THESEUS

Cluster 1: Integrated Physiology - Report

CLUSTER 1

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Towards Human Exploration of Space: a EUropean Strategy

Cluster 1: Integrated Systems Physiology - Report

Bone and muscle

Cardiovascular, lungs and kidneys

Immunology

Neurophysiology

Nutrition and metabolism

THESEUS: Towards Human Exploration of Space – a European Strategy

Past space missions in low Earth orbit have demonstrated that human beings can survive and work in space for long durations. However, there are pending technological, medical and psychological issues that must be solved before adventuring into longer-duration space missions (e.g. protection against ionizing radiation, psychological issues, behaviour and performance, prevention of bone loss, etc.). Furthermore, technological breakthroughs, e.g. in life support systems and recycling technologies, are required to reduce the cost of future expeditions to acceptable levels. Solving these issues will require scientific and technological breakthroughs in clinical and industrial applications, many of which will have relevance to health issues on Earth as well.

Despite existing ESA and NASA studies or roadmaps, Europe still lacks a roadmap for human exploration of space approved by the European scientific and industrial communities. The objective of THESEUS is to develop an integrated life sciences research roadmap enabling European human space exploration in synergy with the ESA strategy, taking advantage of the expertise available in Europe and identifying the potential of non-space applications and dual research and development.

THESEUS Expert Groups

The basis of this activity is the coordination of 14 disciplinary Expert Groups (EGs) composed of key European and international experts in their field. Particular attention has been given to ensure that complementary expertise is gathered in the EGs.

EGs are clustered according to their focus:

Cluster 1: Integrated Systems Physiology
Bone and muscle
Heart, lungs and kidneys
Immunology
Neurophysiology
Nutrition and metabolism

Cluster 2: Psychology and Human-machine Systems
Group/team processes
Human/machine interface
Skill maintenance

Cluster 3: Space Radiation
Radiation effects on humans
Radiation dosimetry

Cluster 4: Habitat Management
Microbiological quality control of the indoor environment in space
Life support: management and regeneration of air, water and food

Cluster 5: Health Care
Space medicine
Medication in space

Identification of Research Priorities and Development of the THESEUS Roadmap

Each Expert Group based their work on brainstorming sessions dedicated to identifying key issues in their specific field of knowledge. Key issues can be defined as disciplinary topics representing challenges for human space exploration, requiring further attention in the future. These key issues were addressed to the scientific community through an online consultation; comments and inputs received were used to refine them, to consider knowledge gaps and research needs associated to them, as well as to suggest potential investigations.

The outcomes and main findings of the 'Integrated Systems Physiology' EGs have been synthesised into this report and further integrated to create the THESEUS roadmap.

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1 Integrated Systems Physiology

Introduction

The next phase of bioastronautics and human spaceflight

Human bioastronautics programmes have grown from the culmination of 50 years of human spaceflight experience, including both short- and long-duration missions on a variety of platforms. Medical and physiological findings from these missions have demonstrated that spaceflight has a dramatic impact on almost all physiological systems including muscle atrophy, bone demineralisation, cardiovascular and metabolic dysfunctions, impaired cognitive processes and reduced immunological competence, and nutrition/metabolism. These adaptive responses lead to a physiological de-conditioning in space and have the potential to affect crew health and performance both in space and upon return to Earth. In many instances, countermeasures have been implemented to mitigate some of the maladaptive changes associated with space flight, including drugs, nutritional supplements and physical exercise on various workout devices. Although no countermeasures are able to fully mitigate the negative effects of space flight, several have proven to be very effective, allowing crew to live and work nominally on-orbit.

Undoubtedly, significant knowledge has been accumulated on the physiological changes associated with the adaptation of humans to short-term space flights. Europe scientists have contributed largely to this knowledge database and acquired undisputable expertise in basic space physiology and countermeasures through both spaceflight experiments and a strong and complete bed rest programme.

Human spaceflight is currently entering the next phase of space exploration towards the Moon and Mars, and with such ambitious goals come inherent medical challenges. Knowledge regarding human (mal)adaptation to microgravity is limited to that obtained during 6-month missions, with majority of information lying on short-term physiological changes. Therefore, the primary focuses of the next phase of bioastronautics research will be to further expand knowledge on the effects of long-duration space flight on crew health and performance, to further develop efficient countermeasures and to facilitate post-flight readaptation to the terrestrial environment. Such basic and upstream research is clearly a pre-requisite for long-term spaceflight, interplanetary travel and living on planetary surfaces. This objective is far from trivial and priorities have yet to be defined.

Although space medicine has been practiced for more than half a century, it is quite nascent relative to the physiological and clinical knowledge and capability required for long-term space missions. For example, a significant challenge in the evolution of space medicine will be to determine how the physiological adaptation to space may alter the physiopathology of disease or the manifestation of illness and injury in space. Answers can be found by reviewing the clinical experience of flight physicians who treated diseases in space, but the strongest approach is to create an integrated model of the physiopathological adaptation of multiple organ systems to microgravity. The exploration of space requires a systematic understanding of human body, from the molecular to integrated systems levels, as it responds to the unfamiliar environment of space and microgravity.

Towards a necessary integrated physiology approach

This new integrated physiology approach is undoubtedly necessary for future bioastronautics research. Even though it has long been recognised as an essential scientific approach, for decades research has been conducted on individual body systems (e.g. muscle, bone, cardiovascular system, and nutrition researched independently). The limits of such an approach are easily seen through the incomplete success of current countermeasure programmes in which scientists focus on specific organ systems and symptoms in a piecemeal fashion, rather than using a whole body approach. For example, the dual effect of amino acid supplementation which was positive on muscle mass but negative on bone, demonstrates why a holistic approach to space adaptation is absolutely essential to support future space exploration.

The transition of space research from independent physiological systems to a more rigorous, integrated approach requires a clear, focused, competitive research strategy for solving targeted risk areas of human health and performance in space. Reaching these goals will not only provide the basis for critical, high quality health care for crews on-orbit but also result in a wealth of physiological data. Examination of this data will certainly yield solutions for significant medical challenges for long-duration space flight and exploration. The data will also provide the basis for well-conceived and evidence-based countermeasures to deal with critical areas of concern including radiation exposure, immunology, mineral metabolism, protein synthesis, chronobiology, cardiology, and food and nutrition in space, for both micro and low gravity.

Considerations of the physiological effects of Lunar and Martian gravity

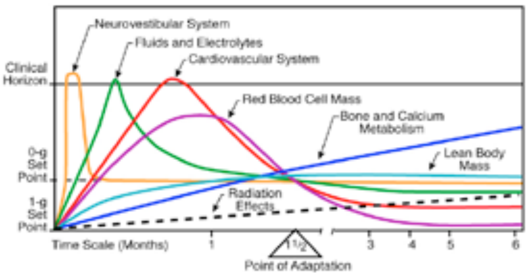

Figure 1: Changes of various body systems during adaptation to microgravity (Credit: NASA)

Another essential research topic that must be considered to enable future planetary exploration is human adaptation not only to weightlessness, but also reduced gravity. The biological effects of long-duration exposure to reduced gravity levels that will be experienced during stays on the Moon (0.16 g) and Mars (0.38 g) are completely unknown. It seems unlikely that the countermeasures developed on-board the International Space Station (ISS) will adequately protect crews on a journey to Mars and back over a 30-month period, or prevent the effects of a long-duration exposure to reduced gravity on the Moon or Mars. There is therefore a need to obtain basic knowledge on physiological adaptations to reduced gravity levels. Also, new insights could then be used in designing an "integrated countermeasure" for preventing the detrimental effects of weightlessness and/or reduced gravity on the physiological systems of the human body.

The overlooked ground-based applications of bioastronautics

Lastly, it is essential that ground-based applications of bioastronautics are utilised to their fullest potential and communication between researchers is enhanced. For decades, clinicians and physiologists performing research in space have done so separately, unaware of the likely possibility of having very similar research questions and goals. One example includes researchers on aging and chronic diseases, searching for environmental factors that fuel the pandemic of chronic diseases. Although sedentary lifestyle has been highlighted for decades as one of the main factors triggering the development of current chronic diseases such as obesity, insulin resistance, hypertension, muscle disuse, and bone demineralisation, the physiology of physical inactivity has received little attention. Clearly, the causal relationships between sedentary behaviours and the aforementioned diseases are essentially based on epidemiological studies or on the indirect beneficial effects of exercise training. None of these studies provide evidence to support a cause-and-effect relationship, but they indirectly suggest that sedentary behaviours and poor nutrition are the second leading cause of death in the USA, right after tobacco, and are major contributors to diseases associated with aging.

Likewise, certain physiological adaptations to microgravity stem from an adaptation to physical inactivity, which is exceedingly well simulated in ground-based bed rest analogues. In addition to space medicine related questions, bed rest studies are able to provide unique models to investigate mechanisms by which physical inactivity leads to the development of current societal chronic diseases, and also to test the efficacy of countermeasure programmes in preventing the development of these diseases. More importantly, because bed rest studies are conducted in healthy subjects that will recover, new therapeutic avenues can be explored.

Finally, the adaptation to reduced loading of the musculo-skeletal system is a major aspect of aging, as well as an adaptation to the space environment. With the new evolving era of proteomics, genomics, researchers can now investigate and try to understand why and how mechanical loading mediates some physiological and biological processes towards "unhealthy" behaviours.

Cluster and expert group objectives

The priorities of research necessary to support future space exploration beyond low Earth orbit present a unique set of issues whose solutions demand an in-depth understanding of whole body integrated physiology and cross-disciplinary work between life scientists, engineers and technologists. The objective of this expert group was to gather interdisciplinary European expertise and create synergies, allowing for an integrated physiology system based on identified research priorities. Due to the necessary holistic approach, those research programmes obviously required the involvement of scientists whose expertise is disseminated across Europe.
The specific objectives include:

1. To delineate the priorities of high quality research in physiology needed to support the next phase of space exploration.
2. To define these priorities on a new integrated approach of the deconditioning syndrome based on which a new generation of countermeasures are to be tested in the context of Mars exploration.
3. To better utilise the results of space physiology research and ground-based analogues to strengthen knowledge on the role of sedentary behaviours in the development of current societal chronic diseases.

The following sections present the conclusions of two expert workshops dedicated to the integrated physiology priorities for space exploration, conducted in 2010. The workshops were organised in splinter sessions, focusing on the main physiological functions to regroup expertise and draw a clear picture of the key questions to address, the latest developments, gaps to fill, and the Earth-based applications. Those splinter sessions were intertwined with plenary discussion to delineate the foreseen interactions between physiological functions that will require investigations.

2 Bones and Muscles

2.1. Relevance of Research on Bones and Muscles

2.1.1. Relevance for space exploration missions

The musculoskeletal system is central to work, locomotion, and posture. Maintaining its integrity is essential to mission completion as well as to astronaut health during and after the mission and over the lifespan of former fliers. One of the principal obstacles facing the design and implementation of long-duration exploration class missions is the fact that, without countermeasures, all components of the musculoskeletal system adapt to the microgravity environment, and also incur damage to tissue structure and function due to radiation exposure. Notably, bone mass and strength are lost (1). Muscle mass is lost and morphology is altered, with a loss of muscle strength and endurance (2). Tendon elasticity declines, reducing the power transmission of muscle contractions. Inter-vertebral discs elongate, causing potentially debilitating back pain. Also, many astronauts and cosmonauts have made multiple flights, further challenging the integrity of the musculoskeletal system.

During an exploration mission, astronauts will have endure a long-duration spaceflight in weightlessness, then adapt to live and work in partial gravity, undergo another long-duration spaceflight, and then finally return to a 1-g environment. In order to function properly, the astronaut's musculoskeletal system must adapt to each gravitational change. Operating in a gravitational field with a musculoskeletal system adapted to microgravity would result in impairment of performance due to reduced strength and endurance, increased risk of falling and increased risk of bone fractures. Also, the process of re-adaptation itself may increase risk of injury as different musculoskeletal components may recover at different rates. Thus, to diminish the impairment of performance and risk of injury, it is essential to develop countermeasures that maintain muscle strength and endurance, bone mass, and postural balance throughout the mission. Such countermeasures must be properly designed in order to meet their physiologic goals, to be carried out without an excessive burden of crew time, and to avoid injury or illness associated with their use.

The knowledge required to develop effective countermeasures will derive both from experience in low earth orbit spaceflights of relatively short durations (<6 month) and from extensive ground based studies involving human bed rest models and mechanistic animal studies.

While maintaining the integrity of the musculoskeletal system is central to crew health and function, it is also important to consider the interaction of the musculoskeletal system with other physiologic systems. In order to maximise the large investments made by NASA and ESA in developing and flying exercise hardware, exercise protocols should be modified to also maximise known positive impacts on cognition, behaviour, and immune function, which have been established in ground based studies.

In conclusion, maintaining the integrity of the musculoskeletal system is of high importance due to the known deleterious effects of the spaceflight environment on injury risk and performance, and due to the potential benefits of exercise in increasing crew health in other physiologic areas.

2.1.2. Earth benefits and applications

Understanding the effects of spaceflight on the musculoskeletal system entails both studies and countermeasures that are directly relevant to Earth populations, such as the elderly, subjects with muscle wasting syndromes, or those in prolonged enforced bed rest. The strongest translational potential of musculoskeletal research in the spaceflight context involves the study of age-related osteoporosis and sarcopenia. Although aging and spaceflight may involve changes in morphology and function by fundamentally different cellular and molecular pathways, they share the common feature of adaptation to changing levels of strain (3). Thus, studying musculoskeletal system adaptation from microgravity to partial or 1g parallels the adaptation needed to function in the context of age-related atrophy of bone and muscle tissue. Further, the types of countermeasures required to maintain function in altered gravity environments must take into account preservation of muscle strength, endurance, bone strength and postural balance. Similar approaches are relevant to the prevention of falls and fractures in elderly subjects.

Translational potential also exists for technologies such as imaging techniques used to monitor musculoskeletal status in space. The use of unloading analogues in ground-based research is relevant to patient populations that are subject to prolonged disuse. Bed rest studies allow us to separate the effect of disuse from those associated with co-morbidities, both in the context of fracture healing and in atrophy due to prolonged hospital stays. In summary, research into the musculoskeletal effects of long-duration spaceflight is rich in translational potential in both elderly and other populations affected by disuse atrophy.

Figure 2: ESA astronaut Frank De Winne equipped with a bungee harness, exercising on a treadmill on the ISS (Credit: ESA/NASA)

2.2. Bones and Muscles – Key Issues

Eight key issues were identified which are relevant to understand the changes in, and to maintaining the health of the musculoskeletal system during spaceflight in order to provide a framework for planning future research. For each identified key issue, the latest developments, knowledge gaps and research needs, proposed investigations and recommendations, as well as trans-disciplinary aspects are presented.

2.2.1. Key issue 1: Sex-based differences in the preservation of musculoskeletal tissue during space flight

Brief review of latest developments
Some recent case-study reports of individual male and female astronauts who have spent ~6 months on the ISS have led to the intriguing observation that women, in general, better preserve their musculoskeletal tissues during missions compared to men (4). However, there are many unanswered questions regarding these observations including medication use (including estrogen), pre-flight BMDs, exercise countermeasure profiles, etc.

Knowledge gaps and research needs

- While recent bed rest studies involving women have shed new light on the response of women to unloading and inactivity (5-8), there is still much to be learned.
- It is critical to identify the mechanisms for the different

patterns of musculoskeletal deconditioning that have been observed in women compared to men.

- To date, most women on long-duration missions have inhibited their menstrual cycles through pharmacological intervention. However, this may not be a safe practice for missions to Mars, for example, which may last up to 3-years, and research into this issue is needed.
- The effects of space radiation in the presence of estrogen are unknown and require further investigation.

Proposed investigations and recommendations

- There is an urgent need for bed rest studies in which men and women are exposed to exactly the same conditions and countermeasures during the period of confinement. It is possible that data from control subjects at NASA's Flight Analog Research Unit in Galveston, TX may already have some appropriate data that could be mined. Similarly, side-by-side animal studies using male and female animals need to be conducted in order to explore sex-based differences at the level of cellular and molecular kinetics. The response of females to simulated and actual unloading in relation to menstrual cycles needs to be studied.
- The design of exercise-countermeasure equipment must take differing body dimensions of men and women crewmembers into account. Such equipment must be designed to be adjustable so that women can exercise over a full range of loads and motions without undue hardship.

Figure 3: There are questions regarding sex-based differences in physiological responses to microgravity (Credit: NASA)

Trans-disciplinary aspects

- Links must be made with the endocrinology research community for joint work on the hormonal basis for sex-differences in response to altered gravity. Also of interest is the central nervous system regulation of bone and an examination of the role of estrogen and the hypothalamic-pituitary-adrenal axis in homeostasis of the musculoskeletal system.
- Radiation effects on bone and muscle may also exhibit sex-based differences and these should be examined in collaboration with radiation biologists.
- Sex-based differences in nutrition and micro-nutrition interaction and their influence on the musculoskeletal system also need to be studied.

2.2.2. Effects of micro-gravity on musculoskeletal injuries and healing processes (ligaments and tendons, bone fracture, back pain)

Brief review of latest developments

Information from spaceflight studies on fracture healing may prove to be a useful guide to studies of fracture healing in subjects during extended bed rest and those with bone loss due to disuse atrophy. Since Fibroblasts, muscle cells, and extracellular matrix are sensitive to alterations in gravitational forces (9, 10). Sporadic pieces of data from space-flown rats have shown that the repair process of load-bearing bone and skeletal muscle may be hindered during acute exposure to microgravity (11, 12). Furthermore, since many subjects in bed rest studies experience back pain, results on the management of this condition may be useful to evaluate the effect of deconditioning on back pain in a hospital-based population without the confounders associated with examining deconditioning in sick patients. Information from Earth-based studies should inform experiments on the healing of ligaments and tendon since unloading is a common form of treatment on earth.

Ligaments and tendons

- There is recent evidence that collagen fibre orientation in tendons may be altered by microgravity (13, 14). If verified, this may have important implications for recovery of soft tissues from long-duration spaceflight.
- There is data to support that unloading of the rat hind-limbs for 3 or 7 weeks inhibits dense fibrous connective tissue wound healing processes (15, 16), suggesting that minimal mechano-transduction may be useful for connective tissue repair.
- There is evidence of injury to soft tissues in a bed rest study which included the level of aggressive resistance exercise that may be necessary to maintain bone and muscle during long-duration missions.
- A high rate of injury has been observed in high-intensity exercise in the elderly. Since it is often said that spaceflight mimics aging, this may be a cautionary observation that is relevant to long-duration spaceflight.
- A recent literature review of shoulder injuries attributed to resistance training (17) has indicated that predictors of soft tissue injury remain unknown and cited the need for further research in this area.

