differences also have a significant impact on our national mission of space exploration. Women now represent a significant percentage of National Aeronautics and Space Administration's (NASA's) astronaut corps and will play an important role in the International Space Station program, and in other space exploration activities this century, perhaps even missions to Mars. We currently have little, if any, data relating to long-term health, safety and performance of women in space.

Without a concentrated, integrated focus on the impact of sex on fundamental biology and biomedical science, our nation will remain unable to fulfill fundamental health care goals, maintain an efficient workforce, or meet the demands of harsh environments encountered in space exploration, military deployment or other specialized endeavors of our society.

The above issue provided the foundation for the workshop, the results of which are outlined in this report. The workshop arose out of a joint effort by the University of Missouri-Columbia and NASA and included scientists and clinicians from the NASA, National Institutes of Health (NIH), National Science Foundation (NSF), Food and Drug Administration (FDA) and other governmental agencies and the nation's top academic institutions. These institutions and individuals teamed together to explore pathways to answer the question of "Does Sex Matter?" as applied specifically to NASA's mission for extended human exploration of space and, more generally, our nation's efforts in challenging environments on earth. Ultimately, these endeavors will lead us to a better understanding of both women's and men's health in terrestrial environments.

This landmark workshop was held November 12-14, 2002 at the University of Missouri in Columbia, Missouri. This workshop report details the findings and recommendations for research priorities for sex based differences in six areas of biology, all of which are critical for the success of NASA's missions, success of human endeavors in challenging environments on earth, and success in improving men's and women's health.

Meredith Hay, Ph.D.
Director, National Center For Gender Physiology and Environmental Adaptation
University of Missouri-Columbia

ACKNOWLEDGMENTS

The Planning Committee would like to thank the efforts and dedication of all the workshop participants. The many pre-workshop conference calls, planning meetings and late night discussions during the workshop all contributed tremendously. The committee is especially grateful to the working group co-chairs who presented the informative "state-of-the-science" talks to the workshop participants and helped set the stage for this report.

The Planning Committee would like to offer a special thank you to each of the keynote speakers who gave presentations during the 2-day workshop. Special acknowledgement is given to: Dr. Kathie Olsen, Associate Director, Office of Science and Technology Policy, for her vision and commitment to this workshop and for her keynote presentation on the importance of sex based research to NASA's mission; Dr. Ellen Baker, Astronaut and Medical Officer at NASA for her insightful and informative talk on the role and contributions of women to the NASA astronaut program; Dr. Des Lugg, Chief of Medicine of Extreme Environments for NASA for his interesting and lively presentation on the importance of fundamental sex-based biomedical research to our understanding of survival and performance in harsh environments on earth; Dr. Vivian Pinn, Director of the Office of Research on Women's Health at the National Institutes of Health, for all of her efforts to support women's health and sex-based basic and clinical research and her thoughtful presentation to the workshop participants on the history and current status of women's health research; and Dr. Carol Otis, Women's Sports Medicine, Kerlan Jobe Orthopaedic Clinic, Los Angeles, CA for her inspirational talk about women in sports past and present.

The workshop and report were made possible by the generous support of NASA's Office of Biological and Physical Research and by the National Center for Gender Physiology and Environmental Adaptation at the University of Missouri. We would like to acknowledge that travel support was provided by the National Institute of Health Office of Research on Women's Health, National Institute of Child Health and Human Development, National Institute of Mental Health, National Institute on Aging, National Institute for Deafness and Communication Disorders, Food and Drug Administration, Federal Aviation Administration and the Society for the Advancement of Women's Health Research.

EXECUTIVE SUMMARY

Introduction

In order to certify that men and women can live in space, NASA needs to know the physiological changes that occur during space travel. NASA pioneered bedrest studies utilizing healthy humans. Thus far, flying men and women in space has not revealed gender response differences that cause major health concerns. However with longer duration stays in space, it is increasingly important for NASA to be armed with the knowledge needed to ensure the health and safety of all male and female astronauts.

The application of sex based similarities and differences in healthy people are not restricted to space. Nor are these differences inconsequential. Sex-based biomedicine is important to exposures and occupations as extreme as the Antarctic, high altitude, deep sea, and to communities as diverse as the military, international aid workers, emergency and rescue workers, the elderly and children.

The NIH Revitalization Act of 1993 began to address the issue of better understanding sex-based biomedicine by requiring the inclusion of women and minorities in clinical research studies and the analysis of similarities and differences. This Act set the foundation for future research initiatives. As identified in this workshop report, the scientific and medical community still needs the knowledge gained from fundamental basic research in sex differences in health and disease. To address this important need, this report recommends that models including human, animal and computer be used to analyze for sex-based differences in physiology.

With NASA's vision and the University of Missouri's leadership, this workshop capitalizes on the experience of nationally recognized scientists and clinicians. It takes the first step in defining what is required for policy and implementation, resources and infrastructure, and establishing research priorities to fully understand the impact of sex and gender on biomedical science and health.

Scope of the Workshop

The objective of this workshop was to define and report on the direction of research needed to increase our fundamental knowledge of gender and sex-specific factors that influence humankind's ability to adapt to challenging environments on Earth and in Space. This knowledge will be critical for the United States to meet fundamental health care goals, maintain an efficient work force, and meet the demands of harsh environments encountered in space exploration and challenging endeavors.

This workshop reviewed the current status of research on sex-based differences regarding fundamental biomedical questions relating to human adaptations to challenging environments and made recommendations regarding the research priorities in critical areas as well as the type of research infrastructure that is necessary to enable progress in these areas. Six working groups were formed from the nation's top scientists and clinicians from NASA, NIH, NSF and the nation's top academic institutions. These working groups evaluated research questions that are fundamental to the NASA's Bioastronautics Critical Path Roadmap (CPR). The CPR, developed by NASA, represents an opportunity to develop and implement an evolving program of research and technology designed to prevent or reduce risk to humans exposed to the space environment that may be applicable to other challenging environments.

The six work groups individually focused on issues in the musculoskeletal, cardiovascular, immunological, neurovestibular, reproductive and human behavior risk areas. Each work group was co-chaired by an individual representing NASA research and a scientist from another federal agency or academic institution. The members of each working group included clinical and basic science experts, aerospace medicine representatives/astronauts and representatives from other federal agencies and organizations. The 2 co-chairs of each risk area working group were invited to give a 20 minute talk on the status of sex-differences in a particular area of biomedical science and the responses of a given biological system to challenging space and earth environments. At the end of the workshop, each working group was responsible for ensuring that a brief, cogent report based on work group discussions was submitted and presented during the closing session of the workshop. Workshop participants were responsible for reviewing the current status of research in their selected work group area and to recommend research priorities and infrastructure needs.

Summary Recommendations

There were common recommendations that surfaced from the reports from the six working groups. These recommendations serve as the cornerstone of this report.

- Improve the understanding of the influence of sex on how biological systems adapt to challenging environments. The ability of humankind to successfully explore the far reaches of space and survive the challenging environments on earth will require a full understanding of human physiological responses to these challenges.

- Develop realistic models (human, animal, computer) for sex-based differences in fundamental physiology. The development of successful, sex specific countermeasures to environmental challenges will require the development of non-human animal and computer models in which the effect of sex and sex hormones can be specifically studied.

- Encourage complementary research in animal models and humans to ensure basic research can be translated towards understanding differences and similarities in male and female physiology and medicine.

- Explore mechanisms of sex differences in transgenic models and gene expression.

- Develop education and research training opportunities to nurture the future generation of scientists to think in terms of sex similarities and differences in their approaches to research and medical cases.

- Develop collaborative programs between NASA and other agencies to expand research opportunities in biology and medicine.

Resources and Infrastructure Needed to Fulfill Recommendations

The 6 working groups also developed a list of common resources and infrastructure needs in order for the prior recommendations to be implemented.

- Provide the appropriate resources, such as small space suits, which would enable female astronauts to participate on short and long duration space missions, including the International Space Station, in order for them to be able to serve as research subjects.
- Establish a databank and resource center for basic science and clinical observations and discoveries regarding sex based similarities and differences in biology.
- Create a tissue specimen bank on all astronauts (male and female) and all spaceflown animals, in order to maximize access to unique biological materials.
- Enable the development of shared national resources to facilitate access to animal models, tissue, data, etc. thus minimizing barriers and reducing costs to performing basic biomedical research in both sexes.
- Develop a multi-agency initiative to fund interdisciplinary/translational research relevant to sex differences in fundamental biological processes.
- Develop inter-institutional/shared Hormone and Drug Assay Core Laboratories. These shared facilities are necessary to give consistent results with all the hormone and drug assays.
- Develop and provide vivarium infrastructure for large animal models to study sex-based differences in biological systems.
- Develop analogs for space flight and challenging earth environments to facilitate study of sex- based differences in these conditions.

Working Group I Report

Current Status of the Research on Sex Based Differences and Adaptations to Challenging Environments in
MUSCULOSKELETAL PHYSIOLOGY

Osteoporosis is a progressive disease characterized by low bone density and deterioration of the microarchitecture of bone tissue, resulting in increased bone fragility and susceptibility to fracture. Osteoporosis and the consequences of compromised bone strength -- particularly vertebral and hip fractures – are a significant cause of frailty, increased morbidity and even mortality and hence are a serious public health problem in the elderly population. There are striking sex-based differences in bone strength and the risk of fractures. These differences, which favor the male skeleton, can be attributed to differences in patterns of bone accretion and age-related changes in skeletal geometry and rates of bone loss. Sarcopenia, a condition characterized by muscle wasting, weakness, and increased fatigability is common in older individuals on Earth, where it is due primarily to age-related decreases in muscle mass. Although data on sex-based differences in patterns of muscle mass across the lifespan are limited, age-related rates of loss of muscle mass in men appear to parallel those in women, whereas decrements in muscle strength appear to be greater in men.

Recent advances in cellular and molecular biology have provided insight into the regulation of bone formation and resorption and muscle synthesis and degradation. However, even with regard to terrestrial studies, the role of sex differences for these *in vitro* studies is limited and remains to be fully defined. The application of sex-based differences in age-related osteoporosis and muscle atrophy to the flight setting requires a comprehensive approach to understanding the impact of genetic, nutritional, hormonal and biomechanical factors in the setting of extended duration exposure to microgravity.

In spite of the participation of 37 American women in spaceflight, the database concerning bone adaptations is limited to pre- and post flight dual energy x-ray absorptiometry (DEXA) measurements after short duration (< 16-d) shuttle flights and for a very few women following long duration missions. Available DEXA data on women reveals site-specific changes in bone mineral density (BMD) following spaceflight similar to that seen in men, with loss of BMD observed primarily in the pelvis, the femoral neck and the lumbar spine. However, the limited database and high inter-individual variability do not permit meaningful comparisons with the rates of bone loss observed in male astronauts.

At this time we are not aware of published studies concerning the impact of flight on muscle function or muscle mass in women of adequate statistical power for comparison to the response in men. Magnetic resonance imaging (MRI) of the intrinsic lumbar muscles and calf muscles of 2 male and 2 female astronauts demonstrated significant decreases in muscle volume, particularly of the back muscles. Muscle biopsies from the lower limb have been obtained from at least 3 female astronauts, but data from these biopsies were pooled with those derived from male astronauts and hence were not analyzed for sex differences. The pooled data revealed significant loss of muscle mass and alterations in muscle biochemistry after only 11 days of spaceflight.

