ARTIFICIAL GRAVITY

Gilles Clément
Angie Bukley
Editors

Space Technology Library

Artificial Gravity

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FOREWORD

William H. Paloski, Ph.D.
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Artificial gravity is an old concept, having gotten its start in the late in the 19th century when Konstantin Tsiolkovsky, considered by many to be the father of the Russian space program, realized that the human body might not respond well to the free fall of orbital space flight. To solve this problem, he proposed that space stations be rotated to create centripetal accelerations that might provide inertial loading similar to terrestrial gravitational loading. Einstein later showed in his equivalence principle that acceleration is indeed indistinguishable from gravity. Subsequently, other individuals of note, including scientists like Werner von Braun as well as artists like Arthur C. Clarke and Stanley Kubrick, devised elaborate solutions for spinning vehicles to provide “artificial gravity” that would offset the untoward physiological consequences of spaceflight.

By 1959, concerns about the then-unknown human responses to spaceflight drove NASA to consider the necessity of incorporating artificial gravity in its earliest human space vehicles. Of course, owing in part to the relatively short durations of the planned missions, artificial gravity was not used in the early NASA programs. We learned from these early missions that humans could tolerate short periods of zero-G, but a fear remained that longer exposures would lead to more profound effects, and that eventually an exposure threshold would be reached, beyond which crew health, safety, and performance might be compromised to the point of placing individual crewmembers or entire missions at unacceptable risk. Therefore, throughout the 1960s, NASA sponsored many forums to debate the need for artificial gravity on longer duration human spaceflight missions.

During the 1970s, we learned from the Skylab program that humans could tolerate many weeks of zero-G exposure without reaching any untoward thresholds. During the last two decades, we’ve learned from the Mir and ISS programs that system-specific countermeasures (e.g., resistive and aerobic exercise emerged) can provide moderately successful physiological protection for six-month missions in low Earth orbit (LEO). But recently, NASA’s thoughts have turned to more distant destinations, focusing first on long-duration stays on the Moon and moving on to 1000-day missions to Mars or other locations well beyond LEO. These goals have led to a renewed interest in artificial gravity, stimulating workshops to develop international consensus on the open artificial gravity research issues and engineering studies of feasible designs for spinning transit vehicles.

Physiological deconditioning is not the only factor challenging human space exploration. Psychological factors (e.g., boredom, isolation, small group dynamics), environmental factors (particularly radiation exposure), and logistics (e.g., air, water, and food supplies) will also present increasingly significant challenges as mission durations increase. Each of these factors could potentially limit the duration of future human missions. Therefore, accessible distances will be dictated by the available propulsion systems. To maximize the potential for any given propulsion system, it will behoove space-faring nations to invest in research and development efforts focused on reducing the impact of each of the four areas. Optimal solutions will not only maintain crewmembers fitness-for-duty throughout the mission and protect their long-term health, but will do so with high reliability using minimal mission resources (i.e., mass, volume, crew time).

Because the primary factor affecting physiological deconditioning during spaceflight is the loss of gravitational loading and stimulation, there is little doubt in my mind that the most effective physiological countermeasure would be to bring gravity along, probably in the form of centripetal acceleration. Spinning the vehicle would likely be the most reliable and efficient physiological countermeasure, since it would be passive and omnipresent, would add no mass or volume above the basic vehicle design, and would require energy inputs only during ramp up and down from the desired angular velocity, presumably at the beginning and end of the transit phase of the mission. If designed correctly to minimize the impact of Coriolis accelerations, a rotating vehicle would also have salutary effects on some aspects of psychological deconditioning because many of the cumbersome, inefficient systems required in the galley, waste collection system, sleeping, exercise, and other areas could be eliminated as standard terrestrial designs would suffice. Intermittent, short-radius artificial gravity designs would have fewer advantages during transit, but might be critical during extended sojourns in the hypo-gravity environments of many of the celestial objects targeted for exploration, including Moon, Mars, Mars moons, asteroids, and other destinations, where it would not be useful to remain within a (continuously rotating) habitat throughout the surface stay.

As space agencies seek to undertake human missions to distant destinations, they must inevitably consider artificial gravity designs and the physiological and human factors research necessary to develop optimal artificial gravity prescriptions for their crews. This book should prove to be an invaluable reference to those scientists, engineers, and program managers responsible for future artificial gravity research.

Drs. Clément and Bukley have assembled for the first time in one volume all of the key findings and the key unknowns relevant to designing effective artificial gravity countermeasures. Since many of the chapters were written by today's leaders in space physiology and artificial gravity research, the book captures well the current state of knowledge of the physiology of artificial gravity and provides good guidance on the critical issues that must be addressed before a practical artificial gravity countermeasure can be realized. It has been a pleasure to collaborate with them on this book. I hope that you, the reader, will benefit from our efforts.

William H. Paloski
Houston, 1 December 2006

PREFACE

Human space exploration has been limited thus far to low Earth orbit and to short visits to the Moon. These missions typically last only a few days to a few weeks, with the exception of extended stays on Mir and the International Space Station. For the short-duration missions, the adverse effects of weightlessness on the human body are minimal. However, once we begin extended exploration of the Moon and beyond, as is currently being studied by many space agencies around the world, mission durations will increase significantly, thus exposing the crews to the detrimental effects of weightlessness. The consequences of long-term weightlessness include undesirable physiological adaptations that impede the ability of astronauts to function efficiently upon the return to an environment with gravity. The more serious of these affects include sensory-motor and cardiovascular deconditioning, orthostatic intolerance, muscular atrophy, and bone demineralization (see Clément 2005, *Fundamentals of Space Medicine*, in this *Space Technology Library* series).

Countermeasures that reduce the effects of weightlessness have been developed and some are commonly employed. For example, muscular exercise, extra dietary calcium, and other pharmaceuticals can be used to mitigate physiological adaptations to weightlessness. Such countermeasures focus only on certain organ systems and symptoms and most require specially adapted therapeutic equipment. These techniques are time consuming and demand a high degree of individual discipline. Unfortunately, these countermeasures are only partially effective.

Artificial gravity has the potential to fully mitigate the physiological deconditioning that results from long-term exposure to weightlessness. Today's approach to countering the deleterious effects of microgravity is piece-meal, whereas artificial gravity provides an integrated countermeasure affecting multiple physiological systems. It could replace terrestrial gravity with inertial forces generated by centrifugation or sustained linear acceleration. In fact, many Mars mission designs in the early days of the space program recommended such an approach. Most concepts called for the use of spinning transit vehicles, which were not implemented in part due to technical issues associated with system complexity and cost in mass and energy.

Even though new technologies exist to allow construction of such vehicles, there remain many unknowns as to how humans can adapt to a rotating environment and then re-adapt to a non-rotating environment (e.g., when they arrive on Mars). These human aspects are the primary focus of this book. Recent studies suggest that humans can adapt to high rates of rotation at short radius. Therefore, an alternative to rotating the entire habitat is to provide a short-radius centrifuge within the habitat and deliver therapeutic doses of artificial gravity. This would result in an overall simpler and more affordable design.