Bone fracture

- Studies using the hind-limb suspension (HLS) model of unloading have revealed a contradictory finding for fracture healing in the rat tibial and femur. Whereas the tibial HLS model shows impaired healing, such was not the case in the femoral HLS model. These changes need to be replicated and explained.
- There are indications that HLS affects angiogenesis and vascularity (18, 19). These findings needs need to be further examined in relation to the validity of the HLS model for weightlessness.
- A 2002 study (20) reported that skeletal unloading increases adipocyte differentiation concomitantly with inhibition of osteoblast differentiation. Thus, bone marrow becomes more fatty in unloading. Prolonged exposure to microgravity may potentially lead to profound alteration of skeletal metabolism, perhaps including reduced osteogenic response to exercise.
- There is some evidence that immune compromise and bacterial virulence increases in the spaceflight environment (21). This may be relevant to soft-tissue infection after injury during spaceflight.

Back pain

- Lower and upper back pain is highly prevalent in returning crew members.
- Recovery from back pain shows persistence of pain without clear evidence of morphologic change
- There are indications that core muscles show poor recovery after bed rest

Knowledge gaps and research needs
Ligaments and tendons

- There is a lack of information in general about the effects of altered gravity on ligaments and tendons. These tissues have been somewhat ignored in favour of studies of bone and muscle.

- The enthesis is a common source of problems in sports and orthopedic medicine (22). However, information on the response of the enthesis (22) to altered gravity is absent from the literature.
- What is the effect of particular exercise activity on tendons and ligaments?
- What are the predictors of injury to tendons and ligaments?
- Rotator cuff injuries are common in astronauts during training and flight (23).

Bone fracture

- The contradictory results in fracture healing of the femur and tibia in hind-limb unloaded animals needs to be explained.
- Medical management procedures for in-flight fractures need to be elucidated and standardised.

Back pain

- The mechanisms of spaceflight-related back pain need to be elucidated.

Proposed investigations and recommendations

Ligaments and tendons

- There is a need for a comprehensive critical review of the literature in the areas of ligament and tendon in spaceflight. Ideally, this could lead to an identification of the key risk factors for injury.
- Little is known about enthesis during space flight and animal studies to address this issue are needed.
- It would be beneficial to consider the effects of specific countermeasure exercises in key soft tissue structures that are at risk of injury.
- Research which will safeguard the integrity of the shoulder in space is urgent.

Bone fracture

- Experiments with rodents in which fractures are induced immediately prior to flight would be instructive.
- The above experiments would be complemented by the induction of fractures while in space.
- There is a need to model of different types of fracture fixation. The conventional models (such as the classical Einhorn model (24)) are not relevant to human fractures because they require an intramedullary rod, which would not be a feasible treatment in space.
- There are opportunities to use animal models to simulate telemedicine and autonomous medical management. These opportunities should be exploited as a complement to human studies.
- Currently, it appears that ultrasound is likely to be the major form of medical imaging that will be available in space. Research needs to be focused on the diagnostic and therapeutic use of ultrasonic techniques.

Back pain

- Animal models of conditions leading to back pain need to be developed in order to understand etiologic factors and to test interventions.
- In human studies, there is a need to do more correlative studies between activity, exercise, spine morphology, etc. to gain insight into predictors of back pain.
- There is a need for detailed studies of the various tissue compartments (muscles, discs, ligaments, etc.) whose changes are associated with back pain.
- A more thorough understanding of the mechanisms of lower back pain in micro/partial gravity needs to be developed.

Trans-disciplinary aspects

Ligaments and tendons

- Bone and muscle have been considered as separate rather than interdependent tissues for much too long in spaceflight research, and the anatomical junction between muscle and bone (the enthesis) is an excellent metaphor for their close relationship. The gap in knowledge regarding changes in this junction with unloading needs to be filled.

Bone fracture

- Information is emerging regarding changes in the vascularisation of bone during fracture healing in the setting of unloading (25). Collaboration with vascular physiologists would be beneficial as these studies move forward.
- Any impairment of immune function could delay fracture healing and this area needs to be explored with collaborative research.
- If the spaceflight environment (microgravity and radiation) alters hematopoiesis, this may affect the process of fracture healing, as osteoclast precursors derive from the hematopoietic lineage.
- Interaction of the spaceflight environment with mesenchymal stem cells may affect the number and function of osteoblastic cells involved in fracture healing.

Back pain

- Back pain has the potential to affect crew performance and crew-crew interactions. These effects should be studied with physiotherapists and psychologists with the aim of devising strategies to minimise mission impact in the event of acute in-flight episodes of back pain.
- Pain affects sleep duration and quality, and research is needed to examine ways of attenuating the effects of acute in-flight episodes of back pain on sleep.
- Back pain has other cascading effects on the nervous system and these effects require further elucidation.
- Exercise compliance in the presence of back pain is likely to be poor and this could lead to an overall deterioration in the crew member's health. Alternative exercise prescriptions need to be devised so that crew members can exercise despite acute in-flight episodes of back pain. Emphasis may be given on the acquisition by the crew of a biomechanically sound exercising technique when using exercise apparatuses, an element that may have been underestimated as a potential factor merely responsible for initiating lower back pain.

2.2.3. Key issue 3: Role of genetics in musculoskeletal performance, preposition to injury and overall adaptation to micro-gravity

Brief review of latest developments

- Genome-wide association studies have identified specific genes associated with performance and fracture in epidemiologic studies.
- Animal models show differences in muscle and bone phenotypes based on genetic variation

Knowledge gaps and research needs

- At present, there is a dearth of integrated knowledge in this area that can be directly applied at the human level to activities such as crew member selection with flight-based genetic profiling.
- Experimentation on the wide variety of genetically modified animals has, to date, been confined to 1-g studies.

Proposed investigations and recommendations

- Detailed family histories of musculoskeletal diseases, including the incidence of osteoporosis and fractures, should be collected on all crew members and these data should be compared with pre- and post-flight measurements of musculoskeletal status.
- Better animal facilities are urgently needed on the ISS and animal studies with genetically modified rodents should focus on animals that have shown resistance to the loss of musculoskeletal during 1-g based models of unloading.

Trans-disciplinary aspects

There is vast potential for overlap in the study of genetic predisposition to changes in the musculoskeletal system during spaceflight with all other areas of health and performance. Work in this area should always be multidisciplinary.

2.2.4. Key issue 4: Biomechanics and impact of partial gravity on the musculoskeletal system

Brief review of latest developments

- Recent lunar simulations have indicated that ground reaction forces under simulated EVA load conditions are low and unlikely to be osteoprotective.
- Suspension simulations of reduced gravity locomotor activities are now more readily available.

Knowledge gaps and research needs

- Biomechanical modelling techniques have been underutilised for the estimation of whether or not various loading scenarios are likely to be osteoprotective in partial gravity.
- Lunar exploration through the Apollo programme showed that preferred gaits on the moon were different from those on earth. Preferred gaits on Mars are not known.
- Insight is needed regarding how altered patterns of locomotion in partial-g scenarios may lead to increased risk of injury.
- The kinematics and kinetics of simulated construction, exploration, and EVA activities are not well-known.
- Comprehensive simulations of work tasks in partial gravity should be conducted to aid in the assessment of fitness for duty after prolonged exposure to partial gravity and to assess the risk of injury.

Proposed investigations and recommendations

- Acceleration Monitoring Units (AMUs) should be added to spacesuits and space footwear in order to monitor motion during actual and simulated activity.
- Ground-based suspension models offer considerable possibility for simulation of locomotor and other activities (such as jumping, work tasks, etc.) and these approaches should be exploited.
- Musculoskeletal modelling techniques ought to be refined to generate validated loading estimates of structures that are at risk for bone loss (such as the proximal femur).
- Simulation of altered gait patterns in partial gravity that might lead to injury should be conducted.
- Biomechanical analysis of work tasks in partial gravity needs to be conducted.
- Biomechanical information on preferred gaits and task requirements is critical for the design of spacesuits and footwear for EVA.

Trans-disciplinary aspects

- Coordinated movements require sensorimotor integration which may be altered by prolonged exposure to altered gravity. Collaborative studies with specialists in this area would be beneficial.
- Surface activity during Apollo EVAs indicated significant metabolic demands and exploration of the cardiovascular consequences of exploration activities are warranted in conjunction with biomechanical studies.

2.2.5. Key issue 5: Effects of radiation exposure experienced during space flight on the musculoskeletal system

Brief review of latest developments

Recently published animal studies have shown that exposure to heavy ions simulated galactic sources of radiation induce rapid transient osteoclastic bone resorption (26). Studies of cultured osteoblasts have shown deleterious effects of radiation on osteoblast proliferation and function (27). Other studies have examined the effects of drug and nutritional interventions on musculoskeletal status (28, 29) in the simulated space environment of hindlimb unloading and radiation exposure.

Knowledge gaps and research needs

The full extent of the space radiation risk to bone is not yet known, and the cellular and molecular pathways require continued delineation, although good initial progress has been made. The effect of space radiation on muscle function is also not yet understood. Knowledge is lacking regarding the efficacy of preventive or restorative therapies and the extent and mechanisms underlying recovery of lost function.

Proposed investigations and recommendations

Definition of the risk posed by the space radiation environment on musculoskeletal tissues requires continuation of current animal studies establishing cellular and molecular pathways to bone loss, and extending these studies to examine effects on muscle as well. These mechanistic studies should involve different radiation types, and examine effects in the context of microgravity as simulated by the hindlimb unloading model (30). These mechanistic studies should also define the ability of radiation damaged musculoskeletal tissues to recover function, and further animal studies should begin to assess the effect of countermeasure approaches to radiation induced bone and muscle loss, including anti-resorptive therapies for bone, and anti-oxidants for bone and muscle.

Trans-disciplinary aspects

Understanding the effect on musculoskeletal tissues and function of exposure to space radiation will require a multidisciplinary approach integrating information from the central nervous (CNS), immune and vascular systems, as well as the hematopoetic (27) and mesenchymal niches in the bone marrow. Investigations of radiation effects should take into account the CNS, as it is of primary interest as a target of space radiation and is the source of input to skeletal muscle as well as the recipient of sensory information. Recent studies have also pointed to the role of the CNS in regulating both the formation and resorption arms of bone remodelling.

There is extensive literature on the immune response to radiation exposure. Radiation exposure is also known to affect angiogenesis, a key element of the skeletal muscle and bone repair. Finally, radiation is known to impact the progenitor cells of the mesenchymal and hematopoietic niche. Osteoblastic and muscle satellite cells derive from the same lineage, and osteoclasts derive from hematopoietic monocytes. Thus space radiation exposure may affect the reparative and remodelling functions of bone and muscle tissue.

On Earth, the closest clinical analogy to space radiation is clinical radiation therapy, which involves entirely different doses and types of radiation. However, information gained from mechanistic studies may shed light on potential cellular and molecular pathways by which bone and muscle may be affected in the clinical radiation therapy setting.

2.2.6. Key issue 6: Ground-based human studies

Ground-based human studies are relevant to all mission types, but are especially important for simulation of long-duration exploration missions. These studies are required to overcome the main drawbacks of space-based research, which generally have low sample sizes and uncontrolled experimental conditions. Human studies of sufficient sample size, with carefully controlled conditions, are essential to obtain pre-flight baselines and correctly evaluate the effectiveness of various countermeasures. Such examinations may eventually have to take place in one-year missions to the ISS, as yearlong bed rest studies are considered to be neither ethical nor practical.

Brief review of latest developments

Recent bed rest studies have demonstrated the ability of countermeasure approaches to attenuate disuse bone loss. These include high intensity resistance exercise (31, 32), resistive vibration (33, 34), and also pharmacologic interventions (alendronate and pamidronate) (8, 12, 35-37).

Knowledge gaps and research needs

Exercise protocols have not yet been optimised in regards to time efficiency, and there is still relatively little information about the molecular mechanisms of the countermeasure action on bone and muscle (38). For techniques such as vibration, it is still not known if the effect derives from muscle contraction or impact forces (39, 40). Although studies have demonstrated positive effects of aerobic exercise on brain and immune function on Earth populations, there is little knowledge of these relationships in a spaceflight setting. With respect to pharmaceutical treatment, there is a lack of information on dose-response relationships and on synergies between exercise and anti-resorptive treatment. Because of bisphosphonate side effects, there is a need to explore alternative anti-resorptive treatments that are newly available, such as denosumab.

Proposed investigations and recommendations

Continued research with larger sample sizes and controlled conditions will be required to optimise exercise protocols for efficacy and time efficiency. Achieving this goal will require further studies to elaborate the mechanisms of countermeasure effectiveness in bone and muscle. The amount of crew time required for exercise protocols, and the expense devoted to design and placement of the equipment justify efforts in determining the efficacy of exercise for protecting other physiologic systems from the effects of spaceflight, such as brain (behaviour/cognition/performance) and immune systems. For pharmacologic interventions, dose response studies are required, and new pharmaceuticals should eventually be tested, such as denosumab, which may provide fewer side effects than bisphophonates. Finally, there is a need to examine how exercise and drug treatment can operate synergistically.

Figure 4: Bed rest studies are frequently used as spaceflight analogues for physiology research (Credit: ESA/Vista S.T.I.)

Trans-disciplinary aspects

Exercise is inherently multidisciplinary, integrating cardiovascular, skeletal-muscle and skeletal physiology. Future investigations will require collaborations with neurophysiologists and cognition/behaviour specialists as well as immune and nutrition researchers.

Ground-based studies are highly translational in that they can be used to model long-term bed rest without the confounding effects of comorbidities. Additionally, prolonged bed rest is a useful clinical paradigm for the study of insulin resistance.

2.2.7. Key issue 7: Ground-based animal studies

Although animal research with hindlimb unloading models has the limitation of imperfect mapping of animal models to humans and hindlimb unloading to microgravity, ground-based animal studies continue to be a high priority. Ground-based animal studies are relevant to all mission types but are especially important for simulation of long-duration exploration missions. These studies provide mechanistic information that is otherwise impossible to obtain in humans, notably the interaction of radiation with disuse and the healing of fractures and wounds in general in radiation and microgravity environments. Animal studies also offer the advantages of large sample sizes, as well as the ability to carry out gender studies and manipulate estrogen status. Further, by use of transgenic animals it is possible to understand the effect of manipulating key genes, as exemplified by the myostatin knockout mouse (41).

Brief review of latest developments

Recent studies using rodent models and accelerator facilities have discovered high bone loss and deterioration of bone structure associated with exposure to radiation fields simulating deep space. The high bone loss has been attributed to a rapid transient activation of osteoclasts. Other studies have yielded conflicting results of fracture healing with hindlimb unloading, with open tibial fractures demonstrating delayed healing compared to loaded controls, but with femoral fractures showing the opposite tendency. Other developments have included preparation of new facilities for ISS, including the Italian Mouse Drawer, and the ESA Mice in Space Facility.

Knowledge gaps and research needs

Conflicting results from hindlimb unloading models point to the need to fly fractured animals in space to derive conclusive information regarding microgravity and fracture healing. The discovery of powerful space radiation effects on bone points to the need to systematically explore radiation interaction with skeletal muscle. Animal studies are also needed to study musculoskeletal effects of radiation and microgravity induced alterations of neural function and vascularisation/angiogenesis.

Proposed investigations and recommendations

Activation of the American animal facility is of high priority for increasing sample sizes necessary for mechanistic studies. Unfortunately, there are no current plans to fly such a facility. High scientific priority should be given to investigations of space radiation and skeletal muscle, and in particular, to the interaction of radiation with fracture healing and wound healing in general.

Trans-disciplinary aspects

The studies described above involve interactions between multiple disciplines. These include interactions between musculoskeletal sciences and radiobiology, genetics, immunology, neural and vascular studies.

Animal studies in simulated microgravity provide mechanistic information about disuse osteopenia and sarcopenia, and allow for studies of genetic manipulations in these disease areas. They also allow for mechanistic information about the interaction of different physiologic systems in these disease areas and others.

2.2.8. Key issue 8: Optimise countermeasure efficiency and utilise an integrated physiology approach

Brief review of latest developments

Recent results indicate that exercise is effective for attenuating muscle and bone loss in long-term bed rest (5, 6, 8). Initial results from a bed rest study led by Cavanagh indicate that specific protocols tailored to each subject that replace that subject's 1g loading attenuates bone loss. Amelioration of bone loss and muscle atrophy has also been observed with similar results observed for resistive vibration countermeasures (33, 42). It has been also demonstrated that mechanical stimulation of the plantar foot surface attenuates unloading-induced muscle atrophy both in humans (43, 44) and rats (45, 46). Other advances include the development of new multifunctional exercise devices suited for exploration class spacecraft, as well as a growing volume of data on subjects that exercised with second generation treadmills and resistive exercise devices on the ISS. Treadmill countermeasure exercise on the ISS has also been recently shown to elicit less force under the feet than similar exercise on earth, suggesting that restraining loads from the subject load devices (SLDs) are inadequate (47).

Knowledge gaps and research needs

While bed rest studies have indicated the value for resistance and resistive vibration exercise in attenuation of bone and muscle loss, there are significant gaps in determining how such countermeasures should be applied, as well as the effectiveness of nutritional and pharmacologic interventions with and without exercise. Information is lacking on the efficacy of intermittent timing of exercise bouts, on gender differences in exercise countermeasure efficacy, as well as the efficacy of exercise for protecting other physiologic systems, such the immune system and brain. Although a flight study of alendronate for prevention of bone loss is underway, the information on this and other bisphosphonates is incomplete, and there will be an eventual need to investigate therapies such as denosumab, which may offer anti-resorptive capability without the gastrointestinal side effects of alendronate. Lastly, there is a lack of information in spaceflight and bed rest scenarios using a combination of countermeasure approaches, such as timed nutritional-exercise countermeasures, combined exercise and anti-resorptive treatment, and the use of anti-oxidants to combat both radiation and disuse.

Figure 5: NASA Astronaut Steve Lindsey using the advanced Resistive Exercise Device (aRED), providing high loads to weight-bearing bones (Credit: NASA)

Proposed investigations and recommendations

Exercise countermeasure efficacy should be evaluated in side by side gender comparisons. Attention should also be given to testing exercise approaches that combine resistance exercises with balance and proprioception. Novel analogue environments such as EnviHab should be utilised to determine the protective effect of exercise on brain and immune function when exercise is carried out in isolation environments. Studies should be carried out that combine nutritional and pharmacologic approaches with exercise to determine if there are synergistic effects. Finally, exercise studies in transgenic rodent models should be carried out to better elucidate the mechanisms of exercise efficacy.