A limited number of bed rest studies have included women as subjects, but none with adequate numbers of male and female subjects to provide adequately powered statistical comparisons. A series of 17-week bed rest studies have included 5 women and 13 men, but no sex differences were noted in biochemical markers of bone formation and resorption, in calcium balance, nor in DEXA measures of BMD. The women were still experiencing menses at the end of the bed rest period. However, reproductive hormones were not measured to assess alterations in endocrine function. Interestingly, MRI and DEXA measures of muscle volume (intrinsic back muscles, calf, thigh) revealed greater % decreases in women than in men after this bed rest period. Earlier data suggest that following 120 days of bed rest there are no significant differences in muscle strength changes between the two sexes.

A small number of animal studies have reported changes in bone and muscle in female rats flown in space or subjected to the ground-based hindlimb suspension (HLS) model of microgravity. To our knowledge, only pregnant and ovariectomized (OVX) female rats have flown in space. Earlier ground-based studies examining the impact of long-term immobilization of one hindlimb and/or OVX in female rats clearly demonstrate an additive effect of unweighting and estrogen deficiency on cortical and cancellous bone. Separate studies have demonstrated greater muscle atrophy with unloading in OVX rats than in intact controls. Recent studies on adult retired breeder rats subjected to HLS reveal differential effects between males and females, with a greater loss of cancellous BMD in males. Other investigations on adult rats reveal very few differences in the bone response to HLS, so there is no consensus as of yet.

Some of these same changes in muscle are observed in men or women exposed to other unique environments such as high altitude, submarines, or over-winter stays in the Antarctic. We are unaware of reports of bone-related measures in these populations. These normal gravity environments should provide a reasonable minimum gravitational loading to preserve bone, but progressive muscle atrophy, should it occur, would likely impact on bone in the affected limbs. The mechanisms for muscle and bone loss in these situations are more likely to be related to impaired nutritional intake, inactivity, confinement, disrupted acid/base balance, alterations in hormonal status, or other factors unique to these environments.

Research Priorities in Sex Based Differences in
Adaptation to Challenging Environments in
MUSCULOSKELETAL PHYSIOLOGY

I. Increase knowledge regarding basic effects of spaceflight on women.

- ❖ Create a database of relevant bone and muscle parameters that have already been collected pre- and post-flight on past or current astronaut corps members, providing masking of individual identifiers.
- ❖ Create a tissue specimen bank on all astronauts (male and female) and all spaceflown animals; in order to maximize access to unique biological materials.
- ❖ Conduct comprehensive multi-modality (DEXA, quantitative computed tomography, quantitative ultrasound, and MRI) assessments of multiple bone sites (hip, spine, calcaneus, phalanges, radius, tibia, whole body) in astronauts immediately prior to and following space missions of one month or longer in duration. In addition, follow-up data should be acquired a year or so after return in order to monitor recovery.
- ❖ Investigate the impact of spaceflight on appetite and resulting nutritional intake, with sex-specific analyses.
- ❖ Determine whether nutrients important to muscle and bone metabolism (e.g., amino acids, calcium, Vitamin D) are absorbed normally in the gut during spaceflight, with sex-specific analyses.
- ❖ Evaluate impact of reduced caloric intake on bone and muscle responses to microgravity, with sex-specific analyses.
- ❖ Assess whether extravehicular activity results in eccentric-contraction-type muscle damage with sex-specific analyses.
- ❖ Evaluate impact of spaceflight on endocrine factors in women important to maintenance of muscle and bone: GH, IGF-I, estradiol, cortisol, 1,25-vitamin D, and PTH.
- ❖ Investigate the use estrogen and/or progestin supplementation for long duration spaceflight.
- ❖ Determine the efficacy of various physical training devices, electrical stimulation, and other rehabilitation strategies to be applied after prolonged spaceflight in maximizing recovery of muscle strength and BMD without increasing risk of injury.
- ❖ Explore sex differences in the time course of bone loss by comparisons of data from missions of varying durations.

2. Determine the nature of sex differences in the musculoskeletal response to bed rest and other disuse situations as well as the sex-specific efficacy of proposed countermeasures to be used as prevention before or during flight, or afterwards during rehabilitation.

- ❖ Design long-term bed rest studies (4-6 mo) with male and female subjects to explore potential sex differences with adequate statistical power. This may require multi-center trials. Maximize data collection from each set of subjects using inter-disciplinary teams to comprehensively study factors affecting muscle and bone to answer these questions:
  - ✓ Does altered blood flow or hydrostatic pressures contribute to bone and/or muscle changes during bed rest?
  - ✓ What are the neurogenic contributions to muscle changes with disuse?

- ✓ Are there sex-specific alterations in muscle metabolism with prolonged disuse? What is the impact of altered skeletal muscle function on cardiovascular disease (e.g. CAD) or metabolic disease such as insulin resistance/Type II diabetes?
- ✓ How much of the inter-individual variability in muscle and bone responses to disuse can be explained by studying gene expression profiles in the two tissues? This requires the acquisition of blood samples or, ideally, muscle and bone biopsies in order to apply the most current molecular technologies, including cDNA microarrays.
- ✓ Does muscle mass decrease more in women than men after bed rest and if so, why?
- ✓ What are the relative contributions of muscle wasting versus changes in growth factors, cytokines or other non-mechanical factors on the subsequent bone loss?
- ✓ Which specific strength and endurance training protocols applied during bed rest are effective in women minimizing changes in BMD, bone geometry, muscle mass, and muscle strength, endurance, and power generation?
- ✓ Are other countermeasures already tested on male subjects (e.g., pharmacological interventions) also safe and effective in women?
- ✓ What are the effects in men and women of these countermeasures on other important factors such as sleep patterns, psychological state, and endocrine changes?
- ✓ Define the efficacy of various physical training devices, electrical stimulation, and other rehabilitation strategies to be applied before and/or after prolonged bed rest as preventive or restorative measures.

- ❖ Determine whether a standard decrement in BMD or alteration in bone geometry increases fracture risk to the same or even greater degree in women as in men. This could be biomechanical studies as well as modeling of fracture risk.
- ❖ Determine if the pharmacodynamics and pharmacokinetics of commonly used agents, especially those likely to be used as countermeasures for bone or muscle loss, show sex-specific change with weightlessness.

3. Ground-based and flight experiments with appropriate animal models can provide important mechanistic data about sex differences in the musculoskeletal response to microgravity.

- ❖ When possible, use non-human primates to assess sex-specific effects of immobilization and disuse on muscle and bone parameters, and especially endocrine profiles. This would be the definitive animal model for answering whether estrogen deficiency and microgravity have additive or synergistic effects on bone loss.
- ❖ Define the impact of sex or hormonal differences on bone marrow osteoprogenitor cell function with *in vitro* cell culture studies and primary cultures of marrow cells from small rodents exposed to spaceflight or hindlimb suspension.
- ❖ The mouse HLS model should be more fully described in order to facilitate use of transgenic models to answer focused research questions about sex and gender differences.
- ❖ Can the inter-individual variability in muscle and bone responses to disuse be explained by studying disuse-induced changes in the gene expression profiles in the two tissues?

RESOURCES AND INFRASTRUCTURE

- ✓ The integrity of bone and skeletal muscle is essential to astronaut health and well being before and during flight and upon return to earth. A number of non-invasive and low-risk methods exist to measure important bone and muscle variables. An appropriate process should be developed to maximize collection of data from all humans who fly in space, consistent with the Institute of Medicine recommendations about Category I research (low risk and non-invasive measures directly related to astronaut safety and health). Standardization of methodologies in testing human subjects is especially critical if we are to learn from the relatively small numbers of women astronauts who fly in space.

- ✓ Tissue specimen banks should be developed for all animals and humans flown in space.

- ✓ Procedures must be developed to publicize and promote access by qualified investigators to these routinely collected biomedical data on the astronaut corps and to specimen bank materials, following established NASA guidelines for access to data. These procedures must be linked to appropriate camouflaging of individual data as far as is possible, and protection of individual privacy.

- ✓ Multi-center bed rest studies can be facilitated by providing access to established bed rest facilities and General Clinical Research Centers that can accommodate bed rest studies for qualified investigators.

- ✓ Improved food systems specific to women astronauts may be required, as judged necessary by (future) research findings of sex differences in appetite, taste sensation, or digestibility.

- ✓ Improved technology for monitoring of muscle and bone health in-flight is required. Develop miniaturization of devices for imaging bone and muscle, and analysis of whole blood samples, should be pursued. Calcaneal DEXA and quantitative ultrasound may be good candidates due to portability, size, weight, and high cancellous content of targeted site (over 90%). An on-board biochemical analysis system (e.g., mass spectrometry) for analyzing blood, urine, and saliva samples should be developed to provide real-time, in-flight data on sex and gender differences. Improvements in assays for biochemical markers of bone formation and resorption are required before these can be routinely used for in-flight monitoring of individuals. Potential challenges associated with monitoring biochemical markers in space include 1) difficulty of data collection in microgravity, 2) high biological (within-person) variability due to diurnal fluctuations, menstrual cycle, seasonal changes, and stress levels, and 3) the requirement for minimal processing.

CONCLUSIONS/RECOMMENDATIONS

1. The existing flight and bed rest data base on female astronauts and female bed rest subjects is quantitatively and qualitatively deficient --- studies with adequate numbers of female and male subjects will be required to determine if gender differences exist in muscle or bone responses to the weightless environment of space. A coordinated effort of Johnson Space Center researchers and flight surgeons with outside investigators will be essential to maximize the science return on

data collected on the small number of humans exposed to the space environment. Standardization of data collection is also essential.

2. Emphasis must be placed on operationally relevant research with countermeasures tested in controlled, prospective trials with adequate numbers of subjects.

4. Due to the high cost of human bed rest studies and non-human primate studies, there must be coordination across disciplines to maximize tissue sharing and data collection for these projects.

5. To maximally leverage potential research funding, we strongly encourage inter-agency cooperation in promoting and supporting relevant studies. These data are highly relevant to the missions of the NIH, the Department of Defense, the Department of Education (via its National Institute of Disability and Rehabilitation Research), and the Food and Drug Administration (FDA).

Working Group II Report

Current Status of the Research on Sex Based Differences and Adaptations to Challenging Environments in
CARDIOVASCULAR PHYSIOLOGY

The state of the field of sex specific physiological changes in cardiovascular function:
Orthostatic intolerance. There are sex-related differences in the occurrence of orthostatic intolerance (presyncope or near fainting during a stand or tilt test) before, and especially following space flight. Evidence exists in the scientific literature to support the hypothesis that women have less tolerance to upright posture or gravitational stress than men primarily because of a reduced ability to maintain venous return and cardiac output. Generally, women have lower blood pressure and peripheral vascular resistance and higher heart rates than men. Mechanisms responsible for sex differences in blood pressure control have not been elucidated. Women respond to cardiovascular stress with greater heart rate increases, whereas men respond primarily with greater increases in vascular resistance. In an examination of post-flight orthostatic intolerance, the presyncopal astronauts were found to have greater increases in heart rate, greater decrease in blood pressure, and less of an increase in peripheral resistance in response to the postflight stand test than their nonpresyncopal counterparts. One notion was that indirect vasodilatory effects of estrogen in premenopausal women may contribute to smaller vasoconstrictive responses in women compared with men during orthostatic stress. While data for long-duration spaceflight are very limited, six American astronauts (5 men) tested after 4-6 month flights aboard Mir had an 85% failure rate during the post flight tilt test. Thus, it appears that sex-related differences may be overridden by long duration flight. Specific mechanisms contributing to individual susceptibility are not well understood but they appear to be multifactorial. Postflight orthostatic hypotension is aggravated by the greater loss of plasma volume in females. Presyncopal astronauts are defined primarily by their smaller standing plasma norepinephrine levels and total peripheral resistance compared with orthostatic tolerant astronauts. It is likely that changes in vascular function as well as cardiac function contribute to the etiology of this complex response.