To our knowledge, there is currently no book entirely dedicated to the subject of artificial gravity. Research in this area is only documented in conference proceedings and a few journal articles. Therefore, this book is unique, timely, and addresses artificial gravity from a multidisciplinary standpoint. The first chapters cover the history, fundamental principles, and rationale for using artificial gravity during space missions. Also described are current options proposed for generating artificial gravity, including a short-radius centrifuge contained within a spacecraft. In the subsequent chapters, experts provide recommendations on the research needed to assess whether continuous or intermittent artificial gravity prescriptions (mostly centrifugation) can limit deconditioning of sensory-motor, cardiovascular, and musculo-skeletal systems. These chapters summarize what is known about the effects of micro- and hypergravity in each discipline, and what is still to be learned.

Space research has revealed that plastic changes are induced in multiple physiological systems following exposure to weightlessness. These systems interact with each other, resulting in combined effects. Developing countermeasures for mitigating the deleterious effects of weightlessness, therefore, requires an integrative focus. Three chapters address the interdependences between physiological systems, including the autonomic and immune systems as well as nutritional considerations. In the last chapters special attention is given to medical, psychological, and safety issues related to artificial gravity implementation. Finally, we propose a number of recommendations for additional research.

We have constructed this book in such a way that each chapter stands on its own. Therefore, those who read the book in its entirety will notice a few redundancies. This is intentional so that readers wishing to investigate a specific topic can go to the chapter addressing that subject matter and understand that material in the overall context of artificial gravity research.

It is our hope that the information provided herein will inspire new research in artificial gravity and one day be used in the planning and design of future long-duration space missions.

Gilles Clément and Angie Bukley
Athens, 23 November 2006

ACKNOWLEDGEMENTS

The inspiration for this book was derived from the work of the *European Space Agency* (ESA) Topical Team on Artificial Gravity. The Topical Team was formed as a result of a proposal submitted to an International Space Life Sciences Research Announcement in November 2004. Dr. Gilles Clément chaired the Topical Team. The group worked together electronically for nearly a year and finally convened in Noordwijk, The Netherlands in November 2005, where much of the content of this book was defined. We sincerely appreciate the inputs that were provided by all the participants in the Topical Team and especially the support provided by ESA.

Other inputs for this book were derived from papers and discussions that occurred during a series of five *National Aeronautics and Space Administration* (NASA) symposia organized by Dr. Ashton Graybiel and convened between 1965 and 1970 in Pensacola (Florida, USA) on the topic of "The Role of the Vestibular Organs in Space Exploration". Another milestone was the Workshop on Artificial Gravity organized by Drs. William Paloski and Laurence Young in 1999 in League City (Texas, USA), which was sponsored by NASA and the National Space Biomedical Research Institute. Another primary source of the material in this book originates from the results of an *International Academy of Astronautics* (IAA) Study Group on the subject of artificial gravity.

The proceedings of all the meetings mentioned above are included in the references following this acknowledgement. We wish to thank all of the people who participated in these meetings for their valuable inputs. This book is a legacy of their work.

The editors are extremely grateful to the authors who wrote selected chapters of this book, some of whom are shown in the photograph below, and especially to Dr. William Paloski for coordinating and co-editing several sections. We also thank Oliver Angerer and Millard Reschke for reviewing the final manuscript.

This book was compiled during Dr. Clément's stay at Ohio University in Athens, Ohio. His appreciation is extended to the Department of Chemical and Biomolecular Engineering, the Faculty and Staff of the Russ College of Engineering and Technology, and in particular to Dean Dennis Irwin.

Thanks to Mr. Philippe Tauzin, from the Service Commun Multimédia of the Université Paul Sabatier in Toulouse, for his help with some of the artwork. We also appreciate the great work done at NASA and ESA to document, catalogue, and provide access to their archives and multimedia galleries.

Dr. William Paloski provided exceptional contributions to this book. His pioneering research on artificial gravity at the NASA Johnson Space Center

brings together a multidisciplinary team of physiologists, engineers, and physicians and provides a model for future studies.

Finally, thanks to Dr. Harry (J.J.) Blom and to Dr. James R. Wertz who continue to offer us the opportunity to publish in the *Space Technology Library* series.

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Group photo of the participants in the ESA Topical Team Workshop on Artificial Gravity convened in Noordwijk, The Netherlands from 28-30 November 2005. Participants to this Workshop provided many valuable inputs to this book. From left to right: Eric Groen, Gilles Clément, Oliver Angerer, Angie Bukley, Pierre Denise, Guglielmo Antonutto, Marco Narici, Anne Pavy-Le Traon, Guido Ferreri, Jochen Zange, Floris Wuyts, Bill Paloski, Jörn Rittwegger, Joan Vernikos, and Pietro Di Prampero.

Contents

Chapter 1

THE GRAVITY OF THE SITUATION

Gilles Clément,[1,2] Angie Bukley,[2] and William Paloski[3]

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Prolonged exposure of humans to a weightlessness environment can lead to significant loss of bone and muscle mass, cardiovascular and sensory-motor deconditioning, and hormonal changes. These adaptive changes to weightlessness present a formidable obstacle to the human exploration of space, particularly for missions requiring travel times of several months or more, such as on a trip to Mars. Countermeasures that address each of these physiological systems separately have shown only limited success. One possible remedy for this situation is artificial gravity because it influences all of these systems across the board.

Figure 1-01. Astronauts returning from long-duration space missions have difficulty standing upright and moving around. Photo courtesy of NASA.

1 WHY ARTIFICIAL GRAVITY?

Ongoing manned spaceflight efforts are now focused on preparing for human interplanetary missions to Mars in the not-too-distant future. These missions will have durations measured in years; therefore, the Mars exploration crews will be at risk of catastrophic consequences should the systems that provide adequate air, water, food, and thermal control fail. Furthermore, the crews will be exposed to radiation en route as well as on extraterrestrial surfaces that may result in serious health or safety risks. Behavioral issues associated with the prolonged isolation and confinement, and severe physiological deconditioning due to *weightlessness*[1] are other hazards with which the explorers will face.

Mitigating the harmful effects of prolonged exposure to space radiation and weightlessness is one the most significant challenges that must be addressed to realize the long-duration exploration missions currently envisioned. Given the fact that the astronaut explorers who will undertake these missions will be exposed to these deleterious effects for up to several years while they travel to and from Mars, it is of extreme importance that effective *countermeasures*[2] are identified, developed, tested, and proven prior to undertaking such challenging missions.

Without the protection of an atmosphere, astronauts will be exposed to high levels of radiation through a steady flux of cosmic particles. Only one year in low-Earth orbit results in a radiation dose that is 10 times that of the annual dose on Earth. Experts predict that the dose of radiation received during a 30-month journey to Mars will amount to about 1,000 times that of the annual dose on Earth, resulting in a high risk of developing chromosomal aberrations in blood lymphocytes and cancer later in the astronauts' lives. Protective shielding and protective drugs may lower this risks to an acceptable level (Cucunotta *et al.* 2001).

More immediate physical effects are those induced by prolonged exposure to weightlessness. These include the loss of bone density, muscle mass, and red blood cells; cardiovascular, circulatory, and sensory-motor deconditioning; and changes in the immune system (Figure 1-02). These effects have been noted in astronauts and cosmonauts exposed to weightlessness for durations of significantly less time than those that will be experienced by future explorers of Mars. Body changes that occur after entering microgravity represent normal homeostatic responses to a new environment. The body's control systems recognize the lack of gravity and begin to adapt to this unique situation, not realizing that the ultimate plan is to return to normal gravity after a transient visit to microgravity. While such reactions by the body may be completely appropriate in the microgravity

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[1] *Weightlessness* is the experience (by people and objects) during freefall, of having zero g-force (0 g) or zero apparent weight. This condition is also known as microgravity, since weightlessness in a spaceship is not perfect.