Trans-disciplinary aspects

Finding the optimal exercise protocol and/or the correct combination of exercise and nutritional/pharmacologic countermeasures will require a multidisciplinary approach, integrating information from the musculoskeletal, sensorimotor, neuro-behavioural, radiation biology and immunology fields.

Countermeasure studies are highly relevant to health on Earth in that they are developing countermeasures that address both bone loss and muscle loss as well as balance/fall risk, two factors that underlie the vast public health problem of fractures in the elderly.

2.3. Conclusion

Overall, eight key issues have been identified in the field of muscle and bone research in space, including sex-based differences, musculoskeletal injury, genetic predisposition, biomechanics, radiation, ground-based human studies, ground-based animal studies, and countermeasures.

Much still remains unknown about the response of women to altered gravity. While this is not surprising given that women crew members have represented less than 20% of all astronauts to date, there is a compelling need to address sex-based disparity in information and research.

Injury to musculoskeletal tissues during spaceflight has the potential to be mission-critical. Many situations can be envisaged in which crew members will be unable to carry out important, and in some cases life preserving, manoeuvres because of musculoskeletal injury. Bone fracture has, appropriately, been the focus of most prior spaceflight injury research, but even in this area much remains to be learned and contradictory findings need to be explained. However, injury to ligaments and tendons, which are very common in terrestrial workplace and sports settings, are also likely to occur during long-duration spaceflight in the future and very little research to data has address mechanisms for healing in altered gravity. The potential for varying rates of recovery of muscle, tendons, ligaments, and bones from injury upon return to Earth presents significant challenges to post-flight rehabilitation. Back injuries have also proven to be one of the most common complaints of returning crew members to date, and it is critical that a better understanding of its etiology and treatment be achieved.

At some point in the future, it is likely that pre-flight investigations will identify genetic predisposition for bone and muscle loss in altered gravity and this may become part of the selection matrix for potential crew members. However, such methods are currently not available and the focus of activity must remain on animal studies.

Biomechanical issues are also important for understanding a number of aspects of long-duration spaceflight. Locomotion during EVA on a surface with altered gravity has received some attention in the past but much remains unknown, particularly on Mars where no empirical evidence is available and few simulations have been conducted. Knowledge of typical locomotive patterns is also important for the design of habitats where increased vertical movement during gait and enhanced vertical jumping ability will require additional headroom. Biomechanical insights into typical exploration work tasks are important for task scheduling, suit design, and injury prevention.

The environment of deep space involves exposure to galactic and solar radiations that are largely deflected by the Earth's magnetic field. Recent studies have indicated that exposure to this radiation may play an important role in bone loss, however the effect on muscle is not yet known. Thus, a mechanistic understanding of radiation-induced bone loss, based on realistic simulations of the space environment, is essential to understanding the magnitude of the risks involved and to development of countermeasures. While there is some evidence that radiation disrupts muscle tissue at the fibre level, the state of knowledge is much less advanced than it is for bone, and development of the field is of high priority. This work will be highly interdisciplinary and is likely to produce knowledge that will be of value to the study of other physiologic systems.

Continued investment in human bed rest and other ground studies is essential due to the sample sizes and controlled conditions available to obtain information that can serve as a rational basis for selection and optimisation of countermeasure (both in terms of efficacy for protecting the musculoskeletal system, and for determination and optimisation for protective effects on other physiologic systems).

Expanded investment in ground-based animal studies is required to generate mechanistic information to serve as the basis for the development of countermeasures to microgravity and the radiation environment of space. The ability to model radiation and fracture healing effects are two key aspects of animal studies that address major spaceflight risks, but which cannot be ethically studied in humans. Further development of flight-based animal facilities is essential for exploitation of the unique features animal models can offer.

Lastly, the development of effective, time-efficient and comprehensive musculoskeletal countermeasures are essential to mission success, since integrity of musculoskeletal tissues and function is indispensable to optimal performance and injury avoidance on partial gravity surfaces. This will inevitably be a long-term effort and much work still needs to be done in order to clarify sex-based differences and to test combination countermeasure approaches.

2.4. References

Lang T, LeBlanc A, Evans H, Lu Y, Genant H, Yu A. Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. J Bone Miner Res 2004;19:1006-12.

Adams GR, Caiozzo VJ, Baldwin KM. Skeletal muscle unweighting: spaceflight and ground-based models. J Appl Physiol 2003;95:2185-201.

Lecker SH, Jagoe RT, Gilbert A, et al. Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. FASEB J 2004;18:39-51.

Ellman R, Sibonga J, Bouxsein M. Male Astronauts Have Greater Bone Loss and Risk of Hip Fracture following Long Duration Spaceflights than Females. J Bone Miner Res 2010;25 (Suppl 1).

Trappe S, Creer A, Minchev K, et al. Human soleus single muscle fiber function with exercise or nutrition countermeasures during 60 days of bed rest. Am J Physiol Regul Integr Comp Physiol 2008;294:R939-47.

Salanova M, Schiffl G, Puttmann B, Schoser BG, Blottner D. Molecular biomarkers monitoring human skeletal muscle fibres and microvasculature following long-term bed rest with and without countermeasures. J Anat 2008;212:306-18.

Smith SM, Zwart SR, Heer M, et al. WISE-2005: supine treadmill exercise within lower body negative pressure and flywheel resistive exercise as a countermeasure to bed rest-induced bone loss in women during 60-day simulated microgravity. Bone 2008;42:572-81.

Chopard A, Lecunff M, Danger R, et al. Large-scale mRNA analysis of female skeletal muscles during 60 days of bed rest with and without exercise or dietary protein supplementation as countermeasures. Physiol Genomics 2009;38:291-302.

Saito M, Soshi S, Fujii K. Effect of hyper- and microgravity on collagen post-translational controls of MC3T3-E1 osteoblasts. J Bone Miner Res 2003;18:1695-705.

Liu Y, Wang E. Transcriptional analysis of normal human fibroblast responses to microgravity stress. Genomics Proteomics Bioinformatics 2008;6:29-41.

Kaplansky AS, Durnova GN, Burkovskaya TE, Vorotnikova EV. The effect of microgravity on bone fracture healing in rats flown on Cosmos-2044. Physiologist 1991;34:S196-9.

Chappard D, Alexandre C, Palle S, et al. Effects of a bisphosphonate (1-hydroxy ethylidene-1,1 bisphosphonic acid) on osteoclast number during prolonged bed rest in healthy humans. Metabolism 1989;38:822-5.

Carnino A, Roffino S, Chopard A, Marini JF. Effects of a 14-day spaceflight on soleus myotendinous junction ultrastructure in the rhesus monkey. J Gravit Physiol 2000;7:S65-8.

Roffino S, Carnino A, Chopard A, Mutin M, Marini JF. Structural remodeling of unweighted soleus myotendinous junction in monkey. C R Biol 2006;329:172-9.

Provenzano PP, Martinez DA, Grindeland RE, et al. Hindlimb unloading alters ligament healing. J Appl Physiol 2003;94:314-24.

Martinez DA, Vailas AC, Vanderby R, Jr., Grindeland RE. Temporal extracellular matrix adaptations in ligament during wound healing and hindlimb unloading. Am J Physiol Regul Integr Comp Physiol 2007;293:R1552-60.

Kolber MJ, Beekhuizen KS, Cheng MS, Hellman MA. Shoulder injuries attributed to resistance training: a brief review. J Strength Cond Res 2010;24:1696-704.

Wilkerson MK, Muller-Delp J, Colleran PN, Delp MD. Effects of hindlimb unloading on rat cerebral, splenic, and mesenteric resistance artery morphology. J Appl Physiol 1999;87:2115-21.

Fei J, Peyrin F, Malaval L, Vico L, Lafage-Proust MH. Imaging and quantitative assessment of long bone vascularization in the adult rat using microcomputed tomography. Anat Rec (Hoboken) 2010;293:215-24.

Ahdjoudj S, Lasmoles F, Holy X, Zerath E, Marie PJ. Transforming growth factor beta2 inhibits adipocyte differentiation induced by skeletal unloading in rat bone marrow stroma. J Bone Miner Res 2002;17:668-77.

Gueguinou N, Huin-Schohn C, Bascove M, et al. Could spaceflight-associated immune system weakening preclude the expansion of human presence beyond Earth's orbit? J Leukoc Biol 2009;86:1027-38.

Shaw HM, Benjamin M. Structure-function relationships of entheses in relation to mechanical load and exercise. Scand J Med Sci Sports 2007;17:303-15.

Fincke EM, Padalka G, Lee D, et al. Evaluation of shoulder integrity in space: first report of musculoskeletal US on the International Space Station. Radiology 2005;234:319-22.

Bonnarens F, Einhorn TA. Production of a standard closed fracture in laboratory animal bone. J Orthop Res 1984;2:97-101.

Sarmiento A, Schaeffer JF, Beckerman L, Latta LL, Enis JE. Fracture healing in rat femora as affected by functional weight-bearing. J Bone Joint Surg Am 1977;59:369-75.

Bandstra ER, Thompson RW, Nelson GA, et al. Musculoskeletal changes in mice from 20-50 cGy of simulated galactic cosmic rays. Radiat Res 2009;172:21-9.

Gridley DS, Obenaus A, Bateman TA, Pecaut MJ. Long-term changes in rat hematopoietic and other physiological systems after high-energy iron ion irradiation. Int J Radiat Biol 2008;84:549-59.

Guan J, Stewart J, Ware JH, Zhou Z, Donahue JJ, Kennedy AR. Effects of dietary supplements on the space radiation-induced reduction in total antioxidant status in CBA mice. Radiat Res 2006;165:373-8.

Willey JS, Livingston EW, Robbins ME, et al. Risedronate prevents early radiation-induced osteoporosis in mice at multiple skeletal locations. Bone 2010;46:101-11.

Yumoto K, Globus RK, Mojarrab R, et al. Short-term effects of whole-body exposure to (56)fe ions in combination with musculoskeletal disuse on bone cells. Radiat Res 2010;173:494-504.

Shackelford LC, LeBlanc AD, Driscoll TB, et al. Resistance exercise as a countermeasure to disuse-induced bone loss. J Appl Physiol 2004;97:119-29.

Loehr JA, Lee SM, English KL, et al. Musculoskeletal Adaptations to Training with the Advanced Resistive Exercise Device. Med Sci Sports Exerc 2010.

Belavy DL, Miokovic T, Armbrecht G, Rittweger J, Felsenberg D. Resistive vibration exercise reduces lower limb muscle atrophy during 56-day bed-rest. J Musculoskelet Neuronal Interact 2009;9:225-35.

Belavy DL, Beller G, Armbrecht G, et al. Evidence for an additional effect of whole-body vibration above resistive exercise alone in preventing bone loss during prolonged bed rest. Osteoporos Int 2010.

Vico L, Chappard D, Alexandre C, et al. Effects of a 120 day period of bed-rest on bone mass and bone cell activities in man: attempts at countermeasure. Bone Miner 1987;2:383-94.

LeBlanc AD, Driscol TB, Shackelford LC, et al. Alendronate as an effective countermeasure to disuse induced bone loss. J Musculoskelet Neuronal Interact 2002;2:335-43.

Chopard A, Arrighi N, Carnino A, Marini JF. Changes in dysferlin, proteins from dystrophin glycoprotein complex, costameres, and cytoskeleton in human soleus and vastus lateralis muscles after a long-term bedrest with or without exercise. FASEB J 2005;19:1722-4.

Simonov PV. [The "bright spot of consciousness"]. Zh Vyssh Nerv Deiat Im I P Pavlova 1990;40:1040-4.

Prisby RD, Lafage-Proust MH, Malaval L, Belli A, Vico L. Effects of whole body vibration on the skeleton and other organ systems in man and animal models: what we know and what we need to know. Ageing Res Rev 2008;7:319-29.

Rittweger J. Vibration as an exercise modality: how it may work, and what its potential might be. Eur J Appl Physiol 2010;108:877-904.

McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. Nature 1997;387:83-90.

Rittweger J, Beller G, Armbrecht G, et al. Prevention of bone loss during 56 days of strict bed rest by side-alternating resistive vibration exercise. Bone 2010;46:137-47.

Litvinova KS, Vikhlyantsev IM, Kozlovskaya IB, Podlubnaya ZA, Shenkman BS. Effects of artificial support stimulation on fiber and molecular characteristics of soleus muscle in men exposed to 7-day dry immersion. J Gravit Physiol 2004;11:P131-2.

Infanger M, Kossmehl P, Shakibaei M, et al. Longterm conditions of mimicked weightlessness influences the cytoskeleton in thyroid cells. J Gravit Physiol 2004;11:P169-72.

De-Doncker L, Picquet F, Falempin M. Effects of cutaneous receptor stimulation on muscular atrophy developed in hindlimb unloading condition. J Appl Physiol 2000;89:2344-51.

Kyparos A, Feeback DL, Layne CS, Martinez DA, Clarke MS. Mechanical stimulation of the plantar foot surface attenuates soleus muscle atrophy induced by hindlimb unloading in rats. J Appl Physiol 2005;99:739-46.

Genc KO, Gopalakrishnan R, Kuklis MM, et al. Foot forces during exercise on the International Space Station. J Biomech 2010;43:3020-7.

3 Cardiovascular, Lungs and Kidneys

3.1. Relevance of Research on the Cardiovascular System, Lungs and Kidneys

3.1.1. Relevance for space exploration missions

Ensuring adequate cardiovascular health in the astronaut and cosmonaut population is a critical aspect of long-duration space travel. Experience on the ISS has shown that missions greater than 6 months in duration, even with substantial amounts of exercise, will have significant effects and degradations in cardiovascular function in the form of orthostatic intolerance and a lower level of cardiac performance. In long-duration exploration-class missions, (e.g. a 6 month lunar stay or a visit to a near-Earth object) crew must be able to function adequately in a hypo-gravity or zero gravity environment, and then be able to return safely to Earth. On a very long-duration mission, such as a mission to Mars, crew members must be able to function on the Martian surface after long periods in zero gravity, and then return to Earth after an even longer zero gravity exposure. Several key areas remain unknown or poorly defined to ensure the crew's ability to succeed in these missions at this time.

In such exploration class missions, crews will be exposed to extraterrestrial dusts which will inevitably be transported into the habitats, and these dusts are thought to have a high potential of being toxic. These fine dusts will be inhaled, and in the low gravity environment, will be transported deeper into the lung where they will likely remain for extended periods of time, which will likely enhance their toxicity.

Changes in blood chemistry brought about by spaceflight including blood volume reductions, potential dietary effects, and increased calcium resulting from bone demineralisation all have the potential to increase the risk of developing kidney stones. With the development of kidney stones come significant risks to overall mission success and thus prevention is a critical issue.

3.1.2. Earth benefits and applications

Heart disease is a leading cause of death in the terrestrial population. Space travel results in significant and rapid degradation of cardiovascular performance in a healthy population (astronauts and cosmonauts), providing the potential to understand the factors that lead to cardiovascular disease here on Earth. Many workers are exposed to dusty environments in the workplace and particulate matter in the environment is a known health risk to urban populations. Further, many drugs are now delivered in aerosol form, and so a comprehensive understanding of the deposition and subsequent clearance of deposited particles is of considerable importance in both areas. Developing a more complete understanding of the role of diet and other effects in the development of kidney stones stands to improve the health and reduce the suffering of a large percentage of the Earth population.

3.2. Cardiovascular, Lungs and Kidneys – Key Issues

The expert group on cardiovascular, kidneys and lung functions delineated five key issues of importance for future exploration.

The issues identified here all have the potential to seriously impair a successful exploration-class mission, and to a lesser extent, spaceflight in low earth orbit. They are considered high priority research targets by the Expert Group.

3.2.1. Key issue 1: What are the in-flight alterations in cardiac structure and function?

Relevance for space exploration missions

Cardiovascular deconditioning has always been observed after spaceflight and ground simulations (bed rest, water immersion). This poses a threat to astronauts upon arrival to the Moon and Mars, and after return to Earth.

Earth benefits and applications

Similar problems occur in patients after prolonged bed rest due to trauma surgery and other conditions forcing the patient to stay bedridden for extended periods of time.

Brief review of latest developments

The optimal countermeasure is yet to be defined but planned developments include artificial gravity and various exercise modes.

Knowledge gaps and research needs

Figure 6: Lunar dust stuck to the astronaut's spacesuit will inevitably be transferred into the space habitat (Credit: NASA)

The effects of prolonged space flight on myocardial mass, intrinsic contractility, myocardial compliance and autonomic neuro-regulation are currently unknown. Further, the interaction with peripheral circulation is complex and it is not known whether cardiac changes observed thus far are primarily cardiac or are due to secondary to changes in the peripheral circulation. [Also see following Key Issue].

Proposed investigations and recommendations

- Dynamic responses of cardiac function to exercise/ orthostatic tests simulating different phases of Moon and Mars exploration missions.
- Bed rest simulations of relevant durations, and dry immersion simulations (up to 2 weeks)
- Cardiac muscle structure by advanced echocardiography.
- Simultaneous monitoring of 1) cardiac function (cardiac output), 2) 24-h blood pressure, 3) sympathetic nervous activity, 4) plasma concentrations of vasoactive hormones (vasopressin, catecholamines, natriuretic peptides and renin-angiotensin-aldosterone).
- Monitoring of cardiovascular function during lower body negative pressure and dynamic exercise.
- Develop tolerable 24h blood pressure monitoring.

As a justification for the more complex 24 h arterial blood pressure recording, as compared to single-point measurements, the latter are considered to be much less representative for the state of the subject and can be subject to emotional influences from the procedure itself (white coat hypertension).

Trans-disciplinary aspects

- Thermoregulation changes in microgravity, and may impact both metabolic and cardiovascular control.
- Radiation may interact with cardiovascular degradation/ repair processes.
- Mental stress and sleep disorders are likely to influence cardiovascular health.

3.2.2. Key issue 2: What is the influence of spaceflight on structure and function of blood vessels?

Relevance for space exploration missions

Orthostatic intolerance is frequently found after spaceflight and bed rest simulations, and may be a hazard to the astronaut and/or to other aspects of mission success including activities on the surfaces of Moon and Mars.

Earth benefits and applications

Orthostatic intolerance is frequently observed in patients after bed rest, during circumstances that reduce blood volume, and with the use of certain medications.

Brief review of latest developments

Orthostatic intolerance has a multifactorial causation including reduced blood volume and attenuated constriction of resistance vessels. Recent results implicate central-nervous processing and/or alpha adrenergic receptor dysfunction in post-flight orthostatic intolerance.