Ventricular dysrhythmia/cardiac functions. New data suggest that cardiac dysrhythmias may be of greater concern during long-duration than short-duration spaceflight. We know of no data from in-flight cardiovascular (Holter) monitoring of women on either shuttle or Mir missions. However, there have been several reports of ventricular dysrhythmias in men. In the general population, men in this age group have a greater risk of ventricular dysrhythmias than women. It would, therefore, be expected that in the astronaut population this would hold true as well. Controversy exists as to the changes in myocardial mass, cardiac remodeling, and function in adaptation to space flight of short duration. Little is known concerning the influence of long duration flights for either sex.

Microvascular Function and Local Vascular Control

Once blood is distributed into organs, local control mechanisms predominate: On the high-pressure side of the circulation blood flow distribution within organs is a function of arteriolar tone (involving vascular smooth muscle function and its interaction with endothelium). Evidence exists that estrogen modulates endothelial nitric oxide production, oxidant levels and smooth muscle ion channel expression and activity. Testosterone, surprisingly, can modulate many of the same smooth muscle ion channels confounding understanding of the role of sex hormones in vascular control. These problems are compounded by our inability to translate differences in cellular function to actual sex differences in vascular function.

On the lower pressure side, capillaries and venules are the site of gas, water and solute exchange to and from metabolizing tissue. Body fluid balance in the microvasculature is a function of the forces in the vascular and tissue spaces, exchange area, and the permeability of the wall separating blood from tissue. Starling's Law, the widely used model for volume flux relating these components, has ignored the contributions of interstitial composition and lymphatic. Recently, permeability has been shown to be a physiological variable influenced by sex and capillary pressure subject to regulation. In light of these findings regulation of fluid and solute flux is being revisited. Many of the agents that alter vascular smooth muscle tension and control blood flow into the exchange microvasculature, also alter lymphatic tone and microvascular permeability; the extent to which this occurs also appears to vary with sex. It is thus hypothesized that microvascular mechanisms may contribute to the sex-based reduction of plasma volume during post-flight orthostatic hypotension. While male and female mammals are in volume balance at the level of the microvasculature, the mechanisms of how that is achieved and how they adapt to changes in environment differs with sex. Further, little is known about exchange or blood flow distribution following changes in environment such as occurs on exposure to microgravity or return to 1 g.

Overarching Issues

There are issues addressing sex and gender-based research as it relates to the cardiovascular system in space and extreme environments that will facilitate the ability to move the research forward. These issues are outlined below.

- We require a better understanding of sex differences, across the life span, in normal cardiovascular physiology that may influence physiological adaptations in space and other challenging environments.
    - An important goal is to translate these findings into practice that would allow us to understand potential pre-disposing conditions and to use our knowledge to intervene to mitigate risk in people coping with these conditions.
- Realistic models (human, animal, computer) must be developed and tested for space and challenging environments.
    - All models should be tested under basal conditions and following selected stressors.
    - Utilization of these models, across the life span, should be encouraged.
- More emphasis needs to be placed on understanding the initial stimuli for physiological adaptations to microgravity and challenging environments.
- Better integration of cardiovascular data with data from other organ systems is essential.

- i.e. What is the impact of immune and inflammatory reactions on cardiac and cardiovascular function in males and females under normal and challenging environments?

- It is essential that data relevant to pharmacology and pharmacokinetics be collected under conditions of challenging environments.
- Molecular and cellular approaches must be incorporated at all levels of inquiry.

More specific recommendations regarding the cardiovascular system are outlined below.

Vascular control:

Vascular control addresses the mechanisms responsible for the distribution of blood flow, autoregulation within each organ, and regulation of regional and systemic blood pressure. The recommendations in the form of research questions are listed below.

- Are there sex differences in different vascular beds and how are these differences integrated into regulation of individual vascular beds and then ultimately into the whole organism?
  - i.e. what are the mechanisms resulting in lower peripheral vascular resistance in females relative to males?
- How do central and local changes in adaptation and recovery from microgravity interact? Is this interaction the basis for sex-based differences in peripheral vascular resistance?
- At which levels of the cardiovascular system do adaptation to challenging environments occur? What are the long- term consequences of acute and chronic adaptation?
  - Examine local and systemic vascular biology control mechanisms from sub-cellular to whole body level.

Reflex control:

Reflex control describes the mechanisms responsible for the maintenance of arterial blood pressure ultimately ensuring adequate cerebral and peripheral perfusion. Important research questions and recommendations are listed below.

- What are the differential stimuli that modulate reflex control of efferent systems in males and females and how do they respond and adapt to challenging environments?
  - It is important to understand the uncoupling of control of the adrenal, the renin-angiotensin system and vasopressin from the sympathetic nervous system as it occurs on return from space and/or as a consequence of hemorrhage.
- What are the CNS pathways that underlie control of the adrenal, vasopressin, and sympathetic nerve activity?
- What are the changes in the reflex systems in space and other challenging environments and how do these changes interact to alter vascular and cardiac function (from the cellular to tissue levels)?
- What are the consequences of altered reflex control in males and females?
  - Countermeasures or treatments must be developed to mitigate risks associated with challenging environments.

Fluid Balance:
Normal function requires appropriate distribution of fluids, proteins, and electrolytes amongst the body compartments. Outlined below are the important research questions to be addressed.

- ❖ What are the sex differences in hormonal, neural, and physical forces responsible for total body fluid regulation as it relates to changes in salt and water balance (intake and output)?
    - ▪ The sex differences in body fluid control in response and adaptation to challenging environments need to be examined.
- ❖ What are the sex differences in the microvascular barrier regulation of fluid balance between vascular (blood and lymphatic), interstitial, and cellular compartments?

Cardiac function:
The heart, including systolic and diastolic function and conduction of electrical activity through the heart are central to life. Important research questions are outlined below.

- ❖ What are the sex differences in cardiac function (systolic/diastolic) in response and adaptation to challenging environments?
- ❖ What are the mechanisms and relevance of sex differences in cardiac conduction and repolarization (such as congenital and acquired prolonged QT syndromes)?
- ❖ What is the impact of sex-specific adaptations to chronic changes in physical activity on cardiac and vascular function under basal conditions and in challenging environments?

<u>Resources and Infrastructure Needed:</u>
To achieve the research goals stated above, resources and infrastructure will be necessary.

- ✓ A priority is to establish understanding of normal physiological responses of females and males.
    - o We must improve the ability to perform cardiac monitoring (both sexes) during flight and exposure to challenging environments.
    - o We must encourage use of new nano-technology to gather information in flight.
- ✓ To achieve greater numbers of women in space, NASA must provide the resources to enable women to get into space and perform in ways that are equal to men.
- ✓ A person of authority, with an interest in sex differences, should be identified to shepherd the implementation of the recommendations of the panel.

- ✓ It is critical that a web-based data bank/resource be developed to allow access to data about astronauts and men and women in challenging environments as well as normative data.
- ✓ Resources must be allocated for the development of analogs for space flight and challenging environment so that research can move forward more quickly.
- ✓ Large animal models must be developed that more closely simulate the human condition.
- ✓ There is a need for better communication regarding important findings from research.
- ✓ Resources should be allocated to facilitate and encourage inter-institutional and interdisciplinary collaboration.
- ✓ Access to new models, data and tissue must be made available to those doing research in the field. These resources must become a national resource.

Conclusions and Recommendations

Cardiovascular system interacts with every other system of the body (i.e. vestibular system) and there will need to be an integration of cardiovascular research with other research.

Working Group III Report

Current Status of the Research on Sex Based Differences and Adaptations to Challenging Environments in
IMMUNE FUNCTION

The Institute of Medicine issued a report entitled, "Exploring the Biological Contributions to Human Health: Does Sex Matter?" in 2001, which reviewed the facets of health that are influenced by sex differences. The immune system was highlighted as a system that could be dramatically influenced by sex. The areas of immunity that were highlighted as potentially greatly influenced by sex were: 1) resistance to infectious diseases and immunization, 2) development of autoimmune diseases, and 3) development and resistance to cancer.

Results of models of space flight conditions studies and actual space flight studies have also indicated effects on immune function. Modeling studies have included isolation of humans, disruption of circadian rhythms of humans, chronic bedrest of humans, and antiorthostatic suspension of rodents. The results of these studies have included:

- involution of the thymus of rats
- no effect on antibody production of rats
- Interferon-□□production by rats and mice inhibited
- Interferon□ production by rats inhibited
- superoxide production by neutrophils and killing of phagocytosed bacteria by mice inhibited; no correlation with serum corticosterone levels
- no effects on neutrophil activity of rats
- rat cytokine production inhibited, but no effect on leukocyte subset distribution
- decreased resistance of mice to encephalomyocarditis virus D variant correlated with decreased interferon production
- enhanced production of mouse macrophage- derived cytokines
- enhanced resistance of mice to primary infection with *Listeria monocytogenes*, but decreased resistance to secondary infection
- decreased resistance of mice to *Klebsiella pneumoniae*
- alterations in cytokine production of humans
- no effects on immunization with ϕX-174

Space flight studies have provided results very similar to those observed utilizing models of space flight conditions. The results include:

- thymic hypoplasia induced in rats
- alterations in leukocyte blastogenesis in rats, humans and human cell tissue culture s
- inhibited interferon-□ production but normal interleukin-3 production by rats
- altered interferon-□□ production in humans and tissue cultures of humans and rodents
- altered leukocyte subset distribution in humans, rats and rhesus monkeys
- inhibited response of bone marrow cells to colony stimulating factors in rats and monkeys
- natural killer cell activity inhibited in humans and rats
- when rats were sacrificed on board the space shuttle, leukocyte blastogenesis and natural killer cell activity were inhibited
- no effect on immune parameters of offspring of pregnant rats flown in space
- no ability of interleukin-2 to reverse effects of space flight on the immune system, but changes in immune system induced by this flight were very limited so experiment difficult to interpret
- insulin growth factor treatment appears to reverse some effects of space flight in the immune system
- reactivation of herpesviruses in humans
- delayed-type hypersensitivity reactions of humans inhibited
- total serum antibody levels increased in humans after long-term flight, no effect on antibody levels after short-term flight
- alterations in populations of neutrophils, lymphocytes and macrophages in humans

These alterations in the immune system and resistance to infection have occurred after both-short term and long-term space flights. The modeling studies results parallel the results of actual space flight studies, suggesting that the models will have utility for future studies.

The changes in the immune function observed after space flight fall under the same broad categories of immune responses that are influenced by sex. There have been no studies carried out to date to determine the effects of sex on the immune system in space. Because of the overlap of immune responses affected by space flight and gender, this interaction should be a high priority for study in the future.

Research Priorities in Sex Based Differences in Adaptation to Challenging Environments in
IMMUNE FUNCTION

Recommended approaches to study sex influences function in immune in harsh environments include

- ✓ -Human and animal studies
- ✓ -Ground and space studies
- ✓ -Acute and longitudinal studies
- ✓ -Studies in whole organisms, cells, protein, DNA, mRNA
- ✓ -Descriptive studies

Infection Disease Research Priorities:

- ❖ Examine available databases for infectious disease prevalence in males and females.
- ❖ Investigate sex differences in vaccination challenge.
- ❖ Investigate sex differences in cytokine alteration.
- ❖ Investigate sex differences in cell-cell interactions.