[2] In a military application, *countermeasures* are systems designed to prevent weapons from acquiring and/or destroying a target. By analogy, in space medicine, countermeasures are systems (mechanical, pharmalogical, procedural) designed to neutralize the hazards of the space environment for astronauts' health and performance.

environment of flight, they are indeed quite inappropriate for arrival on the surface of another planet or for the return to Earth (see Figure 1-01).

Space biomedical researchers have been working for many years to develop countermeasures to reduce or eliminate the deconditioning associated with prolonged weightlessness. Despite these countermeasures, most astronauts experience problems with balance, orientation, and fainting during the first few days after landing. They also risk muscle tears and bone fractures and therefore must exercise an added degree of caution during their recovery period (White and Arvener 2001).

Given that the purpose of a human mission to Mars is not to go there and simply survive, more effective countermeasures or combinations of countermeasures must be developed to address the effects of long-term exposure to microgravity. Astronauts arriving at Mars in a weakened physical condition with compromised immune systems who can't manage to ambulate would hardly be able to successfully execute an exploration mission. They would be at risk in the event of a bone fracture, alterations in the heart's rhythm, development of renal stones, or sensory-motor performance failure during piloting, extra-vehicular activity, or remote guidance tasks. Until the problems associated with microgravity exposure are overcome, such missions cannot be seriously considered.

A number of different countermeasures have been employed in an attempt to mitigate the effects of human exposure to microgravity, generally aiming to stimulate a particular physiological system. Exercise workouts stimulate muscles (and to a lesser extent bones and the cardiopulmonary function), while fluid loading countermeasures target the circulatory responses. While these countermeasures have demonstrated only limited success, they are nevertheless the microgravity countermeasures primarily used on board the *International Space Station* (ISS) and the Space Shuttle (Sawin *et al.* 1998)

Artificial gravity is the simulation of the pull of gravity aboard a manned spacecraft by the steady rotation or linear acceleration of all or part of the vehicle (Stone 1973). Artificial gravity represents an alternative approach to addressing the problems of microgravity-induced effects on the human body. Rather than addressing each individual system in a piecemeal fashion, which is only valid if the principle of superposition holds for the combined effect of these interacting subsystems, artificial gravity stimulates all of the physiological systems simultaneously by reproducing the normal Earth gravitational environment. All physical and physiological systems are challenged. Bones are stressed, antigravity muscles are called into action, the otoliths of the vestibular system are stimulated in a manner similar to that on Earth, and the cardiovascular system is similarly stressed. Obviously, artificial gravity cannot address all of the problems associated with long duration spaceflight, in particular that of radiation exposure, altered day/night cycles, and the attendant psychological issues that will no doubt arise from extended confinement and isolation. It does, however, offer a countermeasure with the possibility to address the debilitating and potentially fatal problems of bone loss; cardiovascular deconditioning, muscle weakening; sensory-motor and neurovestibular disturbances, and regulatory disorders. Because artificial gravity addresses all such systems across the board, it can be considered as an integrated countermeasure (Clément and Pavy-Le Traon 2004).

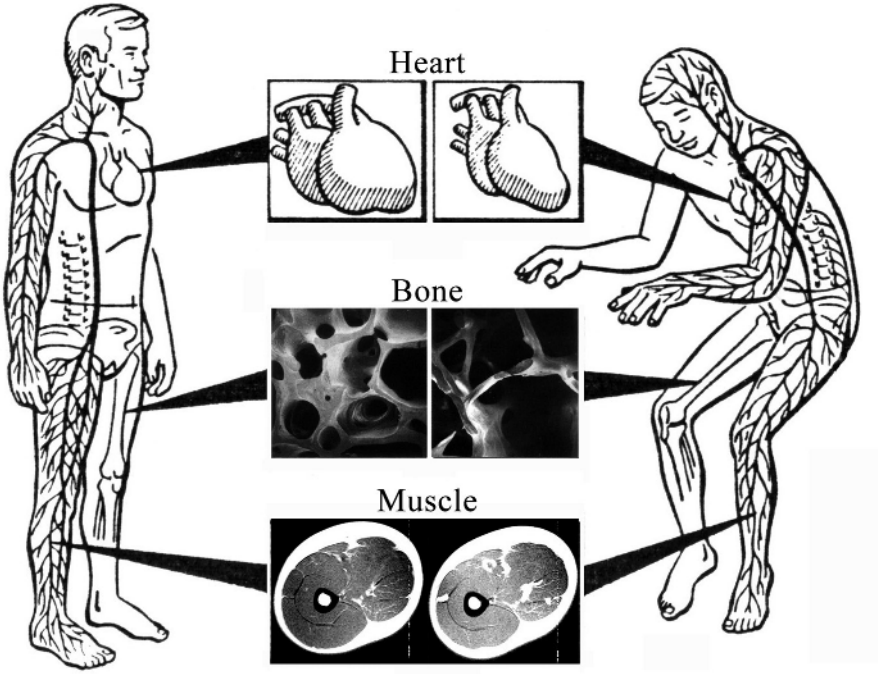

Figure 1-02. The known adverse affects on human beings of long-term stays in microgravity include bone demineralization, muscle atrophy, and reduction in heart size and plasma volume.

2 MARS MISSION SCENARIO

Mars will be the first nearby world that humans will visit. With its recognizable four seasons, clouds, polar ice caps, mountains, dry riverbeds, and dormant volcanoes, Mars is the most Earth-like planet in our solar system. The greatest potential for human habitation lies on Mars. Although it has a very cold, dry climate, surface temperatures at the equator can reach 26°C during the summer.

Scientists believe that conditions on Mars and Earth were similar billions of years ago. Data from past Mars missions suggest that the planet once had a warmer, wetter climate and abundant liquid water in the form of lakes, rivers, and even oceans during its early history. A detailed exploration of Mars could potentially provide insight into the past and future of our own planet. We might also learn if Mars could sustain self-sufficient colonies that might prove to be a lifeboat for humanity's survival in the event of some global calamity. Finally, exploring the planet could create new commercial opportunities and sources of income.

Robotic exploration missions have already provided detailed studies of the planet, located vital sources of water, analyzed soil samples, and identified the best landing sites. At the time this book is being written, the Mars Exploration Rovers *Opportunity* and *Spirit* are still exploring small patches of Mars on opposite sides of the planet. NASA and ESA are planning additional missions slated to land at various locations on Mars. These feature mobile or stationary landers equipped with robotic arms for exploration. The little Mars exploring robots are amazing pieces of engineering and have many discoveries left to make. However, they do have their limitations. It took *Opportunity* 56 days to explore a 20-meter crater. A year was required for *Spirit* to travel two kilometers, something an astronaut or a more capable robot could perform in a couple of hours.