Knowledge gaps and research needs

- The effects of long-term weightlessness on the structure of the arterial resistance vessels and to what degree it counteracts the development of hypertension is currently unknown.
- It is currently unknown why the paradox exists that in space, sympathetic nervous activity is augmented while the arterial resistance vessels are dilated. This has implications for understanding the role of gravity in the development of hypertension.
- Currently, nothing is known about the influence of space environment on the mechanotransduction signals and their influence on endothelial functions. [Also see previous Key Issue]

Proposed investigations and recommendations

- To simultaneously monitor cardiac output, blood pressure, sympathetic nervous activity, and plasma concentrations of vasoactive hormones (vasopressor and natriuretic vasodilatory substances), as well as the distribution of cardiac output to different vascular beds.
- Evaluate the effects of simulated low gravity on structure and function of blood vessels, utilising bed rest and other analogues such as dry immersion.

Trans-disciplinary aspects

The interaction between muscle and peripheral vessels should be considered in the design of experiments and countermeasures.

3.2.3. Key issue 3: What level of cardiovascular function loss is acceptable and what type and quantity of exercise is necessary to ensure that this loss is not exceeded?

Relevance for space exploration missions

Countermeasures aimed at maintaining the full capacity of astronauts have a significant cost in terms of mass, energy and time. However, it may not always be necessary to maintain this full capacity in order to complete a safe and successful space mission, and there may be an acceptable degree of deconditioning.

Earth benefits and applications

Effective methods can also be used to prevent cardiovascular deconditioning or improve rehabilitation of patients on Earth. Also, more effective methods can be used on the ground to regain good health in sedentary populations and to maintain a good health status in aging populations.

Brief review of latest developments

Neither resistive nor aerobic exercise alone is adequate to prevent deconditioning in spaceflight. The current exercise prescription used in ISS does not entirely prevent deconditioning.

Knowledge gaps and research needs

- What is the requirement for cardiovascular performance upon arrival at the Moon or Mars?
- What are the appropriate exercise prescriptions required to achieve such performance?
- How can the level of deconditioning that is acceptable to crews who must be rehabilitated upon return to Earth be determined?

Proposed investigations and recommendations

- On Earth, comparison studies of LBNP/exercise and centrifuge/exercise countermeasures focused on effectiveness on cardiovascular, muscular, bone and neurovestibular systems are suggested.
- Different kinds and duration of exercises must be tested to determine the adequate amount of exercise needed. Short-term, middle-term and long-term bed rest studies are required.

Trans-disciplinary aspects

Countermeasures against cardiovascular degradation could/should be combined with countermeasures against musculoskeletal degradation.

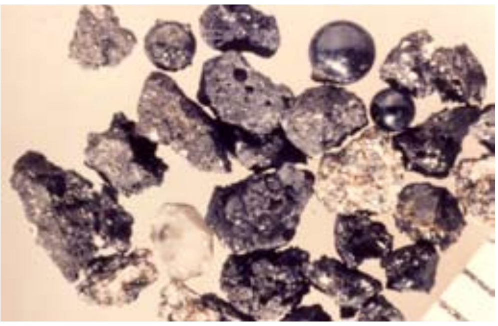

Figure 7: Lunar dust is covered in a glassy coating that can either be smooth or jagged (Credit: Larry Taylor

3.2.4. Key issue 4: What are the risks associated with exposure to extra-terrestrial dust?

Relevance for space exploration missions
In exploration class missions, crews will be exposed to extraterrestrial dusts which will inevitably be transported into the habitats, and these dusts may potentially be highly toxic. These fine dusts can easily be inhaled, and in a low gravity environment, the particles will be transported deeper into the lung where they will likely remain for extended periods of time. This will likely enhance their toxicity.

Earth benefits and applications

Many workers are exposed to dusty work environments and particulate matter in the environment is a known health risk to urban populations. Further, many drugs are now delivered in aerosol form, and therefore a comprehensive understanding of the deposition and subsequent clearance of deposited particles is of considerable importance in both areas.

Brief review of latest developments

The European Space Agency (ESA) has plans for unmanned missions to define the physical and chemical properties of lunar dust in the South Polar Region.

Knowledge gaps and research needs

- Size distribution, toxicity and physical properties of the dust
- The spatial pattern of particle deposition in micro and low gravity is unknown.
- Lung clearance rates in micro and low gravity are unknown. Past and on-going studies suppose clearance rates in low gravity are identical to 1G.
- Individual variation in airway tree geometry might be a major determinant of particle deposition and subsequent clearance.

Proposed investigations and recommendations

- Studies of toxicity of lunar dust and its passivation rate performed either in-situ (would require unmanned lunar surface exploration) or on Earth using samples collected from future lunar missions and stored in appropriate condition to maintain their "freshly fractured" properties.
- Study the effects of micro and low gravity on the clearance rate. This will require access to human suborbital or orbital flights.
- Scintigraphic and/or fluorescent imaging studies of aerosol deposition and subsequent clearance in the lung either in humans or in an animal model with a focus on the alterations in both deposition and clearance that result from reduced gravity.

Trans-disciplinary aspects

Radiation may interact with pulmonary degradation/ repair processes.

3.2.5. Key issue 5: What are the roles of diet and bone demineralisation on kidney stone formation and is it possible to predict the risk of kidney stones?

Relevance for space exploration missions

Despite the fact that astronauts are pre-screened during selection to be non-kidney stone formers, a significant number of events with renal stones have been reported from the US and Russian space programmes. A calculus in the urinary system could have significant health consequences for an astronaut and could also have a negative impact on the mission as a whole.

Earth benefits and applications

A better insight into the factors that cause an increased risk for renal stone formation in astronauts is likely to benefit many individuals on the ground that suffer from renal stones or an increased likelihood of suffering from renal stones. Apart from being extremely painful renal stones may also lead to complications such as infections and hydronephrosis.

Brief review of latest developments

Ingestion of sufficient amounts of fluids and of potassium citrate in astronauts has been shown to counteract changes in urinary composition that are known to favour renal stone formation.

Knowledge gaps and research needs

- Can regimes other than fluid and potassium citrate ingestion mitigate renal stone formation?
- Can potassium citrate ingestion increase the risk for brushite stones?
- How does renal stone formation relate to bone loss during very long space missions?

Proposed investigations and recommendations

- Further studies should be performed of the mechanisms for renal stone formation during the post-flight period.
- Improved methods to identify the risks for renal stones at the time of selection should be developed, since present routines have proven inadequate.
- Improved methods to suppress bone atrophy should be developed.

Trans-disciplinary aspects

The interactions between kidney stone formation and nutrition must be considered, and a close coordination with programmes to prevent bone atrophy appears necessary.

3.3. References

Aubert AE, Verheyden B, d'Ydewalle C, Beckers F, Van den Bergh O. Effects of mental stress on autonomic cardiac modulation during weightlessness. Am J Physiol Heart Circ Physiol. 2010 Jan;298(1):H202-9. Epub 2009 Nov 6.

Baevsky RM, Baranov VM, Funtova II, Diedrich A, Pashenko AV, Chernikova AG, Drescher J, Jordan J, Tank J. Autonomic cardiovascular and respiratory control during prolonged spaceflights aboard the International Space Station. J Appl Physiol. 2007 Jul;103(1):156-61.

Baevsky RM, Moser M, Nikulina GA, Polyakov VV, Funtova II, Chernikova AG. Autonomic regulation of circulation and cardiac contractility during a 14-month space flight. Acta Astronaut. 1998 Jan-Apr;42(1-8):159-73.

Baevsky RM, Petrov VM, Cornelissen G, Halberg F, Orth-Gomer K, Akerstedt T, Otsuka K, Breus T, Siegelova J, Dusek J, Fiser B. Meta-analyzed heart rate variability, exposure to geomagnetic storms, and the risk of ischemic heart disease. Scr Med (Brno). 1997 Jul;70(4-5):201-6.

Baevsky RM, Bennett BS, Bungo MW, Charles JB, Goldberger AL, Nikulina GA. Adaptive responses of the cardiovascular system to prolonged spaceflight conditions: assessment with Holter monitoring. J Cardiovasc Diagn Proced. 1997 Summer;14(2):53-7.

Baranov VM, Demin EP, Kotov AN, Kolesnikov VI, Mikhaĭlov VM, Ushakov BB, Tikhonov MA. Comparative evaluation of several methods preventing orthostatic disorders during simulation of the end-of-space-mission factors. Aviakosm Ekolog Med. 2003;37(4):17-23. Russian.

Baranov VM, Tikhonov MA, Kotov AN, Kolesnikov VI. Some mechanisms of modeling the hydrostatic component of hemodynamics in microgravity]. Aviakosm Ekolog Med. 2000;34(4):27-31. Russian.

Baranov VM, Tikhonov MA, Kotov AN, Kolesnikov VI, Kuchin SN, Letkova LI, Tikhomirov EP. Prevention of respiratory muscles deconditioning and deterioration of aerobic working capacity in prolonged weightlessness and hypokinesia]. Aviakosm Ekolog Med. 1998;32(6):36-42. Russian.

Buckey JC Jr, Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Moore WE, Gaffney FA, Blomqvist CG. Orthostatic intolerance after spaceflight. J Appl Physiol. 1996 Jul;81(1):7-18.

Carpenter, JD, Angerer, O, Durante, M, Linnarsson, D, Pike, WT. Life Sciences Investigations for ESA's First Lunar-Lander. Earth Moon Planets DOI 10.1007/s11038-010-9375-y, 2010.

Christensen NJ, Heer M, Ivanova K, Norsk P. Sympathetic nervous activity decreases during head-down bed rest but not during microgravity.J Appl Physiol. 2005 Oct;99(4):1552-7.

Donina ZhA, Lavrova IN, Tikhonov MA, Kotov AN, Kolesnikov VI, Baranov VM. The dynamic of breathing biomechanics and intrathoracic hemodynamics parameters during microgravity modeling. Ross Fiziol Zh Im I M Sechenova. 2005 Sep;91(9):1091-6. Russian.

Donina ZhA, Lavrova IN, Tikhonov MA, Kotov AN, Kolesnikov VI, Baranov VM. Influence of changes in intrathoracic and central venous pressure on cardiac filling dynamics. Bull Exp Biol Med. 2003 Dec;136(6):540-2.

Convertino VA. Status of cardiovascular issues related to space flight: Implications for future research directions. Respir Physiol Neurobiol. 2009 Oct;169 Suppl 1:S34-7.

Darquenne C, Prisk GK. Deposition of inhaled particles in the human lung is more peripheral in lunar than in normal gravity. Eur J Appl Physiol. 2008 Aug;103(6):687-95.

Fomina GA, Kotovskaia AR, Temnova EV. Dynamics of human cardiovascular responses in different periods of long-term exposure in weightlessness. Aviakosm Ekolog Med. 2009 May-Jun;43(3):11-6. Russian.

Fomina GA, Kotovskaia AR, Pochuev VI, Zhernakov AF. Rearrangement of the hemodynamic mechanisms of orthostatic tolerance of humans on long-term space missions. Aviakosm Ekolog Med. 2005 Nov-Dec;39(6):9-17. Russian.

Fomina GA, Kotovskaia AR. Shifts in human venous hemodynamics in long-term space flight. Aviakosm Ekolog Med. 2005 Jul-Aug;39(4):25-30. Russian.

Goldberger AL, Bungo MW, Baevsky RM, Bennett BS, Rigney DR, Mietus JE, Nikulina GA, Charles JB. Heart rate dynamics during long-term space flight: report on Mir cosmonauts. Am Heart J. 1994 Jul;128(1):202-4.

Grigor'ev AI, Baranov VM. Human cardiovascular system under the conditions of a space flight. Vestn Ross Akad Med Nauk. 2003;(12):41-5. Russian.

Grigoriev AI, Egorov AD. The mechanisms involved in cardiovascular system changes during long space flights. Environ Med. 1996 Oct;40(1):1-11. Review.

Grigoriev AI, Huntoon CL, Morukov BV, Lane HW, Larina IM, Smith SM. Endocrine, renal, and circulatory influences on fluid and electrolyte homeostasis during weightlessness: a joint Russian-U.S. project. J Gravit Physiol. 1996 Sep;3(2):83-6.

Grigoriev AI, Morukov BV, Vorobiev DV. Water and electrolyte studies during long-term missions onboard the space stations SALYUT and MIR. Clin Investig. 1994 Feb;72(3):169-89. Review.

Kotov AN, Miniaev VI, Miniaeva AV, Tikhonov MA, Baranov VM. Dependence of the thoracic abdominal ratio of the respiration parameters on body positioning relative to the vector of gravity. Aviakosm Ekolog Med. 2002;36(1):16-20. Russian.

Kotovskaia AR, Fomina GA. The features of adaptation and disadaptation of the human cardiovascular system in the space flight conditions. Fiziol Cheloveka. 2010 Mar-Apr;36(2):78-86. Russian.

Mayorov oYu, Baevsky RM. Application of space technologies for valuation of a stress level. Stud Health Technol Inform. 1999;68:352-6.

Norsk P, Damgaard M, Petersen L, Gybel M, Pump B, Gabrielsen A, Christensen NJ. Vasorelaxation in space. Hypertension. 2006 Jan;47(1):69-73.

Pavy-Le Traon A, Heer M, Narici MV, Rittweger J, Vernikos J. From space to Earth: advances in human physiology from 20 years of bed rest studies (1986-2006). Eur J Appl Physiol. 2007 Sep;101(2):143-94. Epub 2007 Jul 28. Review.

Peterson JB, Prisk GK, Darquenne C. Aerosol deposition in the human lung periphery is increased by reduced-density gas breathing. J Aerosol Med Pulm Drug Deliv. 2008 Jun;21(2):159-68.

Pietrzyk RA, Jones JA, Sams CF, Whitson PA. Renal stone formation among astronauts. Aviat Space Environ Med. 2007 Apr;78(4 Suppl):A9-13.

Prisk GK. The lung in space. Clinics in Chest Medicine 26: 415-438, 2005.

Robertson D, Convertino VA, Vernikos J. The sympathetic nervous system and the physiologic consequences of spaceflight: a hypothesis.Am J Med Sci. 1994 Aug;308(2):126-32.

Shiraishi M, Kamo T, Kamegai M, Baevsky RM, Funtova II, Chernikova A, Nemoto S, Hotta M, Nomura Y, Suzuki T. Periodic structures and diurnal variation in blood pressure and heart rate in relation to microgravity on space station MIR. Biomed Pharmacother. 2004 Oct;58 Suppl 1:S31-4.

Shiraishi M, Kamo T, Nemoto S, Narita M, Kamegai M, Baevsky RM, Funtova II. Blood pressure variability during 120-day head-down bed rest in humans. Biomed Pharmacother. 2003 Oct;57 Suppl 1:35s-38s.

Sides MB, Vernikos J, Convertino VA, Stepanek J, Tripp LD, Draeger J, Hargens AR, Kourtidou-Papadeli C, Pavy-LeTraon A, Russomano T, Wong JY, Buccello RR, Lee PH, Nangalia V, Saary MJ. The Bellagio Report: Cardiovascular risks of spaceflight: implications for the future of space travel. Aviat Space Environ Med. 2005 Sep;76(9):877-95.

Tank J, Baevsky RM, Funtova II, Diedrich A, Slepchenkova IN, Jordan J. Orthostatic heart rate responses after prolonged space flights. Clin Auton Res. 2010 Dec 25. [Epub ahead of print]

Verheyden B, Liu J, Beckers F, Aubert AE. Adaptation of heart rate and blood pressure to short and long duration space missions. Respir Physiol Neurobiol. 2009 Oct;169 Suppl 1:S13-6.

Whitson PA, Pietrzyk RA, Jones JA, Nelman-Gonzalez M, Hudson EK, Sams CF. Effect of potassium citrate therapy on the risk of renal stone formation during spaceflight. J Urol. 2009 Nov;182(5):2490-6. Epub 2009 Sep 17.

Whitson PA, Pietrzyk RA, Morukov BV, Sams CF. The risk of renal stone formation during and after long duration space flight. Nephron. 2001 Nov;89(3):264-70.

Whitson PA, Pietrzyk RA, Sams CF. Urine volume and its effects on renal stone risk in astronauts. Aviat Space Environ Med. 2001 Apr;72(4):368-72.

4 Immunology

4.1. Relevance of Research on Immunology

Relevance for space exploration missions

Spaceflight is a unique stress model, impacted consistently or intermittently by a myriad of stresses including psychosocial and physical stressors, high G-forces at the time of launch and landing, increased radiation, sleep deprivation, microgravity, and nutritional factors. This multitude of factors has profound immune modulatory effects on humans and animals and can lead to immune suppression with compromised defences against infections. Data have shown that spaceflight conditions and/or analogues affect lymphoid organs, peripheral blood leukocyte subsets, the functions of immune cells and the number of bone marrow-derived colony-forming units.

Additionally, changes in microbial growth characteristics and pathogenicity during spaceflight have been observed for several microorganisms (bacteria can more readily proliferate in space). Thus, opportunities for microbes to establish foci of infection are enhanced because space travel stimulates their growth and has a negative impact on immune functions. Furthermore, antibiotics are less effective in space and microbial pathogenicity and virulence are enhanced under real and simulated microgravity.

Consequently, alterations and weakening of the immune system has the potential to be a serious clinical risk and represents an area that should be considered more thoroughly to ensure long-term survival in space stations and sustainable habitation on the Moon or any planet (i.e. Mars). The possible adverse events could each have an immediate impact on mission objectives.

4.1.2. Earth benefits and applications

Immunology is an emerging field of research in which an international approach is used to gather more knowledge on how the immune system is webbed in the pathology and clinical appearance of disease, from it cellular function to an orchestrated, distinctly balanced action of immune functions in the complex human system. From fundamental to clinical Immunology, the link between organ systems and immune responses can be addressed thanks to the emerging knowledge and methodology in Biomedicine to diagnose immune changes from human blood. From clinical investigations in the healthy and the sick, the lifesaving importance of adequate immunity at the switch between the host and the environment was never clear before.

Besides controlling infections and eliminating germs, immunologic responses are also capable of eliminating non-functional or dysfunctional tissue-cells, e.g. tumour cells. However, failure to establish adequate immune responses and to distinguish between "self" and "non-self" can result in autoimmune diseases (e.g. rheumatoid arthritis), acute and life threatening infections, and overwhelming systemic immune responses (e.g. septicemia) or the development of cancer over time. Changes to this endogenous balance of the immune and other organ systems – the so called homeostasis- due to psychological or environmental factors ("stressors") can impact this finely balanced, endo-, para- and autocrine controlled immune function, resulting in immune dysfunction and disease. The understanding of these deregulations together with appropriate tools can help space travellers as much as people on Earth.