Autoimmunity Research Priorities:

- ❖ Examine available databases for sex differences in autoimmune disease prevalence.
- ❖ Monitor male and female space travelers for autoimmunity.
- ❖ Investigate and develop baseline data on sex differences in autoimmunity, histocombatibility complex (HLA) genotypes.
- ❖ Investigate spontaneous autoimmune disease in male and female animal models.

Cancer Research Priorities:

- ❖ Examine available databases for sex differences in cancer prevalence.
- ❖ Investigate sex differences in spontaneous cancer models.
- ❖ Investigate sex differences in tumor challenge.

General Immunity Research Priorities:

- ❖ Investigate sex differences in route of immunization.
- ❖ Investigate sex differences in innate immunity.
- ❖ Investigate sex differences in types of irradiation.
- ❖ Investigate influence of chronic birth control administration
- ❖ Investigate sex differences in role of alternate portals of antigen entry in immune response

Resources and Infrastructure Needed

To allow studies of the effects of sex on the immune system in space to be completed, appropriate platforms must be provided. These should include fully equipping the International Space Station (ISS) to allow completion of animal studies, fully equipping laboratories on the International Space Station for immunological studies, and fully crewing the International Space Station to allow human and animal studies to be undertaken. Consideration should also be give to providing a free flying platform, which would facilitate space flight experiments on animals exposed to infectious agents and tumors that cannot otherwise be done on a human tended platform like the ISS.

Conclusions and Recommendations

Sex influences on the immune system in space is a crucial area for study to insure crew health and safety and to further knowledge on the effects of sex on the immune system. It is important to:

1) carry out tissue culture, animal and human experiments on the effects of sex on the immune system in space.
2) carry out epidemiological studies on available data and develop new data banks of epidemiological data on the effects of sex on the immune system in space,
3) provide fully equipped space platforms and laboratories to allow completion of the experiments.

Working Group IV Report

Current Status of the Research on Sex Based Differences and Adaptations to Challenging Environments in
NEUROVESTIBULAR/NEUROSCIENCE

There is a paucity of data regarding balance disorders and gender. Based on analysis of data from the 1994/1995 Disability Supplement to the National Health Interview Survey, women show a higher prevalence of these disorders than men do. Moreover, virtually nothing is known about vestibular- and extravestibular-mediated balance function in males versus females during adaptation to altered gravity. Most clinical laboratories report that women present with symptoms of imbalance and disequilibrium at a rate of approximately 2 to 1.

Neurovestibular plasticity following changes in the gravitational environment and accompanying compensation following injury to vestibular systems is widely appreciated. The precise mechanisms and locations of adaptive plasticity in response to altered gravitational environments are not known.

Deficiencies:
No standards for measurement of balance function in humans.
No standards for evaluating balance problems.

Research Priorities in Sex Based Differences in Adaptation to Challenging Environments in
NEUROVESTIBULAR/NEUROSCIENCE

The NASA Bioastronautics Critical Path Roadmap priorities (rev. 9/7/99) for neurovestibular adaptation are:

- Disorientation and inability to perform landing, egress, or other demanding physical tasks, especially during/after g-level changes
- Impaired neuromuscular coordination and/or strength
- Impaired cognitive and/or physical performance due to motion sickness symptoms or treatments especially during/after g-level changes
- Vestibular contribution to cardioregulatory dysfunction
- Possible chronic impairment of orientation or balance function due to microgravity or radiation

The following research goals address the above issues.

- Identify the neurotransmitters mediating vestibular function and central integration of sensory information in altered G. This should be the first step for establishing the complete basic neuroscience foundation for vestibular functions. Discover the connectivity, neurotransmitters and neuromodulators in the vestibular system and sensori-motor pathways critical for vestibular function and adaptation. Assess the effects of sex differences and sex hormones on the functions of these pathways.
- Understand the role of the hormonally mediated stressors on sensori-motor control systems and spatial cognition.
- Determine the role of the vestibular system in modulating cardiovascular and other central regulatory systems.
- Evaluate the nature of and importance of multi-modal interaction and integration throughout the neuraxis during adaptation to altered G and other challenging environments.
- Identify extra-vestibular compensatory strategies that may be used to adapt motor control functions to changing G forces and other challenging environments.
- Develop and extend the pre-flight adaptive training paradigms as preventive measures to minimize adverse effects of long-duration space flight.
- Develop risk and survival models for genetically determined auditory and vestibular disorders that express during midlife.
- Develop population studies of normal sex differences in balance function, including possible differential adaptive properties in the vestibulo-ocular and vestibulo-spinal systems. These studies should evaluate the relative contributions of the semicircular canal and otolith systems.
- Evaluate the application of successful treatment modalities used for patients with vestibular deficits. Develop methods for countering/correcting changes induced by gravitational challenges **(**e.g. vestibular prosthesis, vestibular rehabilitation techniques**)**.

Resources and Infrastructure:
Develop and implement uniform vestibular assessment and data collection protocols. Additionally, bioinformatics tools should be developed for uniform data analysis across major research centers serving the aerospace community (e.g. Naval Air Mediterranean Repair Activity /U.S. Navy; JSC/NASA; Department of Defense Spatial Disorientation Center, San Diego).

Develop a multi-agency initiative to fund interdisciplinary/translational research relevant to sex difference**s** in vestibular mediated adaptive control function(s).

Conclusion and Recommendations:
Vestibular maladaptation produces human performance changes that are potentially life threatening in challenging environments as outlined in the Bioastronautics Critical Path Roadmap. Hence the importance of solving these problems cannot be overstated. However, there is little or no information regarding sex and gender effects on neurovestibular functions even in terrestrial environments. This fact underscores the importance of both basic and translational research toward delivering risk mitigation strategies

Working Group V Report

Current Status of the Research on Sex Based Differences and Adaptations to Challenging Environments in
REPRODUCTIVE BIOLOGY

Current Status of Research: There is very little extant human data on sex-based differences in reproductive biology relevant to spaceflight, although minimal animal research has been done. There is, however, a previous technical report regarding priorities for reproductive biology research in space generated by an expert panel convened by NASA 25 years ago. A copy of the recommendations from this panel is included with the report. In addition, a white paper should be generated by NASA that summarizes and reviews previous space-based and extreme environment research on reproductive biology. This review should include technical reports that are not generally available to the research community.

Research Priorities in Sex Based Differences in Adaptation to Challenging Environments in
REPRODUCTIVE BIOLOGY

The committee recognizes that multiple factors in spaceflight may affect reproductive health. These include microgravity, radiation, sleep disruption, stress, nutritional factors, and environmental toxins. A particularly worrisome factor is space-based radiation on human gonadal function. These exposures may differentially affect males and females. While reproductive constraints are not listed as a priority in the Bioastronautics Critical Path document, problems that affect reproduction are shared with many of the problems (such as osteoporosis and radiation) identified in the Critical Path. Additional reproductive problems of spaceflight include the need for evaluating hormonal therapies, difficulties with urinary voiding, changes in body composition, and differences in reproductive immunology, all of which require further investigation. Detailed priorities in order of priority follow:

Considering the unknown effects of spaceflight (especially cosmic, solar, and trapped radiation) on long term germ cell viability and reproductive function, we suggest the following:

- ❖ Collect longitudinal reproductive data on all long-duration crewmembers to include
    - o Screening for reproductive male factor and female factor health outcomes such as inability to conceive, miscarriage, preterm labor, menstrual disorders (including

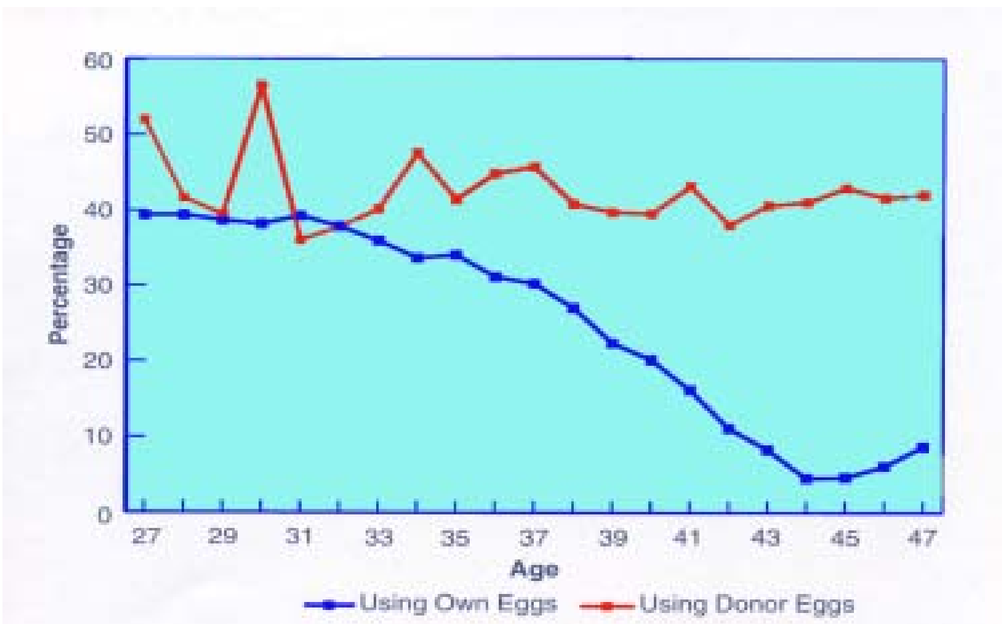
endometriosis), and characteristics of offspring such as birth weight, altered sex ratio, learning and behavioral abnormalities, birth defects, and cancer. The current longitudinal study of astronaut health provides an efficient means to study these outcomes and could easily be augmented to incorporate collection of new data.

- Obtain baseline (twice, 3 weeks apart) and post-flight semen analysis in males exposed to long-duration missions secondary to the concern of genetic damage and gonadal failure. Given the 70-day turn-around cycle of spermatogenesis in humans, semen samples should also be collected within 48 hours of landing. This will determine changes in spermatogenesis and DNA damage resulting during spaceflight or extended exposure in respective hostile environment. Another sample should then be collected in 3 months, 6 months after return to assess changes due to the stress of return and recovery of spermatogenesis. Given within patient variability, each of the 48 hour, 3 months, and 6 month samples should be repeated 3 weeks later for reliability of the assessment. DNA fragmentation analysis should be included in the study protocol. The spermatogonia are especially sensitive to radiation, and this information can be helpful for preflight informed consent, improving gonadal shielding, and possibly help in decision-making regarding prophylactic gamete storage prior to flight.

- Measure gonadal function in males and females that are exposed to long-duration flight with annual hormonal assessment including but not limited to gonadotropin (FSH, LH), sex steroids (testosterone and estrogens), gonadal peptides/proteins (inhibin/AMH). Given the age of the male astronauts when they are likely to spend extended time in spaceflight, testosterone should be measured as total and free, with determinations of sex hormone binding globulin (SHBG) as well. Preflight, in-flight, and post-flight salivary measurements of hormones are also indicated. These studies are to be accomplished to evaluate general reproductive function including concerns of premature ovarian failure in women and gonadal injury in men.

- Offer preflight gamete/embryo storage or ovarian tissue storage for all astronauts because of the unknown effects of particulate radiation on gamete genetics and function. This may also be an advantage for older female astronauts that delay pregnancy for flight assignments that occur during their period of rapidly declining age-related fertility (see graph). Furthermore, current technology for gamete/tissue cryopreservation and in vitro maturization of oocytes need to be optimized.

❖ Live Births per Transfer for Fresh Embryos from Own and Donor Eggs by Age of Recipient, Total USA 1998



❖ Since evaluation of gonadal function is currently difficult, land-based basic research on gonadotropin independent markers of oocyte, granulosal, and testicular cell mass is warranted.