Although robots will always be a required component of any exploration missions, humans are able to go a little further, wonder what's over the horizon, and explore areas that the rovers might not be able to reach. Astronauts will drive for kilometers across the planet's diverse terrain in advanced roving vehicles equipped with specialized tools, drills, and analytical instruments. Much of their time will be spent searching for water and past and present evidence of Martian life forms, as well as conducting a wide range of scientific activities that cannot be accomplished by robotic exploration.

The human explorers must also be shielded from harmful radiation while traveling in their spacecraft and when on the Red Planet's surface. And because the gravity on Mars is only 0.38 g, it is possible that this is not sufficient for counteracting the detrimental effects of microgravity on their body functions experienced during the journey to Mars. Their survival in such an inhospitable environment will be solely dependent on their combined expertise, specialized skills, available equipment, and countermeasures. When unexpected problems and challenges arise, as they undoubtedly will, the astronauts will be required to solve them with little or no help from Earth. Radio communications with mission controllers will be difficult because of the transmission time delay between Mars and Earth. Depending on Mars's distance from Earth, which can range from 75 to 350 million km, radio signals from the planet can take anywhere from 5 to 20 minutes to reach Earth.

No one knows how many billions of dollars a human mission to Mars will eventually cost, and the enormous financial burden must necessarily be shared by many nations. The epic endeavor will be far more dangerous and technically difficult to accomplish than the human missions to the Moon that occurred over four decades ago. The Moon is only 350,000 km away. If an Apollo 13–type disaster were to happen, the astronauts would not be able to return again to Earth.

The urge to explore and natural curiosity are inherent human characteristics that will eventually inspire us to overcome the challenge of sending humans to Mars. The underwater world would not have been so appealing without the visionary human touch of Jacques Cousteau. Thanks to the vision of advocates for human Mars missions, realistic scenarios have been proposed. Since Wernher von Braun first sketched out his *Mars Project* in 1953, a succession of designs and human mission profiles have been seriously studied in the United States and the Soviet Union/Russia. Comprehensive reviews of Mars expeditions projects are available on the Internet (http://www.astronautix.com/craftfam/martions.htm, retrieved 21 April 2005) and in Portree (2001). The most recent studies of potential Mars mission scenarios include the Paine's Report on *Pioneering the Space Frontier* (Paine 1986), Ride's Report of a *Mars Exploration Plan* (1987), NASA *90-Day Study Mission* (Cohen 1989), NASA *Mars Evolution* and *Space Exploration Initiative* studies (Stafford 1991), Robert Zubrin's *Mars Direct* approach (Zubrin 1991), NASA's *Design Reference Missions* (Hoffman and Kaplan 1997), and the latest NASA's *Vision for Space Exploration* (2004) and ESA's *Aurora Programme* (Bonnet and Swings 2004).

Historically, proposed scenarios for human missions to Mars have fallen into two categories: conjunction-class and opposition-class. *Conjunction-class* missions are characterized by low speed transits followed by a long, roughly 500-day, stay on Mars before returning to Earth. The long stay is required because by the time the ship has arrived at Mars, the Earth has traveled too far around the sun to be overtaken on a return trip (Figure 1-03).

Opposition-class missions usually entail faster transits, higher delta-V braking requirements upon arrival, and far shorter stays of roughly 30 to 90 days on Mars. The typical total trip time for such a mission will be approximately 430 days. Often, an opposition-class mission will necessitate the transfer ship crossing inside the orbit of Venus upon return to catch up with the Earth.

As this book is written, a definite timetable for space exploration has not been established. The ultimate time of transit to Mars and back is uncertain because of the undetermined nature of the propulsion system to be employed. Nevertheless, the Mars mission scenario we refer to in this book is a conjunction-class type mission, with an Earth-Mars transit time of about six months, Mars surface stay of about 18 months, and a six-month return flight. Hence, a total mission duration of about 30 months. This scenario is not based on any single specific mission architecture. It reflects the best assessment that can be made at this time concerning the possibility of an extraterrestrial venture. Despite these uncertainties, the authors of this book believe their findings and recommendations regarding the most important health issues facing human exploration, and the potential of artificial gravity as a countermeasure, would apply independent of mission scenario.

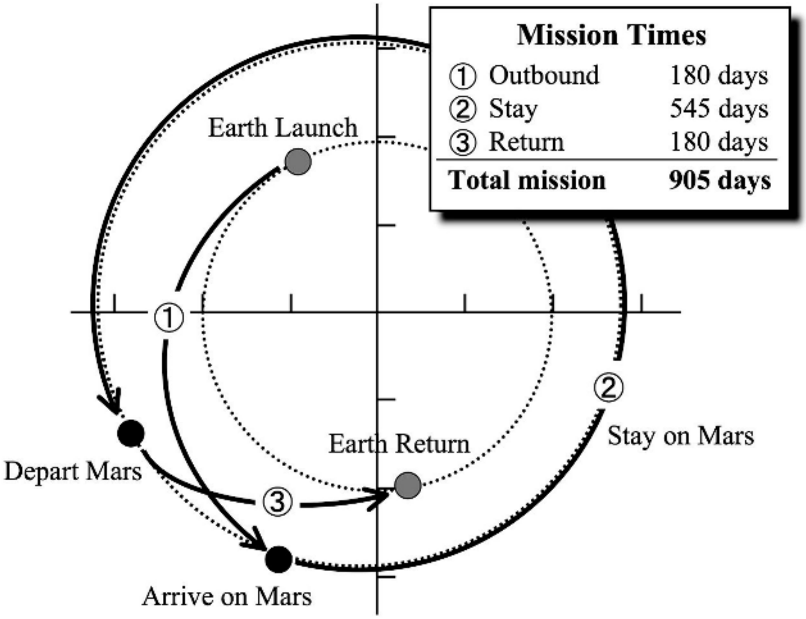

Figure 1-03. During the past several years, several meetings have re-examined potential Mars mission scenarios (Hoffman 1997). This drawing illustrates one feasible scenario for a human mission to Mars. Total mission time is 905 days away from Earth. This conjunction class *mission profile includes a 180-day transit to Mars, a 545-day stay on the surface, and a 180-day return flight.*

3 DETRIMENTAL EFFECTS OF WEIGHTLESSNESS

The effects of the space environment on the human body are well documented. For a comprehensive review, the reader is invited to consult other books in this *Space Technology Library* series, including *Space Psychology and Psychiatry* by Kanas and Manzey (2003) and *Fundamentals of Space Medicine* by Clément (2005). Artificial gravity cannot solve the critical problems associated with radiation exposure, isolation, confinement, and reliability of life support systems. However, it can deal with the detrimental effects of long-duration exposure to weightlessness. These effects are reviewed here, with an emphasis on the health and operational issues facing human exploration missions.

3.1 Bone Loss

Bones are living tissue, constantly being strengthened by dietary calcium extracted from the blood and destroyed by returning calcium to the blood for excretion. Bone maintenance requires a compressive load along the axis of the bone coupled with some high-force impulsive loading. In the absence of these loads that are normally provided by gravity and walking, the major bones that support body weight begin to deteriorate. As a result, a net loss of body calcium occurs, independent of the amount taken in with food or supplements.