Three specific aspects have been identified by the expert group as being highly relevant to life on Earth:

- Understanding stress related immune challenges in space and the knowledge drawn from it is highly relevant to the understanding of the biology of cancer immunology, the balance of Inflammation and endogenous mechanisms to control it or the lack of control (Autoimmunity/Allergies) in the young and ageing population on Earth.
- The translational aspect in highly relevant (e.g. of technological developments for space considered as a highly attractive spin-off, or for the monitoring of immune and health conditions in minute amounts of blood or even non-invasively).

The functions of the immune system can be affected in response to environmental / living conditions (e.g. chronic and acute stress conditions can result in a further parallel interaction between the immune system and other organ systems). As an example, stress causes neurophysiologic responses and hormone liberation which can modulate inflammation but also promote bone resorption. These and other cross-interactions are also likely to occur with metabolic /nutritional changes as well as sedentary life style and aging. These interactions, despite their broad importance for public health and prevention of disease, are not yet acknowledged.

4.2. Brief Review of Latest Developments

Figure 8: During Extra Vehicular Activities (EVAs), astronauts are subject to many environmental stressors (Credit: NASA)

4.2.1. Research using isolated cell systems

It has been shown that activation of T cells is strongly impaired when subjected to the stresses associated with µG (Cogoli et al., Science, 1984, 225, 228-230). Despite important findings on cells proliferation and communication, the pathophysiological cellular pathways and complex molecular mechanisms remain to be investigated. For now and on the basis of current data and recent publications, it can be concluded that the conditions of microgravity are affecting and impairing the communication between cells of the immune system and can results in the alteration of intracellular signalling pathways. "Gravi-sensitive" signal transduction elements were found in several different cell compartments. These were found on the cell surface (such as the IL-2 and the interleukin-2 receptor which is critical in the regulation of the T-cell proliferation and differentiation), in the cytoplasma (e.g. protein kinase C enzyme family controlling function of other intracellular proteins) and in the nucleus (e.g. genes regulating cellular processes of the cells´ proliferation and differentiation). However, the key molecular mechanism(s) of how microgravity affects cells´ signalling are still unknown (summarised from Ullrich O., Huber K., Lang K., Cell Commun Signal. 2008; 6: 9.).

4.2.2. Research using animal experiments: from model organisms to mice

Following the general observations on stress responses, as described by Hans Selye more than half a century ago, it was shown in mice flown on a 13-day mission to space that the murine spleen and thymus masses were significantly reduced as well as the number of splenic leukocytes when they were compared to mice that were kept as ground controls under similar housing conditions. In addition, the responses of immune cells when challenged ex vivo with bacterial peptides were reduced. The same observation was made when these cells were activated through T-cell receptor dependent pathways. This modulation of distinct immune answers indicates increased immunosuppresive mechanisms [Baqai FP, Gridley DS, Slater JM, Luo-Owen X, Stodieck LS, Ferguson V, Chapes SK, Pecaut MJ; J Appl Physiol. 2009 Jun;106(6):1935-42.]. Other studies showed that T cell distribution, function, as well as gene expression pattern were also significantly affected when more complex organisms, such as mice, are subjected to the stressful conditions of space flight.

Along with these observations it is interesting to note that space flight induces significant changes in mRNA expression in the thymus, especially in genes known to regulate stress, glucocorticoid receptor metabolism, and the T-cell signalling activity. Studies performed using an amphibian model showed that space flight may also affect antibody production in response to an antigenic stimulation. Indeed, the expression of the physiological counterpart of mammalian IgA molecules was increased in flown animals, as previously reported in cosmonauts (Konstantinova et al. 1993). Furthermore, the use of the different VH gene subgroups (Boxio et al., 2005), the expression of individual VH genes (Bascove et al., 2009) and the somatic hyper-mutation process were shown to be affected under space flight conditions (Bascove et al., 2011). Together with other results, these data give further evidence of the complex compromise of immunity after animals are subjected to multiple stressors during space flight [Lebsack TW, Fa V, Woods CC, Gruener R, Manziello AM, Pecaut MJ, Gridley DS, Stodieck LS, Ferguson VL, Deluca DJ Cell Biochem. 2010 May 15;110(2):372-814].

4.2.3. Investigations in humans

Astronauts are very important to this domain of research because they allow extending and transferring the knowledge gathered from cell and animal experiments to humans and approaching the consequences of multi-factorial effects of physical stressors and emotional stress in humans. Investigations have been undertaken by applying complementary and elaborated blood, urine and saliva analyses together with questionnaires based emotional stress monitoring, to astronauts exposed to space flight. These investigations in man ranged from very acute gravitational stress challenges (e.g. during parabolic flight) to short (in the range of one to two weeks) and long (4-7 months) ISS increments. These studies revealed that space flight conditions induce a significant modulation of the human immune responsiveness. These alterations range from an alert state of primed innate immune cell after acute gravitational stress to a decrease of phagocytes, NK, T-lymphocytes functional activity and also in their altered capacity to produce important cell signalling molecules (such as cytokines) after returning from the space mission.

Moreover, tests using peripheral leukocyte subsets show that the early T cell activation and the intracellular or secreted cytokine pattern indicate a Th1<Th2 shift. It has also been shown that adrenocortical stress-responses reflecting sympathetic nervous system responses predominate especially after short duration missions. In contrast, month-long missions to space were characterised by glucocorticoid-mediated changes. It is important to note that other, non-catecholamine and non-glucocorticoid, stress-response systems elicit immune targeted properties. Among those, the phylogenetically old and preserved endocannabinoid system was shown to be activated under acute gravitational stress conditions (Choukèr et al, PloSONe2010), as well as in space (Choukèr et al, not published). Complementarily, Earth-bound studies conducted in so-called space flight analogue conditions have provided further evidence of emotional stress-sensitive immune changes in man [also summarised in ELGRA-Ullysee Publikation (Ed. J. v. Loon), chapter 3.2.6 "Human Physiology" by Gilles Clément, Laurence Vico and Alexander Choukèr 2011; Kaufmann I, Schachtner T, Feuerecker M, Schelling G, Thiel M, Choukèr A.; Eur J Clin Invest. 2009 Aug;39(8):723-8.; Morukov VB, Rykova MP, Antropova EN, Berendeeva TA, Ponomarev SA, Larina IM; Fiziol Cheloveka. 2010 May-Jun;36(3):19-30; Crucian BE, Stowe RP, Pierson DL, Sams CF; Aviat Space Environ Med. 2008 Sep;79(9):835-43.; Stowe RP, Sams CF, Pierson DL; Aviat Space Environ Med. 2003 Dec;74(12):1281-4. ; Choukèr A, Kaufmann I, Kreth S, Hauer D, Feuerecker M, Thieme D, Vogeser M, Thiel M, Schelling G.,PLoS One. 2010 May 21;5(5):e10752].

4.3. Immunology – Key Issues

4.3.1. List of key issues

The Expert Group identified eight key issues as important aspects to be considered in the future:

- Identification and quantification of stress factors and their impact on the immune system
- Are immune system development, response and regulation as efficient in space (ISS/Moon/Mars) as on Earth?
- Consequences of long-duration (≥1 year) missions on the degree of immune-suppression
- Consequences of "chronic" immune changes on disease during and after long-duration missions
- Effects of Lunar or Mars dusts, habitat environment & other chemicals on immune performance
- Are the observed stress-dependent virus reactivation patterns linked to cancer development?
- Interaction between the immune system and other stress-sensitive systems (neuro-physiological and others)
- Definition and testing of (immune targeted) countermeasures

In order to understand and track the footprint of space exploration on the human immune system and its interactions with other organ entities, it appears crucial that these key issues are addressed through an appropriate technical and structural framework. In this context, three interlinked approaches are highly recommended:

- Pathophysiological cellular pathways and complex molecular mechanisms need to be considered using isolated cell systems.
- Implementation of animal experiments (e.g. mice) would produce further data, allowing investigations on the complex systemic compromise of the immune system after exposure to multiple stressors during space flight
- Finally, investigations in man have to be performed in a coordinated way to better approach the consequences of multi-factorial effects of physical stressors and emotional stress induced by space flight.

4.3.2. Knowledge gaps and research needs

- In the light of future manned spaceflight for exploration, extension of the ISS Increments for (some) ISS astronauts/cosmonauts to one year or longer has been considered by all EG members of very high importance (and was confirmed by the majority of investigators participating to the online consultation to be of high or very high importance) to answer immune related questions for future, extended space missions to the Moon and Mars.
- The methodological needs to achieve this goal include the development of in-flight hardware to perform easy-to-handle assays and minimal/non-invasive exams to monitor immune and haemostatic changes. This was considered to be of very high importance by the EG as well as by 90% of the consulted specialists.
- To achieve a higher relevance of the data gathered, especially for critical investigations, a need of i) redundant repeating (at least twice) of in-flight experiments and ii) some standardisation of experiment design, methods, assays etc. is requested. Both points were considered of high or very high importance by >90% of the scientists that were consulted.
- Before going to space, test and control experiments should be performed using the full scale of Earth-bound models that can adequately simulate specific spaceflight conditions. 50% of the respondents considered this point as very highly relevant and 40% as highly relevant.
- For space and Earth, the establishment of a bank of tissue and plasma samples available to the scientific community was defined by the majority of EG members and external experts (>90%) to be very important to extract maximal information as well as to re-analyse samples when new tools become available.
- Taking advantage of health data files from ISS crewmembers, with retrospective and prospective access, is necessary in order to estimate clinically relevant changes of health in regard to immune alterations (crew data would be anonymous). E.g. stress-dependent virus reactivation

patterns linked to cancer development and consequences of "chronic" immune changes during and after long-duration space missions on disease development.

4.3.3. Proposed investigations and recommendations

- The immune system is a target and a sensor of change in the environmental conditions ("stressors") affecting the human system as a whole. Therefore, only interdisciplinary approaches can help to understand (immune-) homeostasis and how immune functions are affected through other organ systems, under the conditions of acute or chronic stress in space and on Earth, respectively.
- Multidisciplinary approaches should include the full-scale use of available methods from in-vitro to experimental in-vivo (rodents or other animal models, knock-out models also in space) conditions, as well as clinical and space related earth-bound studies (also for countermeasure development). This will further enhance the understanding and interaction of the immune system response and regulation with other organ systems at the cellular and molecular level.
- There is a need to standardise methodologies used for immune research as well as the consideration to do redundant experiments.
- The establishment of an international biological sample archive (from space crew members) is recommended.
- Provision of access to anonymous health data from crew members, retrospectively and prospectively, is recommended.
- There is a need to diagnose immune changes in minute amounts of blood through new non-invasively technologies, a benefit for both space and Earth.

Figure 9: ESA's Aurora Programme aims to prepare Europe to play a key role in the future human exploration of the solar system. Using the ISS as a test bed/analogue for a Martian mission has been proposed as a necessary research platform for many domains. (Credits: ESA - P. Carril)

4.3.4. Cross-disciplinary aspects

The immune system is one of the largest and most widespread "organs" with hormonal and neuronal control. Moreover, antigenic patterns as well as metabolic factors define immune answers and regulate immunity, respectively.

This understanding shows that the immune system is strongly linked with almost every organ homeostasis and can be affected together with other systems upon stress challenges (e.g.: Stress-> stress hormones which can modulate both immune responses as well as e.g. catabolic, stress permissive bone turnover). Moreover, immune responses are susceptible to exercise and nutritionals factors as well as environmental factors like radiation, and the microbial load and the oxygen tension in the habitat.

Therefore, there are manifold, non-selective interactions with other fields and topics:

- Bone, muscle, kidney
- Neurophysiology, cognitive performance
- Nutrition
- Exercise, cardiovascular & lung
- Habitat environment and design (e.g. oxygen level, changes of psychic stress in respective more comfortable habitat)
- Health: prevention, diagnosis and therapy
- Radiation (immune dysfunction)

The immune system can also be affected directly or indirectly by countermeasures:

- Direct affect countermeasures: e.g. vaccination (boost), pharmacological approaches
- Indirect affect countermeasures: Nutrition, exercise, psychosocial procedures etc.

4.4. Conclusion

Appropriate functioning of the immune system is a critical factor to maintain crew health. Therefore, it is crucial to understand the biology of immune modulation under stress conditions in order to re-establish immune homeostasis under such conditions. To achieve this goal, maximum exploitation of currently available resources on Earth and in space, as well as respective databases, is mandatory. This also applies to testing under conditions in space which are similar to a manned exploration space mission to Mars.

In conclusion, the Expert Group "Immunology" recommends acknowledgement of the abovementioned key recommendations and also, in the light of extended human exploration mission, to take more advantage of the ISS by increasing the increment duration for two to three ISS crew members to 12 months or longer and investigate immune changes under these conditions.

4.5. References (other than included in the text)

Bascove M, Huin-Schohn C, Guéguinou N, Tschirhart E, Frippiat JP. Spaceflight-associated changes in immunoglobulin VH gene expression in the amphibian Pleurodeles waltl. FASEB J. 2009 May;23(5):1607-15.

Boonyaratanakornkit JB, Cogoli A, Li CF, Schopper T, Pippia P, Galleri G, et al. Key gravity-sensitive signaling pathways drive T cell activation. Faseb J 2005;19(14):2020-2.

Boxio R, Dournon C, Frippiat JP. Effects of a long-term spaceflight on immunoglobulin heavy chains of the urodele amphibian Pleurodeles waltl. J Appl Physiol. 2005 Mar;98(3):905-10

Choukèr A (Ed.), Stress Challenges and Immunity in Space. Springer 2011 (in press)

Choukèr A, Thiel M, Lukashev D, Ward JM, Kaufmann I, Apasov S, Sitkovsky MV, Ohta A. Critical role of hypoxia and A2A adenosine receptors in liver tissue-protecting physiological anti-inflammatory pathway. J Mol Med. 2008 Mar-Apr;14(3-4):116-23.

Crucian B, Sams C. Immune system dysregulation during spaceflight: clinical risk for exploration-class missions. J Leukoc Biol 2009;86(5):1017-8.

de Quervain DJ, Aerni A, Schelling G, Roozendaal B. Glucocorticoids and the regulation of memory in health and disease. Front Neuroendocrinol. 2009 Aug; 30(3):358-70.

Gueguinou N, Huin-Schohn C, Bascove M, Bueb JL, Tschirhart E, Legrand-Frossi C, Frippiat JP. Could spaceflight-associated immune system weakening preclude the expansion of human presence beyond Earth's orbit? J Leukoc Biol 2009;86(5):1027-38

Gridley DS, Slater JM, Luo-Owen X, Rizvi A, Chapes SK, Stodieck LS, et al. Spaceflight effects on T lymphocyte distribution, function and gene expression. J Appl Physiol 2009;106(1):194-202.

Kaufmann I, Feuerecker M, Salam A, Schelling G, Thiel M, Choukèr A. Adenosine A2A receptor modulates the oxidative stress response of primed polymorphonuclear leukocytes after parabolic flight. Hum Immunol 2011 (in press).

Meehan RT, Neale LS, Kraus ET, Stuart CA, Smith ML, Cintron NM, et al. Alteration in human mononuclear leucocytes following space flight. Immunology 1992;76(3):491-7.

Pierson DL, Stowe RP, Phillips TM, Lugg DJ, Mehta SK. Epstein-Barr virus shedding by astronauts during space flight. Brain Behav Immun 2005;19(3):235-42.

Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. Nat Rev Neurosci. 2009 Jun;10(6):423-33

Thiel M, Choukèr A, Ohta A, Jackson E, Caldwell C, Smith P, Lukashev D, Bittmann I, Sitkovsky MV. Oxygenation inhibits the physiological tissue-protecting mechanism and thereby exacerbates acute inflammatory lung injury. PLoS Biol. 2005 Jun;3(6)

Sonnenfeld G, Foster M, Morton D, Bailliard F, Fowler NA, Hakenewerth AM, et al. Spaceflight and development of immune responses. J Appl Physiol 1998;85(4):1429-33.

5 Neurophysiology

5.1. Relevance of Research on Neurophysiology

Figure 10: The Soyuz spacecraft landing (Credit: NASA)

Neurological responses to the spaceflight environment challenge the performance of crewmembers at critical times during spaceflight missions. Operational performance may be impaired by spatial disorientation, perceptual illusions, disequilibrium, motion sickness, and altered sensorimotor control, all of which are triggered by g-transitions and persist for some time after the neurological systems adapt to the new gravitational (or gravito-inertial) loading. These neurological changes may have adverse effects on crew cognition, spatial orientation, control of vehicles and other complex systems, and dexterous manipulation skills. While crewmembers eventually adapt to new gravitational environments (e.g., microgravity), subsequent transitions back to the old environment (e.g., 1-g) or to a new environment (e.g., 1/6-g on the Moon or 3/8-g on Mars) will cause a new disruptions to these systems, impairing performance until readaptation (or new adaptation) has occurred. Following such transitions, crewmembers may be unable to accomplish certain entry, landing, and post-flight physical activities, including spatial cognition, vehicle control, maintaining balance and locomotion, and dexterous manipulation. Current methods of pre-flight training and post-flight rehabilitation have not been optimised to minimise the functional impacts of these natural adaptive responses during g-transitions or to restore environment-appropriate sensorimotor functions after g-transitions.

While humans have sensory organs that specifically detect changes in the accelerations and forces acting on our bodies, there are no specific gravity receptors. Instead, the direction and strength of the gravity (or gravito-inertial) vector are deduced from the central integration of information from many types of sensory receptors distributed throughout our bodies, including visual, proprioceptive, haptic, and vestibular receptors. Nevertheless, the morphology and physiology of motor systems have evolved such that the repertoire of movement paradigms enabled survival by accommodating the physical properties of the environment, including gravity. This has resulted in many highly integrated motor control mechanisms that are clearly designed to function in a 1-g environment. One means of understanding how these control mechanisms function is to investigate their routine accommodations of daily function when the gravitational environment has changed.

Changes in sensorimotor functions resulting from changes in gravitational loading also appear to play a role in muscle atrophy, cardiovascular deconditioning, and cognitive deficits, such as poor concentration, short-term memory loss, and alteration in spatial representations, known to occur during spaceflight. Changes in sensorimotor functions are probably not the only factors influencing these other flight-associated changes, but their contributions should be recognised and better understood. Therefore, critical questions should be investigated regarding the functioning of gravity-sensing receptors, motor systems, spatial orientation and cognition in both normal and altered gravity. An integrative approach should be employed to address these questions. Also, the effects of space radiation on the central nervous system need to be better understood, as the potential for damage to neural structures controlling critical life functions and/or adaptive responses is unknown, and methods for detecting and protecting or repairing such damage are poorly understood.