❖ As reproductive research on humans in space is limited by the number of astronauts, as well as confounding factors, it is necessary to perform multigenerational reproductive studies on primates to include mating, hormonal studies, pregnancy, delivery, and evaluation of reproductive outcomes. These studies would most reliably be done on the International Space Station, where all the environmental factors would be space-based and allow for assessment of reproductive risks on expedition-class missions. However, evaluation of the effect of individual factors such as particulate radiation could be accomplished at Earth-based national labs such as Brookhaven.

- ❖ Follow progress and support analysis of data from the National Institute for Occupational Safety and Health (NIOSH) studies of reproductive health among female flight attendants. This analog environment shares some environmental concerns with spaceflight including radiation exposure, circadian shifting, and sleep disruption. Similar studies should be done on male flight attendants and pilots.

- ❖ Considering the potential future need for contraception and the current desire for menstrual suppression in female astronauts as well as the potential need for hormonal treatment of other disorders in flight (e.g. menorrhagia or menopausal symptoms) research should be accomplished on the pharmacokinetics and tissue response to estrogenic and progestational agents. Research should include oral, vaginal, and transdermal preparations. In addition, basic, land-based research on the optimum regimen to maintain amenorrhea is required.

- ❖ Since urinary retention is a recurring problem for both men and women in spaceflight, mechanisms of urinary retention, overflow incontinence, and voiding function are required. This has been a neglected area of spaceflight medical research that needs addressed.

- ❖ Since major body composition changes occur in spaceflight, and these may have major effects on the reproductive function mechanisms that remain poorly defined, land-based studies are required to identify the effects of the required exercise prescription and on-orbit nutrition and how these factors interact with the hypothalamic-pituitary-gonadal axis.

- ❖ The anatomical and hormonal differences between the sexes suggest a strong need for study of male and female-specific organ-based immune function.

- ❖ NF-kB signaling is integral to apoptosis and cytokine production and is directly regulated (by modulating Nf_kB + IKB) by estradiol and progesterone. This cuts across many areas including gonadal failure, osteoporosis, and immunity.

Resources and Infrastructure:

- ✓ Hormone and Drug Assay Core Laboratory is necessary to give consistent results with all the hormone and drug assays. Support may need to be increased to the current laboratory program
- ✓ Primate facility on the International Space Station to enable the necessary primate studies. Should this be impossible, further ground-based studies in primates should be supported at the appropriate national laboratories.
- ✓ Gamete storage protocol and facility
- ✓ Appropriate federal funding to specifically address the described research priorities

Conclusion:

The reproductive group determined that reproductive biology studies interface well and are integral to other studies in the Critical Path, especially those involving shared stressors such as sleep, circadian shifting, radiation, immunology, and adrenal function. These areas of overlap underline the great importance of interdisciplinary research. There may well be specific cell regulatory and signaling pathways that are common to various physiologic systems that are altered in microgravity or other hostile environments. Interdisciplinary approaches to identify and characterize these pathways may reveal common countermeasure approaches to multiple health risks.

In addition, research priorities in reproductive biology set forth in a NASA document 25 years ago remain important and largely unexplored. Now that long-duration spaceflight has arrived and planning for exploration-class missions is underway, it would not be prudent to delay these investigations further. The reproductive panel believe that the resources necessary to accomplish the priorities delineated in this document will provide the means to protect the health of the astronauts and their progeny and provide the scientific basis for improving the reproductive health of those remaining on planet Earth.

Working Group VI Report

Current Status of the Research on Sex Based Differences and Adaptations to Challenging Environments in
HUMAN BEHAVIOR AND PERFORMANCE

Poor Psychosocial Adaptation—Space Flight

NASA Select-In. Current NASA practice and research on select-in criteria is based on a completed task analysis using Russian and U.S. astronauts. So far, researchers have found nonsignificant gender differences in the 10 factors important for long duration. Validation of select-in factors for both men and women has not been validated.

NASA Training. NASA has focused on extensive experiential training to facilitate communication and understanding among mixed gender and culture teams, but there has been no evaluation of training. NASA sponsored confinement studies have found no significant gender differences. In general, mixed gender groups run smoother than only female or only male. The ESA sponsored confinement study found that the one woman in the group acted as "peacemaker" and was not actively involved in various male team members' conflicts. There is one reported ISS simulation with male sexual misconduct toward a female of another country. It worth noting that in addition to the individual misconduct, there was protest to the manner in which the involved agency administration dealt with the issue.

During and after an in-orbit mission. Wood found no gender performance differences in short term missions. Currently, there is no published research protocol on gender differences, although there have been at least 37 women on shuttle flights. Currently, NASA provides astronaut and family support. Ongoing preventive measures include methods for the astronaut to stay connected with the family (teleconferences and videoconferences), meeting individual astronaut's recreational interests (recreational computer software, musical instruments, DVD movies, etc.), and communication links for spouses to communicate with the NASA family support office. Research into the effectiveness of the support system has not been done, so there is no research on the sex-based differences in responsiveness to this service.

Psychosocial Adaptation – Challenging Earth Environments

Select-In Selection. The terms of ability, stability, and compatibility in discussing the successful selection of teams for challenging environments. People working in harsh conditions need to be able to do the tasks required, be emotionally stable and compatible with other team members.

Unfortunately, there is a lack of published research investigating whether there are significant gender differences in those men and women choosing to apply to work in challenging environments. Another study examined personality factors for men who overwintered in Antarctica, but no women were included.

During and post mission. Researchers concluded from their polar research with all women and mixed gender sojourns that women's groups were more likely to assume a cooperative orientation, conclusions compatible with earlier findings that men's groups are more competitive. Salutogenic or positive psychology research shows that team performance and individual growth are frequent aspects of working in the challenging polar environment, effects that continue post mission. However published research does not include analysis of sex differences. It has been noted that individual reactivity, interpersonal relations, and temporal factors are three categories of psychosocial stress that could detrimentally affect adaptation. Antarctica experiences indicate that mixed gender work teams are successful, but sexual jealousy and competition can occur. Other important variables for isolated confined environments include leadership style, but again, gender differences have not been studied.

Neurobehavioral Dysfunction -- Space Flight

Select-out. NASA currently selects out serious neurobehavioral dysfunction during the initial applicant selection process. The efficacy of this program has not been determined because no validation study has been completed at this time.

Training and In Orbit. After selection, an astronaut's effective neurobehavioral functioning will be affected by a number of factors, such as EVA, toxins, trauma, or individual adaptation difficulties in a confined operational setting. It is also possible for selected astronaut candidates to develop a maladaptive disorder that has a later age of onset such as depression, bipolar, obsessive compulsive disorder and somatoform syndromes. Gender differences in these disorders in the general population have been reported, but such differences in the astronaut corps have not been published. Re-adaptation difficulties post-deployment also need to be considered. Although, there have been reports of astronaut neurobehavioral dysfunction, no gender differences have been reported.

Neurobehavioral Dysfunction – Challenging Earth Environments

Although specific sex-based select out data is not available, a ranking of medical events or complaints compiled from over 20 years of analog data places mental disorders as number 5 in a list of 14 medical events, with number 1 being the prime problem. One report indicates that about 5% of people have had serious adaptation symptoms in polar expeditions, while Lugg shows that mental disorders accounted for about 2.3% of all medical cases for a 10-year period from 1988 to 1997. Submarines are a confined and isolated earth environment. Although there are fewer cases of neuropsychiatric illness in submarines that in the general population, submarines have more of such cases than in the surface fleet. Regardless of reported figures, one can speculate that the actual numbers of short-term adaptation problems are under reported because of adverse career consequences or lack of awareness by medical officers or supervisors. Whether there are gender differences in under reporting is not known.

Human System Interface Problems and Ineffective Habitat, Equipment Design, Workload, or Inflight Information and Training Systems

Space human factors engineering has traditionally focused on the interaction of individuals with physical systems. The machines were designed to be an extension of a person's physical functions so the features were designed around the perceptual-motor skills of the operator. Obviously, the sex differences in size and strength have implications for the design of those systems. Increasingly, the machines are used to extend the cognitive capabilities of the operator and so the focus needs to be on the human's role in monitoring and supervising the equipment. The sex differences in this activity are less obvious but should be considered.

The reports from space flight have identified many areas that need to be addressed for optimal functioning. Within the physical environment, noise, in addition to being an obstacle for sound sleep, contributes to difficulties in maintaining concentration. Additionally, crewmembers report unconsciously listening for changes in the sounds as an indicator for mechanical failures. If loud enough, it can also make communication difficult. Another constant in space travel is micro gravity which can result in an unsanitary environment. Any spilled food or drops of beverages or bodily fluids float until captured and put into a container. Additionally, the redistribution of fluids within the body can change the appearance of the face, making facial cues, important for communication, difficult to interpret. Personal space is generally insufficient and privacy severely lacking. A private sleeping space can improve sleep for crewmembers. Size of equipment, especially space suits, can be a major issue for people at either extreme of the size distribution. This has the greatest impact on small women or large men. Waste collection systems need to be easily used by both men and women. Research on male and female aircrew indicate that women, and some men, have used dehydration and fasting to cope with inadequate aircraft waste collections systems, clearly not an appropriate coping strategy for long-duration space flight. For the most part, there is little information on gender differences in response to the physical environment.

Workload. The amount and schedule of work activities can have a major impact on performance of the tasks. Previously space flights have information about when astronauts are best able to take on physically and cognitively challenging tasks.

Entry into space. During the first several days of a mission, crewmembers are responding physiologically to weightlessness, including motion sickness and redistribution of body fluids. They are also experiencing disturbances of their circadian cycles and sleep patterns are most disturbed. During this time, when, optimally, work requirements would be curtailed, the demands of the job require an intensive workload. Additionally, the euphoria experienced at the beginning of a mission may lead to the astronauts overloading themselves with work. During this time, a schedule can be important to maintaining optimal functioning.

Mid-mission. Many accommodations to microgravity and the experience of space flight occur within the first few days with continuing acclimation during the first two to four weeks. During this time, work-rest cycles should be chosen to assure that constant work efficiency and endurance of astronauts. Extra demanding tasks, such as EVA, should be avoided during periods of reduced work efficiency. Scheduling needs to be a joint activity of both the astronauts and ground control.

Irregular events. There are a variety of irregular events that disrupt optimal work-rest cycles. When any type of system repair is required, the task is usually completed during the astronauts scheduled rest time. Schedules on the space station must be adjusted to incoming shuttle flights.

Reentry. Astronauts' workload again increases in preparation for reentry. Their work schedules must again be adjusted to accommodate the demands of the job.

Inflight monitoring. There are several approaches to monitoring performance that have been proposed and used. Russian support teams have relied on the analysis of psychophysiological variables, mainly speech characteristics, to detect changes in performance of crews. In contrast, western experience with inflight monitoring is limited, but feasibility studies have used cognitive and psychomotor tasks to detect deterioration of performance as well as indicators of stress overload. Long duration space flight will require more use of self-monitoring of both stress and performance.

While few studies that have examined what the effect of gender is on workload issues, there is some evidence that women feel that they had to work harder than men.

Sleep and Circadian Rhythm Problems

Research has shown that sleep deficits can erode many components necessary for successfully accomplishing the many demands of contemporary space flight. These include decreased psychological vigilance, decreased cognitive speed and accuracy, deficits in working memory, deficits in complex problem solving, reduced learning, slower reaction time, decreased alertness, and mood disturbances.