The long bones in the legs and the vertebrae lose mass and strength during prolonged bed rest. Similarly, a loss of bone mineral and its excretion are observed in humans during spaceflight. Calcium is lost at a rate of about 1% per month, and the losses are reflected in the density and mass of weight-bearing bones. The rate of calcium loss is not reduced by vigorous exercise. Along with the calcium loss is also a loss of phosphorus. An increase in urinary hydroxyproline, which is a major component of the protein collagen that strengthens the bone, shows that there is a corresponding deterioration of the bone matrix. The increased blood levels of calcium lead to further concern about possible deposition of calcium in the kidneys or other soft tissues. In weightlessness bone resorption decreases slightly, but bone formation decreases more severely (Leblanc *et al.* 2000).

These changes account for the net decrease in bone mass, especially in the weight-bearing bones, during spaceflight. Unless the process reaches a plateau, which has not been observed during missions of up to 14 months duration, a 40% decrease in bone mass might occur for a spaceflight lasting two years. Such a decrease in bone mass increases the risk of fracture and might severely alters the ability of the bone to repair itself. Bone loss represents a serious danger to astronauts, especially during exposure to the stresses of re-entry after a long period of weightlessness.

Bone mass changes continue for up to six months after landing (Vico 2000). Consequently, even after arriving on the Mars surface, astronauts may continue to lose bone mass. If it turns out that the Mars gravity level of 0.38 g is not enough to prevent further bone mass deterioration, astronauts returning from a 30-month mission to Mars will possibly suffer severe osteoporosis. While this bone loss is similar in some ways to osteoporosis observed on Earth, pharmacological countermeasures have not yet been shown to be effective in space. Similarly, the effect of exercise in microgravity has not resulted in minimization of bone loss.

3.2 Muscle Atrophy

Muscles are adaptable tissues. Increase the load on them by lifting weights or other types of exertion, and they grow larger and stronger. Reduce the load by lying in bed or living in microgravity, and they grow smaller and weaker. When a muscle is loaded, its fibers begin a series of intracellular signaling steps. Genes within the cell nucleus make *ribonucleic acid* (RNA), which synthesizes proteins that make up muscle fiber. Lifting weights activates the expression of these proteins, which accumulate and enlarge the muscle fibers. Microgravity has the opposite effect. It reduces the load that gravity naturally places on muscles, interrupting protein synthesis so that fibers begin to atrophy. This loss of muscle mass contributes to reduced skeletal muscle strength when astronauts return to Earth.

Very significant losses of muscle strength, muscle volume, and total body weight are noted during spaceflight. Muscles that manifest the most significant changes are the major muscle groups in the legs and back that work against Earth's gravity to support body weight.

These changes represent the actual breakdown of muscle tissue due to its disuse in weightlessness and a reorganization of the properties of the muscle fibers, which are the primary muscle constituents. Only 14 days in microgravity may cause muscle fiber atrophy of as much as 30% (Edgerton *et al.* 1995). As a result, the muscle generates less force and power. Muscle fibers are of two main types: "slow" fibers that work against gravity to maintain erect posture and "fast" fibers that are involved in rapid, high power movement such as jumping and sprinting. Because slow muscle fibers are the primary anti-gravity effectors, they are affected the most in weightlessness because they are not working against any load. In fact, after long-term exposure to microgravity, the slow muscle fibers begin to behave more like fast fibers when subjected to an external load. Specifically, they contract more rapidly, making them more adapted for rapid bouts of sprinting than for long-term standing or walking. However, they tire quickly.

Studies reveal that about 15-20% of the slow fibers in a thigh muscle convert to fast fibers during a 14-day spaceflight. With longer flights, the degree of fiber switching from slow to fast might increase. A direct consequence of this "reprogramming" of muscle fibers is a decrease in endurance as a function of time in flight, which could have a serious impact on human performance. Furthermore, fast fibers are more vulnerable to injury during contraction. Another matter of concern is the fact animal studies showed that muscle fiber regeneration is less successful in space.

After spaceflight astronauts experience muscle weakness, fatigue, faulty coordination, and delayed-onset response. Muscle atrophy also causes soreness as damaged muscles tear while readjusting to Earth's gravity. Exercise workouts help astronauts fight back. Historically, U.S. and Russian astronauts have relied on aerobic exercises, primarily pedaling a cycle ergometer (an exercise bike) and running while tethered to a treadmill (Figure 1-04). Unfortunately, aerobic exercises are designed to condition the cardiovascular system rather than apply loads systematically to a wide range of muscles. Cycling, for example, applies a good load to the upper leg but not the lower leg or back.

Different types of exercise are required to build strength and resistance to fatigue and injury. Any microgravity exercise routine must maintain not only muscle mass and strength, but also the right mix of proteins to balance fast-twitch muscle power with slow-twitch muscle endurance. On Earth, strength-training programs typically combine isotonic and isometric resistance exercises: high-intensity isotonic motions shorten and lengthen muscles (for example, lifting and lowering a dumbbell), and isometrics fully contract muscles without movement (for example, pushing against a doorway). Theoretically, both types of exercise could potentially reduce muscle atrophy in microgravity (Di Prampero *et al.* 1996). Experiments with rats, however, suggest that isometrics may protect slow fibers better than isotonics because slow fibers develop very little force during relatively fast isotonic motions.

Yet despite rigorous exercise, astronauts return to Earth shockingly weaker than when they left. Exercise alone has not prevented muscle wasting during spaceflight. The ideal microgravity exercise program therefore remains to be defined.

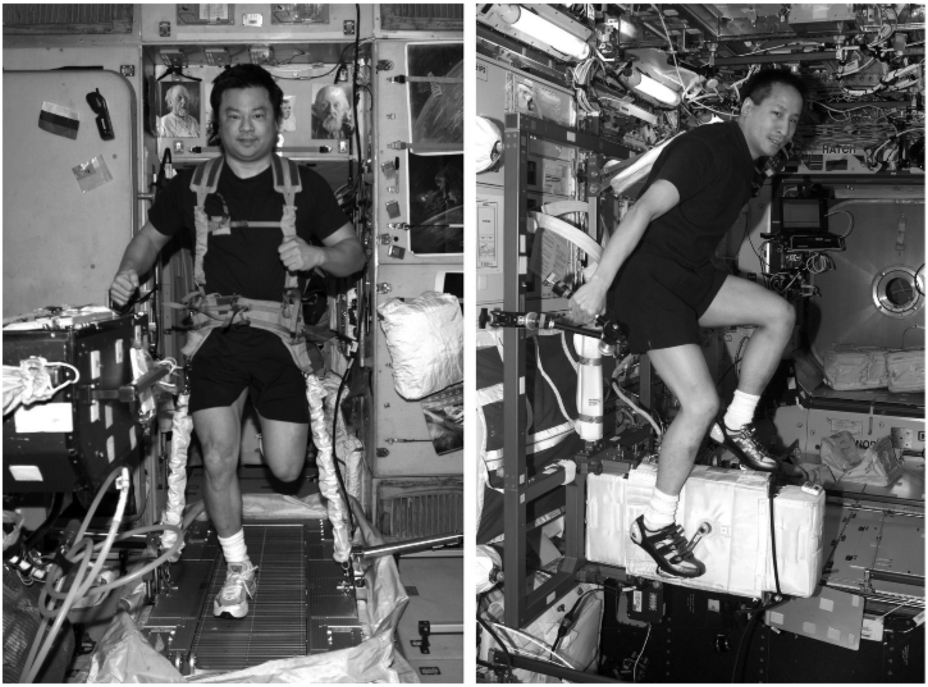

Figure 1-04. Left: Astronauts exercising on the treadmill (left) and on the cycle ergometer (right) on board the ISS. A vibration isolation system reduces the vibration transferred from the devices to the Station structure during exercise. Photos courtesy of NASA.