5.2. Neurophysiology – Key Issues

Five key issues have been identified as space neurophysiology research priorities over the next 10-15 years. Each of these important topics is briefly introduced and motivated. Then, relevance for exploration, earth benefits, proposed investigations, and transdisciplinary aspects are described. Cross-disciplinary elements and potential Earth applications share different key issues and span over other Expert Groups.

5.2.1. Key issue 1: Impacts of spaceflight on the senses

Changes in gravity have been shown to alter the structure and/or performance of various sensory systems (e.g. vestibular, proprioceptive, tactile, olfactory, baroreceptors, etc.) as well as basic perceptions associated with these systems (e.g. graviception, spatial orientation, self-motion, etc.). However, details and mechanisms of these changes during and after g-transitions have not yet been clearly elucidated.

Relevance for space exploration missions

- Altered sensory or perceptual functions can lead to performance decrements (see below), spatial disorientation, or altered situational awareness during critical vehicle control operations that may seriously endanger the mission and the crew.
- Space flight induced changes in sensory and perceptual systems may alter interactions with other physiological systems (muscle, cardiovascular, etc.), further contributing to reduced performance capabilities of the individual.

Earth benefits and applications

Spatial disorientation and situational awareness issues are responsible for up to a quarter of all civil aviation accidents. Diminished manual flying skills during visual flight rules piloting is an increasing problem, especially for search and rescue helicopter pilots required to fly with diminished visual cues. Physical aids (e.g., tactile situational awareness system) and countermeasures developed to aid space travellers might also be useful for commercial and military aviation.

As graviception plays a critical role in spatial orientation perception as well as control of balance, locomotion, and dexterous manipulation (see next key issue), space neurophysiology research will better define the mechanisms underlying the fundamental role of gravity in motor control. It should also help to better understand the interplay between nervous system function and functioning of the cardiovascular and muscular systems as well as some of the cognitive aspects of behavioural performance.

Knowledge gaps and research needs

- While the effects of sustained 0-g on some sensory and perceptual functions have been well studied, little is known about the effects of sustained hypo-g ($0<g<1$) on these functions.
- Similarly, while the transient (adaptive) effects on some sensory and perceptual functions have been well studied following shifts from 0-g to 1-g (and, to a lesser extent, 1-g to 0-g), little is known

about the transient effects on these functions following shifts from 1-g to hypo-g (and vice versa).

- Furthermore, little is known about what happens to sensory and perceptual functions during g-transitions (e.g., during launch or entry, where gravito-inertial forces can vary over by 2-3 g or more during periods of 10-30 minutes) from any starting g-level to any finishing g-level.
- In addition, while Central nervous system (CNS) responses to repeated g-transitions associated with repeated space missions (months to years between missions) have shown some tendencies toward dual-adaptation (e.g., response severities decrease as number of missions increases), the responses to significant g-level changes with shorter recovery times between (e.g., during intermittent artificial gravity exposures every few hours to days) are unknown. How much time is required for significant adaptive responses to manifest themselves during/after g-transitions, and what effects are driven by subsequent g-transitions during/after this time period?
- Sustained hypo-g fields cannot be created on Earth, but sustained hyper-g (g>1) fields can be created easily using rotating habitats. Can transitions between hyper-g and 1-g be used as a valid experimental model for examining neurophysiological responses to transitions between 1-g and hypo-g?
- What are the potential effects of radiation on sensory and perceptual functions? Are they predictable? What countermeasures can be used to detect and/or minimise these effects? What rehabilitation protocols can be used to aid recovery from these effects?
- Artificial gravity created by rotating all or part of a space vehicle might prove to be an efficient, effective multi-system countermeasure, but the unusual force environment created by the rotation (i.e., g-gradients, Coriolis forces, and cross-coupled angular accelerations) will likely affect sensory and perceptual functions. The magnitudes, time courses, reversibility, and consequences of these effects are largely unknown.
- The effects of Extra Vehicular Activities on sensory and perceptual functions have not been studied.
- The effects of pharmaceutical countermeasures (e.g., promethazine) on sensory and perceptual functions have not been studied in any non-terrestrial environment.
- What structural changes occur in neurological systems (e.g., end organs, cerebellum, brain stem, cortex, spinal cord, etc.) when gravity is altered? Are there any long-term health or performance consequences associated with these structural changes?

Proposed investigations and recommendations

- The relationships between g-level and sensations/perceptions must be quantified. What are the g-thresholds for different sensations and perceptions?
- The time courses associated with adaptive responses of the sensory and perceptual systems following launch into space (transition from 1-g to 0-g) should be quantified.
- The time courses associated with adaptive responses of the sensory and perceptual systems following transition between 0-g and hypo-g (or vice versa) should be quantified.
- The time courses associated with adaptive responses of the sensory and perceptual systems in rapidly changing gravitational environments should be investigated (e.g. in rooms rotating at variable rates).
- Alterations in sensory and perceptual systems during launch and entry should be examined.
- The effects of pharmaceutical countermeasures (e.g., promethazine) on sensory and perceptual systems should be studied in non-terrestrial environments.
- Evaluate the effects of Extra Vehicular Activities (EVAs) on sensory and perceptual functions by performing experiments during scheduled EVAs.
- Investigate the causes and effects of reported inflight changes of visual acuity on visual perception and performance.
- Investigate changes in audition, smell, and taste during microgravity.
- Examine the use of (commercial) suborbital flights as a suitable platform for the study of transient responses to changing g-levels.
- Test subjects in prolonged hyper-gravity induced by aircraft or long-radius centrifuges.
- Study subjects that have accumulated significant parabolic experience (i.e., many parabolas).
- Study effects of radiation on neurological function in ground-based accelerator facilities.

- Place an animal centrifuge in space to study structural changes in the nervous system, and effects of sustained hypo-g exposure.
- Place a human centrifuge in space to address issues regarding operations under g-level transitions, g-gradients, hypo-g, flight simulator training, and adaptation to altered gravity.

Trans-disciplinary aspects

Strong links have to be emphasised with issues related to radiation in space (Cluster 3).
The longer a crew member is exposed to the radiation environment of space, the more likely it is that some high energy particle will cause significant damage to a critical CNS neuron/structure that could lead to permanent, functionally relevant structural changes. What are the potential effects of radiation on neurologic functions? Are they predictable? What countermeasures can be used to detect and/or minimise these effects? What rehabilitation protocols can be used to aid recovery from these effects?

5.2.2. Key issue 2: Impacts of spaceflight on sensorimotor performance

Changes in gravity have been shown to alter sensorimotor control (e.g., goal-directed eye, hand, head, limb, or body movements, eye-head coordination, dexterous manipulation, postural control, and locomotive control). However, details and mechanisms of these changes during and after g transitions have not yet been clearly elucidated, nor have their functional/operational significance.

Relevance for space exploration missions

Altered sensorimotor control performance during critical mission activities may seriously endanger mission objectives, mission equipment, or the crew. Furthermore, altered sensorimotor control performance during typical activities of daily living after return from space missions may seriously endanger crew, their friends, or their families. These activities include: controlling space vehicles (e.g., launch, entry, landing, rendezvous, docking, etc.), ground-based vehicles (e.g., rovers, automobiles, watercraft, aircraft, etc.), or remote manipulators (e.g., robotic arms), performing Extra Vehicular Activities, emergency egress, or exercise/sport/athletic activities, etc.

Earth benefits and applications

The altered gravity environments available during spaceflight offer platforms to study the basic neurophysiology of dexterous manipulation (eye hand coordination), balance and locomotion, and vehicle control, providing knowledge that serves to help patients with vestibular, neurological, and motor control problems as well as the elderly. Knowledge gained from studying the training and rehabilitation protocols developed for use with astronauts can be transferred directly to patients with specific lesions or disorders requiring retraining or rehabilitation. Finally, mathematical models developed in the context of a space environment could shed light on mechanisms that can't be observed on Earth (0-g is a model of hypo-activity, which is common in elderly populations).

Knowledge gaps and research needs

- The inaccessibility of operational performance data by the scientific community complicates the study of the relationships between physiological changes and operational performance decrements (e.g., piloting performance, emergency egress, manual control, etc.).
- No experiments have been performed during Extra Vehicular Activities (see Issue 1, above).
- Three-dimensional changes in eye movements have not been tested during spaceflight (e.g., the targets for smooth pursuit and saccade movements have only been tested using a fronto-parallel screen), and therefore, control of vergence movements, in particular, are poorly understood.
- What ranges of radius and angular velocity are required for intermittent artificial gravity to benefit the sensorimotor systems, as well as the heart, bone, muscle, and cardiovascular systems? Are supplemental (concurrent) exercise countermeasures required to optimise this putative countermeasure?
- What ranges of radius and angular velocity are required for continuous artificial gravity (rotating vehicle) to appropriately stimulate the load/acceleration receptors while minimising the Coriolis forces and cross-coupled angular velocity side effects?

Few mathematical models exist to describe sensory motor adaptive responses, especially to altered gravity.

Proposed investigations and recommendations

- Protocols should be established for disclosure of operational performance data to qualified researchers. Developing closer partnerships among the scientific, operations, and training communities might be the best way to achieve this.
- As most of the issues associated with altered sensory or perceptual functions could lead to decreased sensorimotor performance, all of the recommendations under Issue 1 also apply to this Issue.
- Measure three-dimensional eye movement control performance during space flight.
- Perform ground-based and in-flight artificial gravity experiments to determine the optimal radii and angular velocities to promote multi-system (including vestibular-sensorimotor) protection from space flight adaptation issues.
- Install a flight-simulator in space (centrifuge based, if possible) to correlate landing performance with in flight training.
- Develop mathematical models with an explicit dependence on gravity to simulate sensorimotor responses to changed gravity.

Trans-disciplinary aspects

Overarching aspects with links to many scientific disciplines are clearly evident. The inaccessibility of operational performance data to the scientific community complicates the study of relationships between physiological changes and performance decrements (e.g., piloting performance, emergency egress, manual control, etc.) during critical mission phases. Protocols should be established for disclosure of operational performance data to qualified researchers. Developing closer partnerships among the scientific, operations, and training communities might be the best way to achieve this. Furthermore, setting up a shared database and recording past experimental data sets and information on their contexts could be very valuable to enhance the usability of previous data (e.g. challenge the low-N problem in space research).

5.2.3. Key issue 3: Impacts of neurophysiological changes on spaceflight-induced decrements in neuro-behavioural performance.

Changes in gravity have been observed to decrease work capacity, vigilance, cognition, motivation, and other aspects of neuro-behavioural performance. However, details and mechanisms of these changes, especially the role that altered senses and perceptions might play during and after g transitions, have not yet been clearly elucidated.

Relevance for space exploration missions

- The consequences of altered work capacity, vigilance, cognition, and motivation during spaceflight could range from decreased crew efficiency to loss of mission and crew.
- Current countermeasures against motion sickness during and after flight present unacceptable risks to crewmembers and may be inappropriate for exploration missions.

Earth benefits and applications

New information from spaceflight studies on the fundamental mechanisms of spatial orientation perception of slopes, depths, and heights may aid architects in optimising the design of habitats and affordances for the elderly or for those with neurological deficits.

Knowledge gaps and research needs

- The incidence and severity of mission-related operational performance decrements are unknown, except in a few publicly observed examples. The inaccessibility of operational performance data by the scientific community complicates the study of the relationships between neurophysiological changes and neuro-behavioural decrements.
- Mechanisms of decreased or off-nominal performance during mission critical operational tasks (e.g. vehicle control) are unknown. While links between vestibular dysfunction and cognitive deficits have been established on Earth, no such links have been sought in space research.
- The effects of ground-based and in-flight training regimens on neuro-behavioural decrements have not been well studied.

- Effective motion sickness countermeasures having minimal effects on neuro-behavioural or sensorimotor function are currently unknown.

Proposed investigations and recommendations

- Protocols should be established for disclosure of neuro-behavioural performance data to qualified researchers. This might be best achieved by developing closer partnerships and integration of the scientific, medical, and behavioural communities.
- Studies should be performed to elucidate the time course and severity of spaceflight-induced cognitive deficits (e.g., Sopite syndrome (drowsiness), space fog, aka "mental viscosity" or "space stupids"), focusing on the role of neurophysiological changes.
- The effects of ground-based and in-flight training regimens on neuro-behavioural decrements should be studied.
- Effective motion sickness countermeasures having minimal effects on neuro-behavioural or sensorimotor function should be sought.

Trans-disciplinary aspects

Links are clearly evident with psychology, human-machine systems, and health care. In addition, 5 trans-disciplinary aspects need to be highlighted:

Cognitive function

- How do changes in gravitational stimulation of vestibular receptors affect cognitive function? What training methods can be used to reduce these effects?
- How do medications used to relieve symptoms of motion sickness affect cognitive function? What alternative medications could be used to reduce these effects?
- Cognitive function comprises several tasks such as attending, selecting, decision making, recognising, imitating and remembering that involve different parts of the brain. To fully assess the effects of spaceflight on cognitive function and to better characterise the transient spaceflight phenomenon sometimes referred to as the "space stupids," each of these cognitive function tasks needs to be assessed individually with specific tests.

Motivation and vigilance

- How do changes in gravitational stimulation of vestibular receptors and/or symptoms of motion sickness affect crew motivation and vigilance? What training methods or medications could be used to reduce these effects?
- How do medications used to relieve symptoms of motion sickness affect motivation and vigilance? What alternative medications could be used to reduce these effects?

Sleep and circadian rhythms

There is a growing body of evidence suggesting that chronic sleep loss, which has been reported to occur commonly during spaceflight, is associated with neurodegenerative, endocrinological, immunologic, affective, and cognitive/memory, and motor performance deficits. The mechanisms of in-flight sleep loss are not well understood. Many factors may play a role, including light conditions, psychological issues, and vestibular stimulation by gravito-inertial forces. What is the relative importance of these factors? How do changes in gravitational stimulation of vestibular receptors affect circadian rhythm? What training methods or medications could be used to minimise these effects?

Spatial, geographic, and situational awareness

How does loss of the fundamental spatial orientation reference provided by gravity affect spatial processing? What affects does this have on spatial, geographic, and/or situational awareness? What training methods or physical aids could be used to minimise these effects?

Performance

How do changes in sensorimotor control associated with altered gravito-inertial force fields affect crew performance of operational tasks? What training methods, physical aids, medications, or countermeasures could be used to minimise these effects?

How do changes in cognition, motivation, vigilance, or spatial processing further complicate performance? What training methods, physical aids, medications, or countermeasures could be used to minimise these effects?

Previous work has suggested that similar neural substrates are involved in movement execution, observation, and motor imagery, and that the same laws of movement control apply to these processes. How could non-invasive mental imagination and/or observation be used to aid crewmembers in efficiently learning and achieving specific physical tasks in altered gravity?

5.2.4. Key issue 4: Countermeasure strategies to minimise the risks associated with neurophysiological changes during and after G-transitions.

Relevance for space exploration missions

Crewmembers are called upon to perform some of the riskiest tasks associated with spaceflight missions during and after g transitions, which also happen to be the times of greatest environmental effects on the neurological system during a mission. As noted above in Issues 1-3, altered sensations and perceptions, sensorimotor performance, or cognition during these critical mission phases could seriously endanger the mission and the crew.

Earth benefits and applications

The adaptation and training processes used by astronauts to cope successfully with the environmental changes associated with g-transitions during long-duration spaceflight missions may provide insight into rehabilitation in patients with specific CNS impairments and vice versa.

Knowledge gaps and research needs

- The inaccessibility of operational performance data to the scientific community complicates the study of the relationships between physiological changes and performance decrements (e.g., piloting performance, emergency egress, manual control, etc.) during these critical mission phases.
- Only limited research data has been collected during g-transitions to and from space platforms.
- The effectiveness of operational crew training paradigms and training recency on crew performance during these phases has not been systematically evaluated.
- The effects of pre-habilitation (pre-flight training) or other countermeasures on performance during these phases have not been evaluated.

Proposed investigations and recommendations

- Protocols should be established for disclosure of operational and neuro-behavioural performance data to qualified researchers. This might be best achieved by developing closer partnerships and integration of the scientific, medical, and behavioural communities.
- Studies of crew neurophysiological responses and performance should be conducted during and immediately after launch/insertion and entry/landing.
- The effectiveness of operational training protocols and recency should be studied.
- Pre-habilitation or other countermeasures approaches designed specifically for these phases should be studied.

Trans-disciplinary aspects

Links with integrated physiology (especially musculoskeletal system and cardiovascular, lungs and kidney) are highlighted in addition to:

Loss of motor tone

How do changes in gravitational stimulation of vestibular and/or peripheral load receptors affect tonic spinal-motor activation of anti-gravity muscles? What role does this play in muscle atrophy and/or (indirectly) bone loss? What role does it play in post-flight orthostatic function? What countermeasures should be used to minimise these effects?

Vestibular control of cardiovascular regulation

What role do vestibular afferents play in the autonomic regulation of myocardial contractility, vascular tone, plasma volume, and other aspects of cardiovascular regulation? How do changes in gravitational stimulation of vestibular receptors affect cardiovascular regulation? What countermeasures should be used to minimise these effects?

5.2.5. Key issue 5: Understand the role of gravity in the development of the nervous system

Relevance for space exploration missions

Gravity is a fundamental environmental force that has shaped the evolution of species on Earth. The role of gravity in nervous system development is poorly understood though because it is not possible to remove this omnipresent stimulus for more than brief periods on Earth. Spaceflight offers unique opportunities to study neurological development in the absence of gravity, which could provide important insights to terrestrial developmental neurobiologists. In the future, exploration missions will possibly require very long transit times and an inhabitation period on the extraterrestrial body requiring multiple serial generations of space travellers. While developmental neurobiology is rather a fundamental field of research, this endeavour will require deep understanding of the effects of human gestation and development in non-terrestrial gravitational environments..

Earth benefits and applications

Space provides a unique platform to observe consecutive generations of animals (and eventually humans), being born and developing without gravity, allowing the fundamental study of the influence of gravity on development. What is the influence of gravity (or its apparent absence) on development? For example, is there a critical period for development of anti-gravitational reflexes, similar to the critical period for development of vision? Are there synaptic or structural changes in an organism after being in space for long periods of time?

Knowledge gaps and research needs

The role of gravity in nervous system development should be further investigated.

Proposed investigations and recommendations

- Study the neurobiological development of generations of small animal species born and raised in the microgravity environment.
- Place an animal centrifuge in space to study the neurobiological development of generations of small animal species born and raised in the hypogravity environments.