Many factors can affect the sleep patterns of astronauts. Physical factors include spacecraft noise and vibration, noise during dual shifts, uncomfortable sleeping compartments, temperature, light-dark cycles and weightlessness. In addition to the physical environment, the demands of the job affect the opportunities for restful sleep. The amount of work required on a mission, the schedule required to meet exogenous demands and the occurrence of emergency or unusual activities generally result in reduced opportunities for rest. Several psychological factors contributing to sleep disruptions in astronauts include excitement, stress, monotony and experiences of borderline depression. However, hypnotics are the most commonly used during missions as a countermeasure to sleep disturbances.

While there have been many women who have flown on the space shuttles, there were no sex differences analyzed in the space flight literature. Research on earth environments provides examples of gender differences in sleep. In general, the sleep patterns are similar in young men and women although women express more feelings of insufficient sleep. Many years of space flight data have produced results that have well documented the disturbances that astronauts experience during missions. These include reduced sleep duration, longer sleep latency, more frequent awakenings, poor quality sleep, intensive dreams, and subjective feelings of insufficient sleep. Studies of different age groups indication that sleep patterns diverge between ages 30 and 40 with women maintaining their levels of slow wave sleep and men decreasing theirs.

Research Priorities in Sex Based Differences in Adaptation to Challenging Environments in
HUMAN BEHAVIOR AND PERFORMANCE

Below are research goals in order of priority. Overarching goals are very broad, with specific goals by risk factor listed in the next section. Research priorities are in order, with the highest priority risk factors listed in numerical order. Within each risk factor, highest priority research questions are again listed in numerical order.

Overarching Goals

Currently there are almost no studies systematically investigating gender differences in behavior and performance with respect to challenging earth environments, space flight, flight crew, mission control, support crew and staff. Therefore, highest priorities should be given to multidisciplinary research across professions on:

1. Development and evaluation of sex-based criteria for performance assessment.
2. Psychosocial (individual, group, organizational) and neurobiological (circadian, endocrine) and mechanisms underlying sex differences in the effects of psychosocial and physical environment (including coping strategies, individual roles in the group, evolution of the group, morale, leader / member relations, emotional support, formation of relationships, work load, trust, work dynamics, health)
3. Evaluation of sex differences in existing countermeasures (select in, select out, training, monitoring, support) and the development of new countermeasures, pre, during and post flight
4. Human behavior and performance should drive human factors engineering to insure that systems are designed for humans.

Specific Goals by Risk Area

Psychosocial Adaptation in challenging earth environments and space

1. Develop criteria for defining and measuring optimal behavior and factors that affect this for females and males. These criteria can then be used to study the efficacy of select-in procedures for men and women.
2. Investigate sex differences in coping with prolonged isolation and confinement
3. Investigate neurobiologic and psychosocial determinants of depressed affect and other indicators of poor psychosocial adaptation
4. On a gender/sex basis, develop measures for readiness to perform specific tasks at a given time in the mission
5. Conduct gender based research for couple relationships for long duration missions.
6. Examine effect of culturally determined expectations of sex-based roles on social relations and group dynamics of multicultural crews.
7. Develop algorithms for effective leadership styles for women and men for single sex or mixed sex crews.
8. Develop criteria for designing work, recreation, training, and rest schedules for men and women on short and long duration missions.

Neurobehavioral Dysfunction in challenging earth environments and space
1. Develop an evidence-based approach that can be used to better refine tools and select-out criteria to identify and predict risk and/or onset of neurobehavioral dysfunction by gender in the applicant pool.
2. Develop a database that chronicles the prevalence and incidence of neurobehavioral dysfunction by sex and culture in the astronaut corps while in training and/or orbit, insuring confidentiality.
3. Develop tools such as Winscat to provide quantifiable data/results that assess neurobehavioral dysfunction for women and men in orbit.
4. Develop a tool that provides a non self-report assessment of emotional health that can be validated for men and women that can be used regularly over time. This may include behavioral ratings by others.
5. Determine biological diagnostics that can be used in orbit to measure neurobehavioral dysfunction; diagnostics that are sensitive to sex-based differences.
6. Investigate the capability of therapeutic intervention for Shuttle, ISS, and exploration class missions, useful for both sexes.
7. Investigate post mission measures and interventions that are sensitive to sex based differences.

Habitability in challenging earth environments and space
1. Investigate how habitability and sex and gender differences can be accommodated in the ISS and future capsule environments.
2. Determine the impact of excluding a large population of women from EVA based on not developing a suit they can wear.
3. Investigate sex differences in adaptation to high noise levels in terms of hearing loss or performance.
4. Research sex differences in adaptation to low light levels, both in regard to the visual system and performance.
5. Investigation is needed to study sex differences in optimal human machine interfaces.

Workload in challenging earth environments and space
1. Investigate sex differences in tolerance of or ability to perform in an environment with excessive work demands or insufficient work.
2. Research sex differences in the way that men and women address cognitive challenges in spatial rotation/orientation, short-term memory, and long term memory.

Health in challenging earth environments and space
1. Investigate sex differences in astronauts' perceived health risks, e.g. radiation?
2. Determine sex differences in regard to individuals' concerns over catastrophic events in or during a challenging earth or space mission, i.e., effect on sleep, stress hormones?
3. Investigate the role of food (meals, caloric intake, fluid intake, social aspects) in mood, work performance, and stress.

Sleep in challenging earth environments and space

1. Determine optimal protocols for sleep and pharmacologic interventions, relaxation training, and other countermeasures for women and men, e.g. during slam shifting, shiftwork, and chronic sleep restriction.
2. Identify performance effectiveness, emotional and cognitive states, and interpersonal behavior by sex relative to timing and quality of sleep.
3. Identify optimal circadian rhythm patterns by sex for space missions in challenging earth environments or exploration missions.
4. Identify multidisciplinary opportunities to assess sleep and circadian rhythm relative to immunologic, metabolic, musculoskeletal, endocrine function.
5. Develop measures that quantify the benefit of sleep and circadian adaptation with respect to critical levels of performance.

Resources and infrastructure needed:
1. Cognitive, affective, and psychophysiological measures of behavior and performance should be examined in ground based analogue and simulation settings, possibly in relation to current training program used for astronauts, however research must be non-invasive, easy to engage in and be performed by an outside group that has earned the trust of the astronaut corps.
2. Provide the infrastructure and resources needed to increase the recruitment of women in ground-based studies.
3. Provide access to selection data and training data for astronauts.
4. Finish the bioplex.
5. Fund a more robust program of research at JSC, National Space Biomedical Research Institute (NSBRI) with multi year funding. Actively pursue leveraged opportunities with other federal agencies including National Institutes of Health (NIH) and National Science Federation (NSF), Federal Aviation Administration (FAA), Department of Defense (DOD), Defense Advanced Research Projects Agency (DARPA) and with international partners.
6. Ground based study by an independent group from NASA to determine what works that has earned trust of astronaut corp. Specifically test strategies on the ground first that you plan to use for space missions. (ex: effects of a communication response time of 48 minutes to get support).
7. Develop an infrastructure that protects the confidentiality of individuals while allowing access to health, medical or performance data that could or would negatively impact mission safety.

Conclusions.
Given growing awareness of the critical nature of behavior and performance issues for long duration space missions and challenging earth environments, understanding sex differences is crucial.

Planning Committee Contact Information

Meredith Hay, Ph.D.
Director
Center for Gender Physiology &
Environmental Adaptation
University of Missouri
School of Medicine
Columbia, MO 65211
573-874-0044
haym@missouri.edu

Saralyn Mark, M.D.
Senior Medical Advisor
NASA & U.S. Department of Health and
Human Services
NASA Headquarters
300 E. Street SW
Washington, DC 20546
202-358-0531
smark@hq.nasa.gov

Bette Siegel, Ph.D.
Enterprise Scientist
Bioastronautics Division
NASA Headquarters
300 E. Street SW
Code UB
Washington, DC 20546
202-358-2245
bsiegel@hq.nasa.gov

Ellen Baker, M.D., M.P.H.
Astronaut and Medical Officer
NASA Johnson Space Center
Code CB
2101 NASA Rd. 1
Houston, TX 77058
ebaker@ems.jsc.nasa.gov

Angela Bates
National Institutes of Health
Office on Research on Women's Health
Building 1, Room 203, MSC 0161
9000 Rockville Pike
Bethesda, MD 20892
301-402-1770
BatesA@od.nih.gov

John B. Charles, Ph.D.
Co-Lead
Bioastronautics Critical Path Roadmap
Project
Mission Scientist, STS-107, and Co-Lead,
Bioastronautics Critical Path Roadmap
Project
NASA Johnson Space Center
2101 NASA Rd 1
Mail Code SL
Houston, TX 77058
John.b.charles1@jsc.nasa.gov

Susan Curley, Ph.D.
OBPR Congressional Liaison
NASA Headquarters
300 E. Street SW
Washington, DC 20546
202-358-2211
scurley@mail.hq.nasa.gov

Guy Fogleman, Ph.D.
Acting Director
Bioastronautics Research Division
NASA Headquarters
300 E. Street SW
Washington, DC 20546
202-358-0220
gfoglema@mail.hq.nasa.gov

Deborah Harm, Ph.D.
Senior Scientist
Human Adaptation & Countermeasures
Office
NASA Johnson Space Center
2101 NASA Rd. 1
SK3
Houston, TX 77058
281-483-7222
deborah.harm1@jsc.nasa.gov

Charles Macri, M.D.
Director, Division of Reproductive and
Medical Genetics
Department of Obstetrics and Gynecology
Uniformed Services University of the Health
Sciences
School of Medicine
4301 Jones Bridge Rd.
Bethesda, MD 20814-4799
Cmacri@usuhs.mil

Sherry A. Marts, Ph.D.
Scientific Director
Society for Women's Health Research
1828 L Street NW, Suite 625
Washington, DC 20036
202-496-5019
sherry@womens-health.org

Margaret Miller, Ph.D.
Manager of Science Programs
Office of Women's Health
Food and Drug Administration
Mmiller@oc.fda.gov

Louis Ostrach, Ph.D.
Dividion of Fundamental Space Biology
NASA Headquarters
Code UF
300 E. Street SW
Washington, DC 20546
202-358-0870
lostrach@hq.nasa.gov

Mark Shepanek, Ph.D.
Deputy Chief
Medicine of Extreme Environments
NASA Headquarters
300 East Street SW
Washington, DC 20546
Mshepanek@hq.nasa.gov

David Tomko, Ph.D.
Enterprise Scientist
NASA Headquarters
300 E. Street SW
Washington, DC 20546
Dtomko@mail.hq.nasa.gov

Carol Van Hartesveldt, Ph.D.
Associate Dean of Research
College of Medicine
Florida State University
Tallahassee, FL 32306-4300
Carol.varnhartesveldt@med.fsu.edu

Susan F. Wood, Ph.D.
Director
Office of Women's Health
Food and Drug Administration
5600 Fishers Lane, HF-8
Rockville, MD 20857
Swood1@oc.fda.gov

Special Consultant to the University of Missouri

Joan Vernikos, Ph.D.
44 Wolfe Street
Thirdage, LLC.
Alexandria, VA 22314

Participant Contact Information

Group I
Bone Loss/Skeletal Muscle Atrophy

Saralyn Mark, M.D.
Senior Medical Advisor
NASA & U.S. Department of Health and Human Services
NASA Headquarters
300 E. Street SW
Washington, DC 20546
202-358-0531
smark@hq.nasa.gov

Jay R. Shapiro, Ph.D
Uniformed Services
University of the Health Sciences
Room A 1041
4301 Jones Bridge Road
Bethesda, MD 20814-4799
301-295-3600
jshapiro@usuhs.mil

Sherry Sherman, Ph.D.
National Institute on Aging
Gateway Building, Suite 3 E327
7201 Wisconsin Avenue
Bethesda, MD 20892-9205
301-435-3048
shermans@nia.nih.gov