3.3 Cardiovascular Deconditioning

The cardiovascular and pulmonary systems supply the body with required oxygen. On Earth, the heart must constantly work against gravity to push oxygenated blood through the arteries. In space, the lack of gravitational force causes a shift of blood and other fluids to from the lower parts of the body to the head and chest. The upward fluid shift triggers many changes in the cardiovascular system.

Cardiovascular deconditioning begins immediately upon orbital insertion as a result of the shifting of fluid from the legs and lower trunk to the upper body. This produces the first symptoms of fullness of the head and associated discomfort on orbit and initiates an early loss of body fluid, including blood plasma. The relative excess of red blood cells is countered by stopping their production in the bone marrow and additionally by destroying young red blood cells.

Long- and short-term studies of humans in space have documented the incidence of increased heart rate, narrowed pulse pressure, reduced plasma volume, decreased heart chamber volume, and facial edema (Meck *et al.* 2001). Animal studies also indicate that the myocardium may degenerate during microgravity exposure.

The cardiovascular regulating system that maintains adequate blood pressure when we stand up is no longer needed in space. It soon shows signs of deterioration after arrival on orbit. Neither the fluid loss, which because of the reduction in red blood cell mass results in "space anemia," nor the loss of cardiovascular regulation and tone cause any difficulty in orbit. During re-entry and then after landing on Earth, however, the renewed exposure to gravity may cause weakness. Astronauts might feel lightheaded as a result. When they stand up, the blood pressure may drop. This can lead to fainting. These symptoms that arise due to circulatory deficiencies sometimes remain for weeks after landing (Buckey *et al.* 1996).

During flight, cardiovascular fitness is compromised. This situation results in a diminished maximum oxygen consumption capability during exercise. A decreased exercise capacity and orthostatic intolerance may decrease crew performance during descent from orbit and increase their risk should an emergency egress from the spacecraft be required upon landing. The mechanisms behind these phenomena are still uncertain. However, hypotheses include decreased intravascular volume, increased postflight venous pooling due to structural and reflex vascular changes, and alterations in overall cardiovascular reflex control (Churchill and Bungo 1997).

Unlike the cardiovascular system, no pulmonary system (e.g., ventilation and respiration) problems have been associated with weightlessness per se, and researchers have devoted less attention to its physiology in microgravity. However, lung function can be altered by changes in vascular pressure and volume. Scientists have, in fact, reported a drop in partial pressure of oxygen in microgravity.

Figure 1-05. The Expedition Three (white shirts), STS-105 (striped shirts), and Expedition Two (gray shirts) crews assemble for a group photo in the Destiny laboratory on the ISS. Photo courtesy of NASA.

3.4 Sensory-Motor Deconditioning

Sensory-motor deconditioning begins in microgravity with the changes in vestibular (otolith organs of the inner ear) and somatosensory (touch, proprioception, kinesthesis) cues that are associated with spatial orientation and the control of posture and movement (see Clément and Reschke 1996 for review).

Because the only stimulus to the otolith organs in weightlessness is linear acceleration due to translation, but not to tilt, considerable re-interpretation of vestibular signals take place with new sensory-motor strategies developed (Parker *et al.* 1985). A consequence of this process is the common occurrence of space motion sickness during the early phases of the flight, spatial disorientation throughout the mission (Figure 1-05), and postural disturbances and vertigo upon return. Although the incidence of space motion sickness generally vanishes after a few days in space (Davis *et al.* 1988), recurrent episodes have been observed during long-duration missions. The Mir and ISS experiences indicate that about 90% of astronauts and cosmonauts suffer from "mal de débarquement" following missions lasting several months (Jennings 1997). The symptoms are similar to those of space motion sickness experienced during the flight.

In weightlessness, the antigravity muscles are continuously unloaded and the antigravity reflexes, utilized in maintaining posture and locomotion on Earth, are inactive or modified. As a result, there is a loss of extensor reflexes in space. Sensory information about limb position is not interpreted correctly, and voluntary pointing accuracy and perception of static limb position are impaired. Alteration in movement coordination in microgravity is also due to cognitive changes in the mental representation of body (body scheme) along with the environment, or to the conservative use of an internal gravity model. Upon return to Earth after long-duration missions, there is postural imbalance resulting in uncoordinated locomotion. It takes a long time for the astronaut to re-adapt and recover from this condition (Paloski *et al.* 1993). After flights lasting six months or more, some crewmembers must be physically removed from the vehicles on lifters (see Figure 1-01).

A prolonged period of postural inactivation and impairment of locomotion would not be acceptable in the event that an emergency egress was required after landing on Mars. Moreover, the astronauts' ability to accomplish piloting tasks, or even exercise on a treadmill in the Mars gravitational environment might also be seriously impaired. At present, there are no known countermeasures for such impaired locomotion other than re-adaptation during exercise in a 1-g environment.

3.5 Regulatory Physiology

The physiology of humans is composed of a totally integrated set of complex subsystems that maintain critical physiological parameters (e.g., temperature, fluid balance, biological rhythms, and electrolyte levels) at relative stable levels, a function called *homeostasis*. Operational observations and spaceflight experiments have demonstrated changes in these physiological parameters and processes. For example, changes in electrolyte balance, blood cell mass, hormone synthesis, and hormone action have been observed during spaceflight.

Body fluid shifts occurring during spaceflight are complicated by the loss of electrolytes, including sodium and potassium, that continue throughout the duration of the mission. Hormonal responses seem ineffective in preventing the fluid and electrolyte losses. The extent of these electrolyte losses during long flights is unknown and difficult to predict. Several complications could arise from prolonged electrolyte loss, ranging from dehydration to abnormalities in cardiac function. In fact, the incidence of heart rhythm irregularities seems to increase during long-duration exposure to weightlessness (Fritsch-Yelle *et al.* 1998).

Regulation of body fluid and electrolyte balance is a fundamental homeostatic function. Severe dehydration or loss of sodium and potassium can also alter skeletal muscle function, temperature regulation, and cellular electrochemical gradients potentially resulting in circulatory collapse. The regulation of fluid and electrolytes is essential to the ability to respond to physical and emotional stress. The ability of individuals to handle normal as well as emergency procedures after a Mars landing may be severely compromised by a reduction in plasma volume and potassium levels, despite the saline loading procedures executed in an effort to restore plasma volume. At this point, it is not clear just what the relative contributions of hormones and reflexes in controlling fluid balance really are.

The loss of red blood cell mass described above undoubtedly contributes to orthostatic intolerance and decreased postflight exercise capacity. While the primary cause appears to be the influence of microgravity, the etiology is probably multi-factorial, including influences such as hypokinesis, hypodynamia, bone demineralization, bone remodeling, muscle atrophy, altered hemodynamics, modified oxygen demand or oxygen carrying capacity, and nutritional and metabolic disturbances that in turn may be due to exposure to microgravity. Regardless of the duration of the spaceflight, restoration of the lost blood cell mass can require four to six weeks following return to Earth. Although this spaceflight-induced anemia does not appear to compromise the health and performance of astronauts during or after flight, in-flight illnesses or injuries could alter cardiovascular and respiratory requirements to the extent that the reduction in blood cell mass may cause a problem.