5.3. Conclusion

The human nervous system has evolved to respond to gravitational cues. On Earth, the presence of gravity-mediated inputs from an ensemble of somatic receptors sensitive to force and acceleration generate a gravitational reference frame from which spatial orientation is deduced and movements can be planned and executed. Changes in this fundamental reference signal caused by spaceflight or other sustained gravito-inertial force fields cause transient disruptions in performance until the central integration functions can adapt to the altered reference stimuli. Crew health, safety, performance, and, eventually, mission success, can only be assured after effective countermeasures are developed to optimise the adaptation to new gravito-inertial environments. However, such countermeasures cannot be developed without understanding the fundamental mechanisms underlying the adaptive processes involved. Many ground-based studies address learning and transfer of motor skills into novel environments. However, only space flight studies can examine the nervous system responses to reduced gravity. Thus, we conclude that a series of basic and operational scientific experiments into the neurophysiological responses to space flight are required to enable the next steps in human exploration of space.

5.4. References

Books and Compilations:

Buckey JC and Homick JL (eds.) The Neurolab Spacelab Mission: Neuroscience Research in Space. Houston: NASA (NASA SP-2003-535), 2003.

Clément GS and Reschke MF.Neuroscience in Space. New York: Springer, 2008.

Clément GS and Bukley A. Artificial Gravity. New York: Springer, 2007.

Graybiel A (ed.)Symposium on the Role of the Vestibular Organs in the Exploration of Space. Washington DC: NASA (NASA SP-77), 1965.

Graybiel A (ed.)Second Symposium on the Role of the Vestibular Organs in the Exploration of Space. Washington DC: NASA (NASA SP-115), 1966.

Graybiel A (ed.)Third Symposium on the Role of the Vestibular Organs in the Exploration of Space.Washington DC: NASA (NASA SP-152), 1967.

Graybiel A (ed.)Fourth Symposium on the Role of the Vestibular Organs in the Exploration of Space. Washington DC: NASA (NASA SP-187), 1968.

Graybiel A (ed.)Fifth Symposium on the Role of the Vestibular Organs in the Exploration of Space. Washington DC: NASA (NASA SP-314), 1970.

Homick JL and Miller EF. Apollo flight crew vestibular assessment. In: Johnston RS, Dietlein LF and Berry CA (eds.). Biomedical Results of Apollo. Washington DC: NASA (NASA SP-368) pp. 323-340, 1975.

Johnston RS and Dietlein LF (eds.)Biomedical Results From Skylab: Section II Neurophysiology (pp. 74-163). Washington, DC: NASA 1977.

Kanas N and Manzey D. Space Psychology and Psychiatry:Section 3 Human Performance(pp. 49-88). El Segundo CA:Microcosm Press, 2010.

Leach Huntoon CS, Antipov VV, and Grigoriev AL, (eds.)Humans in Space Flight (Books 1 and 2).In: Nicogossian AE, Mohler SR, Gazenko OG, and Grigoriev, AI (eds.) Space Biology and Medicine. Reston, VA: AIAA and Moscow: Nauka Press, 1996.

Nicogossian AW, LeachHuntoon C,and Pool SL (eds.) Space Physiology and Medicine 2nd Edition. Philadelphia: Lea & Febiger, 1989.

Reschke MF, Bloomberg JJ, Harm DL, Paloski WH, and Parker DE. Neurophysiological Aspects: Sensory and Sensory-Motor Function.In: Nicogossian AE (ed.)Space Physiology and Medicine. Philadelphia: Lea and Febiger, 1994.

Sahm PR, Jansen R and Keller MH (eds.) Proceedings of the Norderney Symposium on Scientific Results of the German Spacelab Mission D1. Köln: DFVLR, 1987.

Sawin CS, Taylor GR, and Smith WL(eds.)Extended Duration Orbiter Medical Project Final Report: Section 5 Neurovestibular Dysfunction(pp. 5.2.1-5.5.57). Houston: NASA (NASA/SP-1999-534), 1999.

Original Articles:

Anderson DJ, Reschke MF, Homick JL and Werness SAS. Dynamic posture analysis of Spacelab-1 crewmembers. Exp Brain Res64(2): 380-391, 1986.

André-Deshays C, Israel I, and Charade O, et al. Gaze control in microgravity. 1. Saccades, pursuit eye-head coordination. J. Vestib Res 3:331-344, 1993.

Angelaki DE, McHenry MQ, and Dickman JD, et al. Computation of inertial motion: neural strategies to resolve ambiguous otolith information. J Neurosci19: 316-327, 1999.

Angelaki DE, Shaikh AG, Green AM, Dickman JD. Neurons compute internal models of the physical laws of motion. Nature, 430(6999):560–4, 2004.

Arrott AP and Young LR.MIT/Canadian vestibular experiments on the Spacelab-1 mission: 6. Vestibular reactions to lateral acceleration following ten days of weightlessness.Exp Brain Res64(2): 347-357, 1986.

Augurelle AS, Penta M, White O, Thonnard JL. The effects of a change in gravity on the dynamics of prehension. Exp Brain Res, 148(4):533–40, 2003.

Baumgarten R, Benson A, and Berthoz A, et al. Effects of rectilinear acceleration and optokinetic and caloric stimulations in space. Science 225(4658): 208-212, 1984.

Benson AJ, Kass JR, and Vogel H. European vestibular experiments on the Spacelab-1 mission: 4. Thresholds of perception of whole-body linear oscillation. Exp Brain Res64(2): 264-271, 1986.

Benson AJ and Viéville T. European vestibular experiments on the Spacelab-1 mission: 6. Yaw axis vestibulo-ocular reflex. Exp Brain Res64(2): 279-283, 1986.

Berger M, Mescheriakov S, and Molokanova E, et al. Pointing arm movements in short-and long-term spaceflights. Aviat Space Environ Med 68: 781-787, 1997.

Berthoz A, Brandt T, and Dichgans J, et al.European vestibular experiments on the Spacelab-1 mission: 5. Contribution of the otoliths to the vertical vestibulo-ocular reflex. Exp Brain Res64(2): 272-278, 1986.

Black FO, Paloski WH, and Reschke MF, et al. Disruption of balance control recovery by inertial stimulation following the first international microgravity (IML-1) spacelab mission (STS-42). J Vestib Res 9: 369–378, 1999.

Bloomberg JJ and Mulavara AP. Changes in walking strategies after spaceflight. IEEE Eng Med Biol Mag 22(2): 58-62, 2003.

Bock O, Howard IP, and Money KE, et al. Accuracy of aimed arm movements in changed gravity. Aviat Space Environ Med 63:994-998, 1992.

Bock O. Grasping of virtual objects in changed gravity.Aviat Space Environ Med 67:1185-1189, 1996.

Boyle R, Mensinger AF, and Yoshida K, et al.Neural readaptation to Earth's gravity following return from space.J Neurosci 86: 2118-2122, 2001.

Clarke AH, Grigull J, et al. The three-dimensional vestibulo-ocular reflex during prolonged microgravity. Exp Brain Res 134(3): 322-34, 2000.

Clément GS, Moore ST, Raphan T, and Cohen B. Perception of tilt (somatogravic illusion) in response to sustained linear acceleration during space flight. Exp Brain Res 138: 410-418, 2001.

Crevecoeur F, Thonnard JL, Lefevre F. Optimal integration of gravity in trajectory planning of vertical pointing movements. J Neurophysiol, 102(2):786–796, 2009.

Gurfinkel VS, Lestienne, F, et al. Egocentric references and human spatial orientation in microgravity II. Body-centered coordinates in the task of drawing ellipses with prescribed orientation. Exp Brain Res 95: 343-348, 1993.

Hermsdorfer J, Marquardt C, Philipp J, Zierdt A, Nowak D, et al. Grip forces exerted against stationary held objects during gravity changes. Exp Brain Res, 126(2):205–14, 1999.

Indovina I, Maffei V, Bosco G, Zago M, Macaluso E, Lacquaniti F. Representation of visual gravitational motion in the human vestibular cortex. Science, 308(5720):416–9, 2005.

Jain VL, Wood SJ, and Feiveson AH, et al. Diagnostic accuracy of dynamic posturography testing after short-duration space flight. Aviat Space Environ Med81(7): 1-7, 2010.

Johnsson A and Eidesmo T. Rhythmic biological systems under microgravity conditions. Adv Space Res, 9(11):273–81, 1989.

Kenyon RV and Young LR.MIT/Canadian vestibular experiments on the Spacelab-1 mission: 5. Postural responses following exposure to weightlessness. Exp Brain Res64(2): 335-346, 1986.

Knierim JJ, McNaughton BL, and Poe GR. Three-dimensional spatial selectivity of hippocampal neurons during space flight.Nature Neurosci3(3): 209-210, 2000.

Kornilova LN,et al. Pathogenesis of sensory disorders in microgravity. Physiologist: 34:S36-39, 1991.

Kozlovskaya IB, Barmin VA, et al. The effects of real and simulated microgravity on vestibulo-oculomotor interaction.Physiologist 28(6 Suppl): S51-6, 1985.

Kozlovskaya IB andKirenskaya AV. Mechanisms of disorders of the characteristics of fine movements in long-term hypokinesia. Neurosci Behav Physiol 34(7):747-54, 2004.

Krasnov IB. Gravitational neuromorphology.Adv Space Biol Med 4: 85-110, 1994.

Lackner JR and P. DiZio. Motor function in microgravity: movement in weightlessness. Curr Opin Neurobiol, 6(6):744–50, 1996.

Lipshits MI, Gurfinkel EV, Matsakis F, and Lestienne F. Microgravity effects on sensorimotor interaction during operational activity: visual feedback. Aerospace Environ. Med. 27:22–25, 1993.

Manzey D, Lorenz B, Schiewe A, et al. Dual-task performance in space: results from a single-case study during a short-term space mission. Human Factors 37:667-681, 1995.

McDonald PV, Bloomberg JJ, and Layne CS. Adaptation of musculoskeletal impedance during space flight: Implications for postflight head movement control. J Vestib Res, 7: 239-250, 1997.

McIntyre J, Zago M, Berthoz A, Lacquaniti F. Does the brain model newton's laws? Nat Neurosci, 4(7):693–4, 2001.

Merfeld DM, Polutchko KA, and Schultz K. Perceptual responses to linear acceleration after spaceflight: human neurovestibular studies on SLS-2. J Appl Physiol81(1): 58-68, 1996.

Merfeld DM. Effect of spaceflight on ability to sense and control roll tilt: human neurovestibular studies on SLS-2. J Appl Physiol 81(1): 50-7, 1996.

Merfeld DM. Rotation otolith tilt-translation reinterpretation (ROTTR) hypothesis: A new hypothesis to explain neurovestibular space flight adaptation. Journal of Vestibular Research, 13: 309-320, 2003.

Merfeld DM, Young LR, Oman CM, and Shelhamer MJ. A multidimensional model of the effect of gravity on the spatial orientation of the monkey.J Vestib Res 3(2): p. 141-61, 1993.

Moore ST, Clément G, Raphan T, and Cohen B. Ocular counterrolling induced by centrifugation during orbital space flight. Exp Brain Res 137: 323-335, 2001.

Oman CM, Lichtenberg BK, Money KE, and McCoy RK. MIT/Canadian vestibular experiments on the Spacelab-1 mission: 4. Space motion sickness: symptoms, stimuli, and predictability. Exp Brain Res64(2): 316-334, 1986.

Oman CM and Balkwill MD.Horizontal angular VOR, nystagmus dumping, and sensation duration in spacelab SLS-1 crewmembers.J Vestib Res 3(3): 315-30, 1993.

Oman CM, Pouliot C F, and Natapoff A. Horizontal angular VOR changes in orbital and parabolic flight: human neurovestibular studies on SLS-2. J Vestib Res 81(1): 69-81, 1996.

Oman CM. Human visual orientation in weightlessness. In: Harris L and Jenkins M (eds). Levels of Perception. New York: Springer Verlagpp375-398, 2003.

Paloski WH, Black FO, and Reschke MF, et al. Vestibular ataxia following shuttle flights: Effect of transient microgravity on otolith-mediated sensorimotor control of posture. Am J Otol 14(1): 9–17, 1993.

Paloski WH. Vestibulo-spinal adaptation to microgravity.Otolaryngol–Head Neck Surg 118(3): S38–S43, 1998.

Paloski WH, Oman CM, and Bloomberg JJ, et al. Risk of sensory-motor performance failures affecting vehicle control during space missions: a review of the evidence. J Grav Physiol, 15(2): 1-29, 2008.

Papaxanthis C, Pozzo T, Popov KE, and McIntyre J. Hand trajectories of vertical arm movements in one-G and zero-G environments. Exp Brain Res 120:496-502, 1998.

Parker DE,Reschke MF,and Arrott AP,et al. Otolith tilt-translation reinterpretation following prolonged weightlessness: implications for preflight training. Aviat Space Environ Med 56: 601-606, 1985.

Reschke MF, Anderson DJ, and Homick JL. Vestibulospinal reflexes as a function of microgravity.Science225(4658): 212-214, 1984.

Reschke MF, Anderson DJ, and Homick JL.Vestibulo-spinal response modification as determined with the H-reflex during the Spacelab-1 flight.Exp Brain Res64(2): 367-379, 1986.

Reschke MF, Bloomberg JJ, and Harm DL, et al. Posture, locomotion, spatial orientation, and motion sickness as a function of space flight. Brain Res Rev, 28: 102–117, 1998.

Reschke MF, Bloomberg JJ, and Paloski WH, et al. Effect of six-degree head-down tilt bed rest on postural reflexes, balance control, and functional mobility. Aviat Space Environ Med 80 (5): A45-A54, 2009.

Ross HJ, Brodie EE, and Benson AJ. Mass discrimination during prolonged weightlessness. Science 225(4658): 219-221, 1984.

Ross HJ, Brodie EE, and Benson AJ.Mass-discrimination in weightlessness and readaptation to Earth's gravity. Exp Brain Res64(2): 358-366, 1986.

Ross MD. Changes in rat vestibular system following weightlessness. J Vestib Res 3: 241-251, 1993.

Ross MD. Changes in ribbon synapses and rough endoplasmic reticulum of rat utricular hair cells in weightlessness. Acta Otolaryngol 120: 490-499, 2000.

SangalsJ, Heuer H, Manzey D, et al. Changed visuomotor transformations during and after prolonged microgravity.Exp Brain Res 129: 378-390, 1999.

Scherer H, Brandt U, and Clarke AH, et al. European vestibular experiments on the Spacelab-1 mission: 3. Caloric nystagmus in microgravity Exp Brain Res64(2): 255-263, 1986.

Taube J, Stackman R, Calton J,and Oman CM. Rat head direction cell responses in zero gravity parabolic flight. J Neurophysiol92: 2887-2997, 2004.

Vogel H and Kass JR.European vestibular experiments on the Spacelab-1 mission: 7. Ocular counterrolling measurements pre- and post-flight.Exp Brain Res64(2): 284-290, 1986.

Watt DGD, Money LE, and Tomi LM.MIT/Canadian vestibular experiments on the Spacelab-1 mission: 3. Effects of prolonged weightlessness on a human otolith-spinal reflex. Exp Brain Res64(2): 308-315, 1986.

Watt DGD. Pointing at memorized targets during prolonged microgravity. Aviat Space Environ Med 68: 99-103, 1997.

White O, McIntyre J, Augurelle AS, Thonnard JL. Do novel gravitational environments alter the grip-force/load-force coupling at the fingertips? Exp Brain Res, 163(3):324–34, 2005.

Young LR, Oman CM, Watt DGD, Money KE, and Lichtenberg BK. Spatial orientation in weightlessness and readaptation to earth's gravity.Science225(4658): 205-208, 1984.

Young LR, Shelhamer M, and Modestino S.MIT/Canadian vestibular experiments on the Spacelab-1 mission: 2. Visual vestibular tilt interaction in weightlessness. Exp Brain Res64(2): 299-307, 1986.

Zago M and Lacquaniti F. Visual perception and interception of falling objects: a review of evidence for an internal model of gravity. J Neural Eng, 2(3):S198–208, 2005.

6 Nutrition and Metabolism

6.1. Relevance of Research on Nutrition and Metabolism

6.1.1. Relevance for space exploration missions

Figure 11: Fresh fruit is a special treat on the ISS (Credit: ESA/NASA)

Nutrition plays several key roles during space flights, from the basic nutritive intake to maintain the organism in good health to the beneficial psychosocial aspects related to meals. Because nutrition is the source of energy, the precursors for synthesising the functional body units (cells and their core constituents, the macromolecules proteins, DNA, RNA, cells, etc.), and the numerous co-factors, such as micronutrients, to support enzyme activity and detoxification/repair mechanisms, nutrition is central to the functioning of the body. Conversely, poor nutrition can compromise many of the physiological systems, and also mood and performance.

On the other hand, nutrition is also likely to play a key role in counteracting the negative effects of space flight (e.g., radiation, immune deficits, oxidative stress, bone and muscle loss). As mission duration increases, any dietary/nutritional deficiencies will become progressively more important. It is therefore critical that astronauts are adequately nourished (quantitatively and qualitatively) during missions. It is also important to note that problems of nutritional origin are often treatable by simply providing the appropriate nutrients.

Of particular concern for long-duration missions is the inability to maintain energy balance (1-4). Energy requirements during space flight are similar to those on the ground (1; 5), yet astronauts often consume less food than needed to cover their energy expenditure (1-3), inducing negative energy balance and body mass loss. While such energy deficits are physiologically tolerable for short-term missions because of the availability of body fat stores, a chronic negative energy balance becomes a significant detrimental issue jeopardising health and performance for long-term missions (2). The causes of energy imbalance are, however not fully understood. A pre-requisite to advising astronauts on how to maintain energy balance is to know what the energy requirements are. It is also important to include the additional energy costs of any exercise counter-measures used when determining astronaut energy needs, especially in the light of recent data suggesting that microgravity itself removes one of the central components involved in energy balance regulation (Audrey 2010).

Required energy, macronutrients, micronutrients and vitamins need to be evaluated for long-term missions, and nutrition countermeasures need to be tested. This is especially important for micronutrient metabolisms that receive very little attention in the context of space flight.

Bed rest is an appropriate ground-based model for most systems and particularly for nutrition related matters. For a Mars mission, there are technological challenges of providing a variety of palatable and nutritious foods, and ideally, some fresh foods. This is important not only for the obvious nutritive role of maintaining crew health, but also for the psychological aspects. Nutritional shortcomings can affect mood and behaviour and psychosocial cohesion between the crewmembers.

6.1.2. Earth benefits and applications

The nutritional questions related to bioastronautics research are very relevant to multiple ground-based related health issues. The potential spin-offs are both interesting from technical point of view and are of great clinical importance. Such spinoffs encompass the increasing burden of modern chronic diseases, in which the adoption of sedentary behaviour plays a central role (i.e. the metabolic syndrome, insulin resistance, dyslipidemia, type 2 diabetes mellitus, atherosclerosis, etc.).