Susan Bloomfield, Ph.D., FASCSM
Associate Professor
Dept. of Health & Kinesiology
Texas A&M University
4243 TAMU
College Station , TX 77843-4243
979-862-1181
sbloom@tamu.edu

Marybeth Brown, Ph.D.
Associate Professor of Physical Therapy
University of Missouri- Columbia
106 Lewis Hall
Columbia, MO 65211
573-884-7531
brownb@health.missouri.edu

Mary Anne Frey, Ph.D.
Professor
Community Health
Wright Sate University School of Medicine
P.O. Box 927
Dayton, OH 45401
937-267-8338
Mary.frey@wright.edu

Lynn Gerber, M.D.
Chief
Rehabilitation Medicine Department
National Institutes of Health
Building 10, Room 6S-235
9000 Rockville Pike
Bethesda, MD 20892
301-402-3011
Fax 301-402-0663
Lgerber@nih.gov

Helen W. Lane, Ph.D., R.D.
Chief Nutritionist
NASA Johnson Space Center
Mail Code SA
Houston, TX 77058
281-483-7165
helen.w.lane1@jsc.nasa.gov

Adrian Leblanc, Ph.D.
Director
Division of Life Sciences
Universities Space Research Association
3600 Bay Area Blvd.
Houston, TX 77058
281-244-2012
leblanc@dsls.usra.edu

Keith Wear, Ph.D.
Research Physicist
Food and Drug Administration
12720 Twinbrook Parkway
Rockville, MD 20852
301-443-5020 ext. 148
kaw@cdrh.fda.gov

Group II
Cardiovascular Alterations

John B. Charles, Ph.D.
Co-Lead
Bioastronautics Critical Path Roadmap Project
NASA Johnson Space Center
2101 NASA Road 1
Mail Code SL
Houston, TX 77058
281-483-7224
john.b.charles1@jsc.nasa.gov

Paula Johnson, M.D.
Executive Director
Connot's Center for Women's Health and Gender Biology
Brigham & Women's Hospital
75 Francis Street
Boston, MA 02115
617-732-8985
pajohnson@partners.org

Janice Meck, Ph.D.
Cardiovascular Laboratories
NASA Johnson Space Center
Mail code SK
2101 NASA Rd 1
Houston, TX 77058
281-244-5405
janice.m.meck1@jsc.nasa.gov

Dominick D'Aunno, MD
Assistant Professor
Baylor College of Medicine
National Space Biomedical Research Institute
1 Baylor Plaza, NA 425
Houston, TX 77030
281-483-5542
Ddaunno@ems.jsc.nasa.gov

Eileen Hasser, Ph.D.
Professor
Veterinary Biomedical Sciences
University of Missouri
322 D Crc
Columbia, MO 65211
573-882-6125
hassere@missouri.edu

Virginia H. Huxley, Ph.D.
Professor of Physiology
Dalton Research Investigator
Professor of Veterinary Biological Sciences
M401 Physiology Ummc
University of Missouri
Columbia, MO 65211
573-882-8069
huxleyv@health.missouri.edu

Jane Reckelhoff, Ph.D.
Professor
Physiology
University of Mississippi
2500 North State Street
Jackson, MS 39216-4505
Jreckelhoff@physiology.umsmed.edu

Leona Rubin, Ph.D.
Associate Professor
Department of Biomedical Sciences
University of Missouri-Columbia
E 102 Veterinary Medical Building
Columbia, MO 65211
RubinL@missorui.edu

Richard Summers, M.D.
Department of Emergency Medicine
2500 North State Street
Jackson, MS 39216
Rsummers@emergmed.umsmed.edu

Mike Ziegler, Ph.D.
Director
General Clinical Research Center
Professor of Medicine
University of California-San Diego
214 Dickinson Street
BCTF-C Room 209
San Diego, CA 92103-8341
Mziegler@ucsd.edu

Group III
Immunology Function

Bette Siegel, Ph.D.
Enterprise Scientist
Bioastronautics Division
NASA Headquarters
300 E. Street SW
Code UB
Washington, DC 20546
202-358-2245
bsiegel@hq.nasa.gov

Denise Faustman, M.D. Ph.D
Associate Professor of Medicine
Harvard Medical School
Director of Immunobiology
Massachusetts General Hospital- East
Building 149, 13th Street, Rm. 3602
CNY-3601
Charlestown, MA 02129
617-726-4084
faustman@helix.mgh.harvard.edu

Gerald Sonnenfeld, Ph.D.
Department of Microbiology, Biochemistry & Immunology
Morehouse School of Medicine
720 Westview Dr. SW
Atlanta, GA 30310-1495
404-752-1586
sonneng@msm.edu

Margaret Conner, M.D.
Department of Molecular Virology and Microbiology
Baylor College of Medicine
1 Baylor Plaza, 737E
Houston, TX 77030
Mconner@bcm.tmc.edu

Craig Franklin, Ph.D.
Professor
College of Veterinary Medicine
University of Missouri-Columbia
E 111-1 Veterinary Medical Building
Columbia, MO 65211
Franklinc@missouri.edu

Michael Lockshin, M.D.
Director of the Barbara Volker Center for Women
Professor of Medicine
Hospital for Special Surgery
535 East 70th
New York, NY 10021
212-606-1461
Volckerctr@HSS.EDU

Caroline Whitacre, Ph.D.
College of Medicine and Public Health
Immunology and Medical Genetics
Ohio State University
2078 Graves
333 W. Tenth Ave.
Columbus, OH 43210
614-292-5889
whitacre.3@osu.edu

Group IV
Neurovestibular/Neuroscience

Meredith Hay, Ph.D.
Director
Center for Gender Physiology &
Environmental Adaptation
University of Missouri
School of Medicine
Columbia, MO 65211
573-874-0044
haym@missouri.edu

F. Owen Black, M.D.
Neurotology Research
Legacy Holladay Park Medical Center
1225 NE 2nd Avenue
Portland, OR 97232
503-413-5332
bof@ix.netcom.com

Daniel Sklare, Ph.D.
Program Administrator
Hearing and Balance
Vestibular Sciences Branch
Division of Human Communication
National Institutes of Health/ National
Institute on Deafness and Other
Communication Disorders
Executive Plazas
Rm 400C
3120 Executive Blvd.
MSC 7180
Bethesda, MD 20892-7180
301-496-1804
sklared@mail.nih.gov

Susan Herdman, Ph.D., P.T., FAPTA
Emory University School of Medicine
Dizziness and Balance Center
Department of Rehabilitation Medicine
1441 Clifton Road NE
Atlanta, GA 30322
404-712-0996
sherdma@emory.edu

Sherri Jones, Ph.D.
Associate Professor
Department of Surgery
University of Missouri-Columbia
Columbia, MO 65211
Jonessh@health.missouri.edu

Tim Jones, Ph.D.
Professor
Department of Physiology
University of Missouri-Columbia
202 Dalton D C 375.00
Columbia, MO 65211
Jonest@health.missouri.edu

Kathleen S. Matt, Ph.D.
Associate Director
Arizona Biomedical Institute
Arizona State University
Tempe, AZ 85287-0404
480-965-7906
kmatt@asu.edu

Carol Van Hartesveldt, Ph.D.
Associate Dean of Research
College of Medicine
Florida State University
Tallahassee, FL 32306-4300
Carol.vanhartesveldt@med.fsu.edu

Group V
Reproductive Biology

Sherry A. Marts, Ph.D.
Scientific Director
Society for Women's Health Research
1828 L. Street NW
Washington, DC 20036
202-496-5019
sherry@womens-health.org

Florence Haseltine, M.D., Ph.D.
Director
Center for Population Research
National Institute of Child Health and Human Development
6100 Executive Blvd.
8B07D
Rockville, MD 20852
301-496-1101
haseltif@mail.nih.gov

Richard Jennings, M.D.
Director
Aviation Medicine Center
University of Texas Medical Branch
301 University Blvd.
Galveston, TX 77555-1150
409-772-3458
rjenning@utmb.edu

Jean Fourcroy, MD, Ph.D., MPH
Assistant Professor
Uniformed Services University Health Sciences
6310 Sword Way
Bethesda, MD 20817
301-594-3084
sjlfbehr@aol.com

William Gibbons, M.D.
Director
The Jones Institute for Reproductive Medicine
Department of Obstetrics and Gynecology
Eastern Virginia Medical School
601 Colley Avenue
Norfolk, VA 23507-1627
757-446-8934
gibbonswe@evms.edu

John Rock, MD
Chancellor of the LSU health Sciences Center
Department of Obstetrics and Gynecology
1639 Pierce Drive
Room 4208 WMB
Atlanta, GA 30322
404-727-8600
Jrock@emory.edu

Joseph Tash, Ph.D.
Department of Molecular and Integrative Physiology
Lied Building Room G007
3901 Rainbow Blvd
Kansas City, KS 66160
913-588-7421
Jtash@kumc.edu

Michelle P. Warren M.D.
Director
Center for Menopause , Hormonal Disorders, and Women's Health
622 West 168th
PH 16
New York, NY 10032
212-305-8723
mpw1@columbia.edu

Elizabeth A. Whelan, Ph.D.
Chief, Epidemiology Section
Industrywide Studies Branch
National Institute for Occupational Safety and Health
4676 Columbia Parkway
Mail Stop R13
Cincinnati, OH 45226
513-841-4203
ewhelan@cdc.gov

Steve Young, M.D.
Associate Professor
Department of OB/GYN
N 625 A
University of Missouri-Columbia
Columbia, MO 65211
573-884-1408
youngst@health.missouri.edu

Group VI
Human Behavior/ Performance

Marc Shepanek, Ph.D.
Deputy Chief
Medicine of Extreme Environments
Office of the Chief Health and Medical Officer
NASA Headquarters
300 E. Street SW
Washington, DC 20546
Mshepanek@hq.nasa.gov

Virginia Cain, Ph.D.
Deputy Director
Office of Behavioral and Social Sciences Research
National Institutes of Health
1 Center Drive
Room 256
Bethesda, MD 20892-0183
301-402-1146
cainv@od1tm1.od.nih.gov

Edna Fiedler, Ph.D.
Manager AAM-520
Selection, Training and Organizational Assessment Branch
Civil Aerospace Medical Institute
Federal Aviation Administration
1500 Brookhaven Blvd.
Norman, OK 73072
Edna_fiedler@faa.gov

Ellen Baker, M.D., M.P.H.
Astronaut and Medical Officer
NASA Johnson Space Center
Code CB
2101 NASA Rd. 1
Houston, TX 77058
ebaker@ems.jsc.nasa.gov

Gloria Leon, Ph.D.
Professor of Psychology
University of Minnesota
Psychology N 420 Elt H
75 East River Road
Minneapolis, MN 55455
612-625-9324
leonx003@umn.edu

Des Lugg, MD
Chief of Medicine of Extreme Environments
NASA Headquarters
Code AM
300 E. Street Southwest
Washington, DC 20546
202-358-4790
dlugg@mail.hq.nasa.gov

Carol Otis, MD
Physician
Director
Women's Sport Medicine
Kerlan-Jobe Orthopedic Clinic
6801 Park Terrace
Los Angeles, CA 90045
310-665-7200
Dr.Otis@sportsdoctor.com

Larry Palinkas, M.D.
Professor
Department of Family and Preventative Medicine
Division of International Health & Cross Cultural Medicine
University of CA at San Diego
9500 Gilman Drive
LaJolla, CA 92093-0807
619-543-5493
Lpalinkas@ucsd.edu