White blood cells, which help the immune system identify and destroy external as well as internal pathogens, also appear to experience a reduction in number in microgravity. Pre- and postflight measurements have demonstrated that spaceflight causes a suppression of the cell-mediated immune system thus reducing the ability to fight infection. Immune system function returns to preflight levels within approximately 30 days after return to Earth. Due to limited in-flight data, we do not know whether in-flight levels stabilize at a new depressed spaceflight homeostatic level or continue to decline throughout the flight, and whether recovery will occur after extended duration missions (Taylor 1993).

Although data regarding the detailed responses of the neuroendocrine, hematological, and immune systems to extended spaceflight are limited, it is clear that countermeasures are required. These countermeasures include pharmacological, dietary, chemical, and behavioral manipulations (NASA Advisory Council 1992).

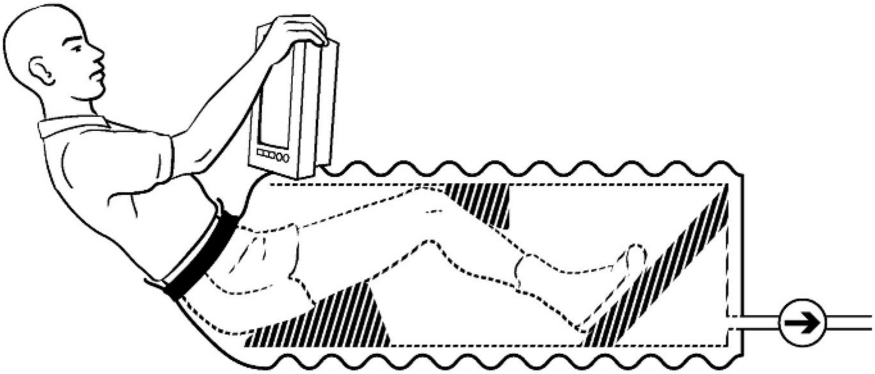

Figure 1-06. The Lower Body Negative Pressure *(LBNP) device encloses the lower abdomen and lower extremities to maintain a controlled pressure differential below ambient. This causes the intravascular blood volume to shift towards the lower extremities in microgravity, in a manner similar to the orthostatic load caused by assuming an upright posture in Earth gravity. Drawing by Philippe Tauzin (SCOM, Toulouse) (Clément 2005).*

3.6 Human Factors

Challenges associate with human factors also arise in weightlessness. These include the constant need for hand or foot restraints for stabilization and the possibility of disorientation within a spacecraft. Other human factors issues present in a weightless environment include waste management, fluid handling, food preparation, and hygiene.

Workstation and computer designs must account for differences in stature, posture, biomechanics, and strength. However, it is not possible for designers to account for all the "new" non-standard orientations that are possible in weightlessness. For example, if a crewmember floats over to the workstation upside down (see Figure 1-05), how might displays and controls be designed so that procedures are not executed backward?

In orbit, feet are nearly useless appendages after the initial push-off. The fingertips are the primary mode of motion control. Pushing on a toggle switch is more likely to result in rotating the operator's whole body than in repositioning the switch unless the operator is restrained. Mobility aids and force restraints are a must when it comes to reducing bumps and bruises when people are moving about in space. This is also important when someone wants to *stop* moving. In partial gravity environments, such as on Mars or the lunar surface, moving from one place to another is extremely different from similar activities on Earth. Video sequences of humans on the Moon show that they tend to bounce around, rather than walk in a typical fashion. Space suits and tools must be designed to take into account the way human locomotion and behavior change in space.

A gravity field is required for natural convection currents to act. As a consequence, hot air does not rise in weightlessness. This means that fans are required to circulate the cabin air if an astronaut wants to breathe fresh oxygen in every breath. Heat from electrical components such as laptop computers does not move away from the device unless energy is used for active cooling. This includes humans, as well.

The confined space of the spacecraft cabin limits the human senses and perceptions. Isolation from colleagues, family, and friends can also alter social relationships, expectations, and support structures (Kanas and Manzey 2003). Daily stress is exacerbated on a daily basis by the hostility of the external space environment and the inherent risk of spaceflight. Everyday tasks become more difficult as a result. There is little to no room for error when it comes to controlling teleoperated robots or programming automated machines. These tasks require a significant amount of time and special skills. A minor mistake or momentary inattention to detail can quickly result in death or mission failure. Consequently every single task, no matter how apparently trivial, becomes much more important.

The nature of spaceflight combined with new human-designed environments and tools for living and working in space impact the ways in which people do things. Solving cognitive problems, meeting unexpected challenges, maintaining safety, staying attentive and motivated on long, boring flights from planet to planet while maintaining teamwork, family ties, and a healthy personality are all aspects of the interaction between a human and the designed environment. And this does not even take into account the fact that sleep and circadian rhythms are also altered during spaceflight (Gündel *et al.* 1997).

Finally, weightlessness also complicates the design and operation of life support systems for human missions, especially for the management of fluids and heat transfer. Because the components of life support systems (e.g., pumps, fluid/air condensers, separators, sublimators) are extensively tested in a 1-g environment, prediction of component behavior and subsequent optimization of the system would be simpler if artificial gravity were present onboard the spacecraft. An artificial gravity design would extend to such performance qualities such as simplicity, reliability, safety, and maintainability (National Research Council 2000).

4 ACTIVITIES ON MARS SURFACE

The ability to function on Mars after a long transit is of paramount importance. Not only is the crew required to manage their vehicle as it enters the Martian atmosphere and lands, but they also must manage the reconfiguration of the ship's systems once it has landed. They must be prepared for contingencies after landing, including repairing or accommodating any damage that might occur after a rough landing as well as the assembly of hardware on the surface. There are substantial concerns regarding the ability of a crew to perform all of these tasks after many months in microgravity.

Studies have already been executed on board Space Shuttle missions to allow pilots to practice their landing skills after prolonged stays in space. These studies were done to ensure that the ability to orient oneself and fly a vehicle are not diminished after long periods in weightlessness. Moreover, as g forces reassert themselves, the amount of blood flowing to the brain can decrease. This leads to possible light-headedness, fatigue, or disorientation, which are symptoms that a Mars vehicle pilot cannot afford to experience.

Some lessons can be learned from the ISS experience. For example, in May 2003, due to a software error, the Soyuz that returned the Expedition-6 crew from the ISS followed a steeper descent path. As a result, the crew was subjected to about 8-10 g during re-entry, and they missed their targeted landing site by nearly 400 km. When they opened the hatch, the crewmembers were still strapped into what had become the ceiling. Having come from almost six months in weightlessness, it took the three crewmembers several hours to drag themselves out of the hatch under the oppression of Earth’s gravity and erect a folded communications antenna to help the searching planes and helicopters find them. During preflight training, such activity was performed in just a few minutes.