6.2. Nutrition and Metabolism - Key Issues

Within the nutrition Expert Group, 6 key issues related to exploration have been identified as space research priorities in nutrition field. Each of these topics is briefly introduced. Then, relevance to space exploration, Earth benefits, knowledge gaps, proposed investigations, and trans-disciplinary aspects are described. Cross-disciplinary elements and potential Earth applications share different key issues and span over other Expert Groups.

6.2.1. Key issue 1: In-flight negative energy balance

As stated above, a negative energy balance is a frequent finding during spaceflight.

Relevance for space exploration missions

- If sustained over the duration of spaceflights foreseen for planetary exploration, the negative energy balance will likely jeopardise the survival of the crew members and the mission.
- A chronic negative energy balance will affect health performance (muscle, cardio-vascular function), mood and behaviour, which will endanger the mission and the crew.

Earth benefits and applications

Managing energy balance for an astronaut requires the development of an accurate system for monitoring nutritional status in space. This would be of tremendous interest to multiple groups on the ground, including the military, physicians working with obese patients, and hospital doctors dealing with patients who are for one reason or another unable to eat normally. Malnutrition amongst hospitalised patients remains a critical problem today. It contributes to increased morbidity, mortality, increased time in the hospital, and hence, the overall cost of health care.

Brief review of latest developments

A new generation of accelerometer-like devices has been developed for studies on Earth that are capable of defining the energy-time budget of humans and wild animals. These devices, coupled with other methods and instruments (i.e. cardiofrequencemetry, heat flow gauge, etc.) for measuring physical activity pattern and energy expenditure, may give an accurate estimation of total energy expenditure in free-living conditions. The recently developed bioimpedance spectroscopy systems accurately measure and determine changes in body composition and thus energy balance changes over time. These instruments are likely to provide critical information on the astronaut's energy budget during missions of varying duration in relation to the different intensities of exercise prescribed as countermeasures. They need, however, robust calibration on the ground prior to use during flight.

Knowledge gaps and research needs

- The lack of an accurate method to assess in real time the changes in energy balance precludes the monitoring of the nutritional status of the individual astronauts. Energy balance status needs to be assessed every other week in other to apply efficient counteractive protocols.
- The system should not be confounded by changes in body composition (e.g. fluid shifts, electrolyte changes) or by physical activity patterns (duration and intensity) or in the rate of energy expenditure and should not be disturbed by microgravity environment.
- The instruments should allow a non-invasive measurement of energy status and be cost-effective.

Proposed investigations and recommendations

- To validate protocols testing different methodologies to detect early changes in energy status.
- The validation of these methodologies, which include bioimpedance spectroscopy and the latest generation of 3-axial accelerometry and heart rate, should be held against a gold standard method such as the doubly labelled water method. This is needed in flight to assess the instruments precision and accuracy in detecting changes in body composition and total energy expenditure.
- The validation of these instruments in-flight is clearly a crucial prerequisite to planetary exploration.
- To counteract negative energy balance, food sciences-derived and/or psychological strategies should be developed to stimulate astronaut's appetite.
- The consumption of high-energy drinks, classically used in sports medicine, should be tested as a countermeasure.
- Some studies have demonstrated the beneficial effects of amino acid supplements on muscle anabolism, however, those results have recently been challenged. Further studies need to be performed to come to conclusions on that important question. A parallel approach that requires attention is the use of the chrononutrition. Chrononutrition has been shown to increase the anabolic capacity of muscle more efficiently than equivalent supplementation divided over the day. This should be tested as a potential countermeasure.

Trans-disciplinary aspects

Because energy allocation is a central necessity for any physiological function, overarching aspects link energy balance regulation to all scientific disciplines.

On the ground, consequences associated with long-term energy imbalance include alterations in mood, performances (6; 7), stress regulation, bone and muscle mass (2; 6-8), cardiovascular function and immunology (9-12). Some of these consequences also give strong insights regarding the implication of energy alterations in several well-described adaptations to space flights. For example, Muslim army pilots undergoing the 1-month partial fast of Ramadan lost weight in a comparable amount to astronauts and show deterioration in their cardiovascular capacity that closely mimic what is described as the space-related cardiovascular deconditioning syndrome. Similarly, data collected from both bed rest and space flights demonstrate that a state of negative energy balance negatively impact the spaceflight-induced muscle atrophy.

Lastly, the development of exercise countermeasure protocols should be clearly revised in close association with nutritionists. A common goal should be that nutritional guidelines and energy prescriptions work together to maintain a stable energy balance over the period of the space mission (2; 13).

6.2.2. Key issue 2: Feeding behaviour

Part of the problem linked to the negative energy balance is a deregulation of eating behaviour during spaceflight. It was consistently shown that astronauts eat on average 30% less than pre-flight consumption (2). As eating behaviour is a complex, regulated process involving energy expenditure itself, gut endocrinology and enteral nervous systems, adipose tissue and numerous other protagonists known and likely unknown, the expert group considered it as a self-standing key issue.

Relevance for space exploration missions

Understanding the factors that affect feeding behaviour during in a microgravity environment would help manage the energy balance and the maintenance of the general health of the crew members. It is likely that mood and social interactions will also be positively impacted by such control.

Earth benefits and applications

The benefits on Earth are the same than those explained previously for key issue 1.

Brief review of latest developments

Figure 12: Astronauts sharing a meal on the ISS (Credit: ESA/NASA)

Much still remains unknown regarding the regulation of food intake on Earth by humans and animals, and it is a direct factor involved in several pathologies (obesity, anorexia, type 2 diabetes mellitus). However, several biomarkers for satiety and satiation are now available. Combining those with imaging techniques on Earth could provide critical information on how the above mentioned environmental factors, independently or combined, affect food intake regulation.

Knowledge gaps and research needs

- What elements of the space environment (hypobaric/hypoxia situations, hypercapnia, stressful situations, motion sickness) affect the regulation of food intake?
- What is the impact of exercise countermeasure on feeding behaviour? Is the impact level related to the exercise training protocol (intensity, duration, volume, type of exercise, etc.)?
- The interaction between exercises of different intensities, hypobaric/hypoxia situations, and hypercapnia environment has to be tightly investigated on feeding behaviour and appetite regulation of astronauts.

Proposed investigations and recommendations

- Investigations on the impact of the different elements of the space environment, independently and combined, on feeding behaviour is recommended.
- Several facilities exist that could allow experiments to separate out the influence of different environmental factors observed in space on feeding behaviour regulation. These include the Concordia station, the ISS

itself, and submarines. There is clearly a dearth of inflight and ground-based data on this topic.
- On the other side of the problem, an improvement in palatability of the items proposed by the space food industries need to be given more attention.

Trans-disciplinary aspects

Feeding behaviour regulation is one of the two big components of the energy balance equation (key issue 1), and therefore it shares the same trans-disciplinary aspects. It is also related to the problem of habitat management since the food industry will have to take into account the impact of food and meals on feeding behaviour.

Because food plays a strong psychosocial role and can help to enhance the cohesion between the crew members, nutrition and feeding behaviour will have to be taken in account by the psychological issues related to space flights as well.

6.2.3. Key issue 3: Metabolic stress

Relevance for space exploration missions

The metabolic stress (high cortisol, hyperinsulinemia, shift in substrate use towards glucose, oxidative stress and low grade inflammation) observed during spaceflight will certainly pose problems during exploration as a large body of data in clinical nutrition shows that it is a strong predictor of type 2 diabetes and cardiovascular diseases (14-17).

Earth benefits and applications

Metabolic stress studies are of direct interest to the growing prevalence of chronic diseases on Earth in which physical inactivity, as during space flight, plays a causative role. This concerns insulin resistance and lipotoxicity, Type 2 Diabetes, obesity, metabolic syndrome, cardiovascular risks, muscle function and bone health.

Brief review of latest developments

While there is an extensive body of data available from recent clinical nutrition research, there is much debate on the actual causes and subsequent development of metabolic stress.

Knowledge gaps and research needs

- In the context of spaceflight, an unresolved issue is the functional consequence of insulin resistance.
- The interaction between the different protagonists involved in the metabolic stress i.e. insulin resistance, low grade inflammation, shift in the fuel mix oxidised and oxidative stress has to be determined.

Proposed investigations and recommendations

- Fundamental research has to be conducted during bed rest studies and basic clinical science protocols.
- Overall, more data on the metabolic responses to (long-duration) space flight is needed so it can be integrated with ground-based spaceflight analogue studies.
- Ground-based studies have shown that in some cases, metabolic stress can be alleviated with macronutrients and micronutrients supplementation. Further work is required here, especially to understand the underlying mechanisms.

Trans-disciplinary aspects

There is a growing body of evidence suggesting oxidative stress and low-grade inflammation play a causal role in muscle disuse atrophy (18; 19). Furthermore, the development of insulin resistance seems to preclude the decrease of resistance to fatigue, which suggests that it may directly impact performances. Those aspects strongly need to be considered in these different areas.

6.2.4. Key issue 4: Micronutrients deficiency

Prolonged micronutrient deficiency is clearly associated on the ground with numerous functional alterations. Those aspects have been overlooked in bioastronautics research.

Relevance for space exploration missions

In the context of planetary exploration, a clear evaluation of the micronutrient status during long term spaceflight is required to maintain health, and more specifically, to maintain muscle and bone mass, insulin sensitivity, to reduce oxidative stress and lipotoxicity. Recent data shows that in the general population, specific micronutrient deficits can leads to moderate cognitive impairment that obviously need to avoided during spaceflight. The corollary is that micronutrients may mitigate to some extent the deleterious consequences of radiation and other related spaceflight deconditioning syndromes.

Earth benefits and applications

Research on micronutrient requirements will likely foster strategies to maintain bone and muscle mass, to control sensitivity to insulin effects, oxidative stress and lipotoxicity in bed-resting ill patients, sedentary and elderly people. It may also help to better face malnutrition problems in some countries.

Brief review of latest developments

Many ground-based studies have well documented the importance of avoiding micronutrient deficiencies. Further studies showed that supplementation in micronutrient may be efficient in activating pathways leading to oxidative defence, oxidative metabolism and low inflammation.

Knowledge gaps and research needs

- So far, the status of general micronutrients (vitamins, minerals) during space flight has been poorly investigated, especially during long-term missions.
- In the area of nutritional supplementation in micronutrients, the primary open question is the applicability of population based ground data.
- A major gap is whether targeted specific micronutrients (e.g. reservatrol, creatine, omega-3 fatty acids) might prove to have unique benefits during spaceflight.

Proposed investigations and recommendations

- Long-duration bed rest studies, fundamental science, and of course studies during actual spaceflight to collect data are the best ways to investigate this key issue.
- If needed, targeted micronutrient supplementation (e.g. resveratrol, creatine, omega-3 fatty acids etc.) should be evaluated as a potential countermeasure in tightly controlled experiments on ground.

Trans-disciplinary aspects

Because micronutrients are involved in intermediary metabolism, regulation of insulin sensitivity, the control of oxidative stress and lipotoxicity, which impact bone and muscle mass as well as muscle performances and cognition, an appropriate micronutrients intake is crucial for the functioning in space.

6.2.5. Key issue 5: Alterations of gut microflora

Perturbation in gut microflora is an understudied area on the ground that is becoming increasingly important (20; 21). Alterations in the gut microflora may affect nutrient absorption, impact on gut secreting peptides and thus metabolism and food intake as well as immune status (22-25).

Relevance for space exploration missions

If gut microflora is altered during spaceflight, this will impact energy intake and assimilation, and thus energy balance, but it will also affect intermediary metabolism and the immune system. Altogether, the maintenance of gut microflora is important for the general health of the crew members.

Earth benefits and applications

Studies conducted in the new domain of gut microflora and the impact of physical inactivity on gut microflora regulation might open new ways to understand diseases such as obesity, in which sedentary behaviours were suggested to be causative of weight gain.

Brief review of latest developments

Molecular biology tools are now available to easily assess changes in gut microflora.

Knowledge gaps and research needs

- So far, the effect of microgravity on the gut microflora, bacteria diversity, etc., has not been investigated.
- The critical need is for relevant data.

Proposed investigations and recommendations

- Bed rest, fundamental science, and of course studies during actual spaceflight are the best direction to investigate this key issue.
- Prebiotics/ Probiotics supplementation might prove to be an efficient countermeasure.

Trans-disciplinary aspects

Because alterations of gut microflora will likely impact energy balance regulation and intermediary metabolism, this issue is related to all the physiological systems.

6.2.6. Key issue 6: Hydro-electrolytic imbalance

The maintenance of hydro-electrolytic balance is required to maintain whole body physiological homeostasis and to optimise performance.

Relevance for space exploration missions

Alterations of the hydro-electrolytic balance by the space environment would negatively impact the health of the crew members and thus jeopardise the success of the mission.

Earth benefits and applications

Research on hydro-electrolytic balance will also have strong benefits on Earth since similar alterations of hydro-electrolytic balance observed in microgravity conditions are observed during exercise, altitude challenges, anorexia, and adaptation to high-protein diet.

Brief review of latest developments

No recent data is available, especially for long-term missions.

Knowledge gaps and research needs

The long-term hydro-electrolytic adaptations to space flight are unknown.

Proposed investigations and recommendations

- Hydration and mineral supplements are the more potent countermeasure to test and apply.
- Spaceflight studies are the only option to investigate such adaptations.

Trans-disciplinary aspects

Hydro-electrolytic alterations could directly impact the renal function and vascular systems, and also indirectly impact the musculoskeletal system.

6.3. Conclusion

In past bioastronautics research, nutrition has not been a high priority given the relative short duration of flights. However, with the International Space Station now completed and the potential of future long-term missions (e.g. Moon, Mars), the interest in nutrition as a countermeasure has increased dramatically. Indeed, an increasing body of data shows a direct relationship between nutrition and the deleterious adaptations to space in regards to both energy balance and regulation of the energy substrate (fuel mix) oxidation.

Finally, investigations on functional adaptations to actual or simulated microgravity need to include nutrition as an important variable in interpreting the observed results. Controlling nutrition as a variable was often over-looked in the past.

6.4. References

Stein tp, leskiw mj, schluter md, hoyt rw, lane hw, gretebeck re, leblanc ad: energy expenditure and balance during spaceflight on the space shuttle. Am j physiol 276:r1739-1748, 1999

Stein tp: the relationship between dietary intake, exercise, energy balance and the space craft environment. Pflugers arch 441:r21-31, 2000

Wade ce, miller mm, baer la, moran mm, steele mk, stein tp: body mass, energy intake, and water consumption of rats and humans during space flight. Nutrition 18:829-836, 2002

Stein tp, leskiw mj, schluter md: diet and nitrogen metabolism during spaceflight on the shuttle. J appl physiol 81:82-97, 1996

Blanc s, normand, s., ritz, p., pachiaudi, c., vico, l., gharib, c., gauquelin-koch: energy and water metabolism, body composition, and hormonal changes induced by 42 days of enforced inactivity and simulated weightlessness. Journal of clinical endocrinology and metabolism 83:4289-4297, 1998

Riley da, thompson jl, krippendorf bb, slocum gr: review of spaceflight and hindlimb suspension unloading induced sarcomere damage and repair. Basic appl myol 5:139-145, 1995

Edgerton vr, zhou my, ohira y, klitgaard h, jiang b, bell g, harris b, saltin b, gollnick pd, roy rr: human fiber size and enzymatic properties after 5 and 11 days of spaceflight. J appl physiol 78:1733-1739, 1995

Biolo g, ciocchi b, stulle m, bosutti a, barazzoni r, zanetti m, antonione r, lebenstedt m, platen p, heer m, guarnieri g: calorie restriction accelerates the catabolism of lean body mass during 2 wk of bed rest. Am j clin nutr 86:366-372, 2007

Taylor gr, konstantinova i, sonnenfeld g, jennings r: changes in the immune system during and after spaceflight. Adv space biol med 6:1-32, 1997

Levine ds, greenleaf je: immunosuppression during spaceflight deconditioning. Aviat space environ med 69:172-177, 1998

Dorfman ta, levine bd, tillery t, peshock rm, hastings jl, schneider sm, macias br, biolo g, hargens ar: cardiac atrophy in women following bed rest. J appl physiol 103:8-16, 2007

Keusch gt, farthing mj: nutrition and infection. Annu rev nutr 6:131-154, 1986

Bergouignan a, momken i, schoeller da, normand s, zahariev a, lescure b, simon c, blanc s: regulation of energy balance during long-term physical inactivity induced by bed rest with and without exercise training. J clin endocrinol metab 95:1045-1053, 2010

Ferrannini e, gastaldelli a, iozzo p: pathophysiology of prediabetes. Med clin north am 95:327-339, vii-viii, 2011

Mangge h, almer g, truschnig-wilders m, schmidt a, gasser r, fuchs d: inflammation, adiponectin, obesity and cardiovascular risk. Curr med chem 17:4511-4520, 2010

Giacco f, brownlee m: oxidative stress and diabetic complications. Circ res 107:1058-1070, 2010

Garcia c, feve b, ferré p, halimi s, baizri h, bordier l, guiu g, dupuy o, bauduceau b, mayaudon h: diabetes and inflammation: fundamental aspects and clinical implications. Diabetes metab 36:327-338, 2010

Lawler jm, song w, demaree sr: hindlimb unloading increases oxidative stress and disrupts antioxidant capacity in skeletal muscle. Free radic biol med 35:9-16, 2003

Kondo h, nakagaki i, sasaki s, hori s, itokawa y: mechanism of oxidative stress in skeletal muscle atrophied by immobilization. Am j physiol 265:e839-844, 1993

Turnbaugh pj, gordon ji: the core gut microbiome, energy balance and obesity. J physiol 587:4153-4158, 2009

Turnbaugh pj, ridaura vk, faith jj, rey fe, knight r, gordon ji: the effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci transl med 1:6ra14, 2009

Backhed f, ding h, wang t, hooper lv, koh gy, nagy a, semenkovich cf, gordon ji: the gut microbiota as an environmental factor that regulates fat storage. Proc natl acad sci u s a 101:15718-15723, 2004

Backhed f, manchester jk, semenkovich cf, gordon ji: mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc natl acad sci u s a 104:979-984, 2007

Caesar r, fåk f, bäckhed f: effects of gut microbiota on obesity and atherosclerosis via modulation of inflammation and lipid metabolism. J intern med 268:320-328, 2010

Muccioli gg, naslain d, backhed f, reigstad cs, lambert dm, delzenne nm, cani pd: the endocannabinoid system links gut microbiota to adipogenesis. Mol syst biol 6:392

5 Annex: Expert Group Composition

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