Naomi Rogers, Ph.D.
Unit for Experimental Psychiatry
Division of Sleep and Chronobiology
University of Pennsylvania School of Medicine
1020 Blockley Hall
423 Guardian Drive
Philadelphia, PA 19104-6021
Nrogers2@mail.med.upenn.edu

Peter Suedfeld, Ph.D.
Professor Emeritus of Psychology
University of British Columbia
2136 West Mall
Vancouver, BC
Canada
604-822-5713
Psuedfeld@psych.ubc.ca

Keynote Speakers

Kathie Olsen, Ph.D.
Associate Director
Office of Science and Technology Policy
Executive Office of the President
1650 Pennsylvania Ave.
Washington, DC 20502
kolsen@ostp.eop.gov

Ellen Baker, M.D., M.P.H.
Astronaut and Medical Officer
NASA Johnson Space Center
Code CB
2101 NASA Rd. 1
Houston, TX 77058
Ellen.s.baker1@jsc.nasa.gov

Des Lugg, M.D.
Chief of Medicine of Extreme Environments
NASA Headquarters
Code AM
300 East Street Southwest
Washington, DC 20546
202-358-4790
dlugg@mail.hq.nasa.gov

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health
Director, Office of Research on Women's Health
National Institutes of Health
Building 1, Room 201
MSC 0161
9000 Rockville Pike
Bethesda, Maryland 20892-0161

Carol Otis, MD
Physician
Women's Sport Medicine
Kerlan-Jobe Orthopedic Clinic
6801 Park Terrace
Los Angeles, CA 90045
310-665-7200
Dr.Otis@sportsdoctor.com

References

Musculoskeletal Physiology

Balagopal P. Schimke JC. Ades P. Adey D. Nair KS. **Age effect on transcript levels and synthesis rate of muscle MHC and response to resistance exercise.** *American Journal of Physiology - Endocrinology & Metabolism*. 280(2):E203-8, 2001 Feb. www.muhealth.org/~library/resources/ejournals.html

Barazzoni R. Short KR. Nair KS. **Effects of aging on mitochondrial DNA copy number and cytochrome c oxidase gene expression in rat skeletal muscle, liver, and heart.** *Journal of Biological Chemistry. 275*(5):3343-7, 2000 Feb 4. www.muhealth.org/~library/resources/ejournals.html

Gretebeck RJ. Siconolfi SF. Rice B. Lane HW. **Physical performance is maintained in women consuming only foods used on the U.S. Space Shuttle.** *Aviation Space & Environmental Medicine. 65*(11):1036-40, 1994 Nov.

Grigoriev AI. Oganov VS. Bakulin AV. Poliakov VV. Voronin LI. Morgun VV. Shnasmall C; Cider VS. Murashko LV. Novikov VE. LeBlank A. Shakleford L. Investigator: Schneider VS. Leblanc A. Shakleford L. **Clinical and physiological evaluation of bone changes among astronauts after long-term space flights.** [Russian] *Aviakosmicheskaia i Ekologicheskaia Meditsina. 32*(1):21-5, 1998.

Rooyackers OE. Adey DB. Ades PA. Nair KS. **Effect of age on in vivo rates of mitochondrial protein synthesis in human skeletal muscle.** Proceedings of the National Academy of Sciences of the United States of America. 93(26):15364-9, 1996 Dec 24. www.muhealth.org/~library/resources/ejournals.html

Shapiro JR. Beck TJ. LeBlanc A. Schneider V. Mustapha B. Shakelford L. Oreskovic T. Ballard P. Ruff CB. Toerge JT. Caminis J. **Patterns of Femoral Neck Bone Loss in Spinal Cord Injury and in Spaceflight.** [Abstract]

Short KR. Nair KS. **Does Aging Adversely Affect Muscle Mitochondrial Function?** *Exercise and Sport Sciences Reviews. 29*(3):118-23, 2001.

Stein TP. Leskiw MJ. Schluter MD. Hoyt RW. Lane HW. Gretebeck RE. LeBlanc AD. Investigator: Stein TP. Schluter MD. Lane HW. LeBlanc AD. **Energy expenditure and balance during spaceflight on the space shuttle.** *American Journal of Physiology. 276*(6 Pt 2):R1739-48, 1999 Jun. www.muhealth.org/~library/resources/ejournals.html

Vico L. Collet P. Guignandon A. Lafage-Proust MH. Thomas T. Rehaillia M. Alexandre C. **Effects of long-term microgravity exposure on cancellous and cortical weight-bearing bones of cosmonauts.** *Lancet. 355*(9215):1607-11, 2000 May 6. www.muhealth.org/~library/resources/ejournals.html

Cardiovascular Alterations

Convertino VA. Goldwater DJ. Sandler H. **Bedrest-induced peak VO2 reduction associated with age, gender, and aerobic capacity.** *Aviation Space & Environmental Medicine. 57*(1):17-22, 1986 Jan.

Convertino VA. **Gender differences in autonomic functions associated with blood pressure regulation.** *American Journal of Physiology. 275*(6 Pt 2):R1909-20, 1998 Dec. www.muhealth.org/~library/resources/ejournals.html

Ludwig DA. Convertino VA. Goldwater DJ. Sandler H. **Logistic risk model for the unique effects of inherent aerobic capacity on +Gz tolerance before and after simulated weightlessness.** *Aviation Space & Environmental Medicine. 58*(11):1057-61, 1987 Nov.

Reckelhoff JF. **Gender differences in the regulation of blood pressure.** [Review] [92 refs] *Hypertension. 37*(5):1199-208, 2001 May. www.muhealth.org/~library/resources/ejournals.html

Reckelhoff JF. Zhang H. Srivastava K. **Gender differences in development of hypertension in spontaneously hypertensive rats: role of the renin-angiotensin system.** *Hypertension. 35*(1 Pt 2):480-3, 2000 Jan. www.muhealth.org/~library/resources/ejournals.html

Immune Function

Belay T. Aviles H. Vance M. Fountain K. Sonnenfeld G. **Effects of the hindlimb-unloading model of spaceflight conditions on resistance of mice to infection with Klebsielia pneumoniae.** *Journal of Allergy & Clinical Immunology. 110*(2):262-268, 2002 Aug.

Hayashi T. Faustman DL. **Implications of altered apoptosis in diabetes mellitus and autoimmune disease.** *Apoptosis. 6*(1-2):31-45, 2001 Feb.

Lockshin MD. **Genome and hormones: Gender differences in physiology - Invited review: Sex ratio and rheumatic disease.** *Journal of Applied Physiology. 91*(5):2366-2373, 2001. www.muhealth.org/~library/resources/ejournals.html

Ryu S. Kodama S. Ryu K. Schoenfeld DA. Faustman DL. **Reversal of established autoimmune diabetes by restoration of endogenous beta cell function.** *Journal of Clinical Investigation. 108*(1):63-72, 2001 Jul.
www.muhealth.org/~library/resources/ejournals.html

Shearer WT. Lee BN. Cron SG. Rosenblatt HM. Smith EO. Lugg DJ. Nickolls PM. Sharp RM. Rollings K. Reuben JM. **Suppression of human anti-inflammatory plasma cytokines IL-10 and IL-1RA with elevation of proinflammatory cytokine IFN-gamma during the isolation of the Antarctic winter.** *Journal of Allergy & Clinical Immunology. 109*(5):854-857, 2002 May.

Neurovestibular/Neuroscience

Belay T. Sonnenfeld G. **Differential effects of catecholamines on in vitro growth of pathogenic bacteria.** *Life Sciences. 71*(4):447-456, 2002 Jun 14.

Grajewski B. Waters MA. Whelan EA. Bloom TF. **Radiation dose estimation for epidemiologic studies of flight attendants.** *American Journal of Industrial Medicine. 41*(1):27-37, 2002 Jan.
www.muhealth.org/~library/resources/ejournals.html

Herdman SJ. Schubert MC. Tusa RJ. **Role of central preprogramming in dynamic visual acuity with vestibular loss.** *Archives of Otolaryngology—Head & Neck Surgery. 127*(10):1205-1210, 2001 Oct.
www.muhealth.org/~library/resources/ejournals.html

Reproductive Biology

Fannon SA. Vidaver RM. Marts SA. **Genome and hormones: Gender differences in physiology—Historical perspectives: An abridged history of sex steroid hormone receptor action.** *Journal of Applied Physiology. 91*(4):1854-1859, 2001 Oct.
www.muhealth.org/~library/resources/ejournals.html

Marts SA. **Interdisciplinary research is key to understanding sex differences: Report from the society for women's health research meeting on understanding the biology of sex differences.** *Journal of Womens Health & Gender-Based Medicine. 11*(6):501-509, 2002 Jul-Aug.

Tash JS. Bracho GE. **Microgravity alters protein phosphorylation changes during initiation of sea urchin sperm motility.** *FASEB Journal. 13*(Suppl S):S43-S54, 1999.
www.muhealth.org/~library/resources/ejournals.html

Tash JS. Johnson DC. Enders GC. **Long-term (6-wk) hindlimb suspension inhibits spermatogenesis in adult male rats.** *Journal of Applied Physiology*. *92*(3):1191-1198, 2002 Mar.
www.muhealth.org/~library/resources/ejournals.html

Tash JS. Kim S. Schuber M. Seibt D. Kinsey WH. **Fertilization of sea urchin eggs and sperm motility are negatively impacted under low hypergravitational forces significant to space flight.** *Biology of Reproduction. 65*(4):1224-1231, 2001 Oct.
www.muhealth.org/~library/resources/ejournals.html

Human Performance and Behavior

Atlis MM. Leon GR. Sandal GM. Infante M. **Decision Processes and Interactions During a Two Woman Traverse of Antarctica.** [Abstract] 2001 Dec 5.

Johnson PJ. Suedfeld P. **Non-Work Activities of Arctic Whalers and Explorers: Coping with Stress through Creating Microcosms of Home and Family.**

Suedfeld P. Groups in Special Enviornments. I*nternational Encyclopedia of the Social and Behavioral Sciences. Vol 9*:6430-4, 2001. Oxford, UK: Elsevier.

Leon GR. **Select-In and Countermeasure considerations for Long-Duration Crews.** *Society of Automotive Engineers, Inc*. 2001. Paper Number 1999-01-2095.

Leon GR. Atlis MM. Ones D. Magor G. **A 1-year, three-couple expedition as a crew analog for a Mars mission.** *Environment & Behavior. 34*(5):672-700, 2002 Sep.

Otis CL. Drinkwater B. Johnson M. Loucks A. Wilmore J. **The female athlete triad.** *Medicine & Science in Sports & Exercise. 29*(5):R 1-R 9, 1997 May.

Suedfeld P. Steel GD. **The environmental psychology of capsule habitats.** *Annual Review of Psychology. 51*:227-253, 2000.
www.muhealth.org/~library/resources/ejournals.html

ACRONYMS

Bone Mineral Density (BMD)
Critical Path Roadmap (CPR)
Defense Advanced Research Projects Agency (DARPA)
Department of Defense (DOD)
Dual Energy X-ray Absorptiometry (DEXA)
Federal Aviation Administration (FAA)
Food and Drug Administration (FDA)
Hindlimb Suspension (HLS)
Histocombatibility Complex (HLA)
International Space Station (ISS)
Magnetic resonance imaging (MRI)
National Aeronautics and Space Administration (NASA)
National Institutes of Health (NIH)
National Institute for Occupational Safety and Health (NIOSH)
National Science Foundation (NSF)
National Space Biomedical Research Institute (NSBRI)
Ovariectomized (OVX)
Sex Hormone Binding Globulin (SHBG)