Under current circumstances, humans arriving on Mars would be in the same undesirable condition as those humans returning to Earth from Mir. The lower level of Martian gravity would not make that much difference. Landing activities and any post landing surface activities would be at risk without a crew in tip-top condition. It is expected that surface activity on Mars will be rather limited for the first several weeks under even the most optimal circumstances for any crew traveling to Mars in microgravity.

Some astronauts and cosmonauts returning from long-duration missions insisted on standing up immediately upon landing to show the public that they were okay after living in space for a long time. However, in many cases, the ability to stand up lasted only a few hours. Standing upright at these postflight media events was, in fact, followed by a 6-week rehabilitation period. Astronauts who actively practice jogging report that after a 16-day spaceflight it takes them several weeks to return to their preflight running conditioning. When astronaut John Blaha came back from Mir, he told the press that he was a “basket case” and that he could not move.

Life on the way to and from Mars is responsible for only some of the issues facing Mars mission planners. Martian space suits must be vastly more attuned to human ergonomics than any currently in existence. Space suits are essentially self-contained spacecraft. These special garments are pressurized to maintain their shape and to provide a suitable human environment. Therefore, regardless of where and how you use a space suit, each motion must work against this pressure making task execution very difficult. The hands have the hardest time when working in a pressurized space suit. The space suits needed for Mars exploration will need to accommodate prolonged movement and activity on the surface, something with which the suits used in microgravity are not required to contend.

In light of the discussion in the above paragraph, it is clear that advanced surface space suits must be developed. The suits designed for use on the Apollo missions, while able to allow the crew to perform their tasks, were rendered useless after their brief employment on the Moon. Apollo-17 astronaut Jack Schmitt spoke of how the lunar dust had managed to work its ways into all of the suit joints such that they did not function at the end of his third spacewalk. The space suits to be used on Mars must be designed for as many as 300 trips across the surface. These trips will last for many hours and require the users to perform a wide array of movements. Current Mars suit designs exhaust their wearers after 10 to 15 minutes of use. The suits also need to be designed for routine maintenance on Mars by the crew, not a contractor back on Earth.

Figure 1-07. This photograph of the middeck of the Space Shuttle configured for return to Earth shows the three crewmembers who have spent four months on board the ISS in their recumbent seats (right) by comparison with the upright seat of the Shuttle crewmembers who have only spent 12 days in space (left). Photo courtesy of NASA.

5 CURRENT COUNTERMEASURES

Countermeasures refer to the application of procedures or therapeutic means, including physical, chemical, biological, or psychological, to maintain physiological balance, health, physical fitness, and mission performance. Countermeasures also reduce risk and improve human spaceflight safety. Countermeasures typically aim at preventing, mitigating, or minimizing the effect of adverse or harmful agents on the crew. This section reviews the countermeasures currently used to moderate the effects of microgravity conditions during space missions, including the constraints they impose on the crewmembers and the mission timeline.

Space biomedical researchers have been working for many years to develop countermeasures to reduce or eliminate the deconditioning associated with prolonged weightlessness. Some procedures are utilized before the flight, such as medical screening and selecting new astronaut candidates, prescribing individualized exercise programs, or providing quarantine just prior to launch in order to limit pathogen access to flight crew. Other countermeasures are utilized during the flight, which include administering drugs and crew exercise on various workout devices, as well as during re-entry. However, most of them have been either marginally effective or present a major inconvenience for the crew or impede the mission timeline. After landing, circadian rhythm shifting, hormone replacement, and physical rehabilitation are performed to accelerate the crewmember return to their normal Earth-based duties.

5.1 In-Flight Countermeasures

Space walks, manual docking with other spacecraft, landing, and other critical activities are not scheduled during the first 2-3 days of a mission to avoid coinciding with episodes of space motion sickness. Intramuscular injection of the antihistamine promethazine has been shown to be quite effective in decreasing the symptoms of space motion sickness in most, but not all, crewmembers. Recent research indicates, however, that this medication can cause deleterious side effects that further degrade human performance and negatively impact memory, mood, and sleep (Paule *et al.* 2004).

A *Lower Body Negative Pressure* (LBNP) system is a device that can be used at the end of a mission for predicting which astronauts will be more susceptible to postflight orthostatic intolerance (Figure 1-06). This device provides a rapid decompression from ambient pressure to –60 mmHg[3].

[3] Millimeter of mercury (mmHg) is a non-SI unit of pressure, but it remains a common unit for the measurement of blood and gas pressure. It is the atmospheric

Therefore, similar effects to postflight orthostatic intolerance can occur when this device is employed. Slower or constant decompression regimes can then be applied to recondition the system for Earth's gravity. There are, however, significant inter- and intra-individual differences in the responses to in-flight LBNP tests, which make it difficult to use as a predictive tool (Arbeille at al. 1997).

Ingesting about one liter of water or juice and eight salt tablets at approximately one hour prior to leaving orbit is another countermeasure used for compensating for fluid loss. This fluid loading protocol produces one liter of isotonic saline in the digestive track, which then leads to absorption and subsequent increase in plasma volume. This technique has proven effective for short-duration missions by reducing the occurrence or severity of postflight orthostatic intolerance. However, the effectiveness of fluid loading is reduced with longer time in orbit. Factors other than cardiovascular deconditioning are suspected to become more important on longer flights with regard to causing orthostatic intolerance.

In the critical period of re-entry and landing, Shuttle astronauts routinely wear anti-gravity suits. These suits contain balloon-like pressure bladders in the pants, which can be inflated by the astronaut. When the astronauts inflate these bladders, they press against the legs, forcing fluids into the upper body. This helps the heart to pump blood more efficiently by pushing the blood out of the lower extremities. The Russians wrap the lower body tightly with elastic strapping to achieve the same effect as the anti-gravity suit.

Anyone who has been on orbit for more than 30 days is required to be returned to Earth in the supine position (hence receiving gravito-inertial forces along the +Gx direction[4]) to reduce the risk of orthostatic intolerance during re-entry and landing. The Space Shuttle is equipped with recumbent seats for returning long-duration crewmembers from the ISS (Figure 1-07). There is, however, a concern that these crewmembers may not be able to egress from the recumbent seat system without some assistance.

Although its effects on orthostatic tolerance are still unknown, an in-flight aerobic exercise program is performed in conjunction with resistive exercise. The ISS crews exercise 2½ hours per day for three days, with some optional change on the fourth day. Several exercise devices are available, including a treadmill to preserve aerobic power, a cycle ergometer to preserve

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pressure that supports a column of mercury 1 millimeter high. 1 mmHg = 133.32 Pa or 1.3158×10^{-3} atm.

[4] Throughout this book, Gx, Gy, Gz indicate the direction of the gravito-inertial force vector along the body x-, y-, or z-axis, respectively. For the definition of the body axes and the sign convention, see Figure 2-02. The gravity level unit is indicated by the letter *g*, e.g., "the subject received 2 g at the feet in the +Gz direction".

aerobic capacity, a resistive exercise device to preserve muscle strength (Figure 1-08), and handgrip equipment to preserve hand strength for extra-vehicular activity.

The treadmill may be used for walking, running, and resistive exercise. Loads are exerted on the subject by restraint harnesses and bungee cords to simulate normal gravity skeletal loading during exercise. There are two modes of operation: (a) the motorized (active) mode provides astronauts with speed control adjustable from 0-16 km/h; and (b) the non-motorized mode allows the astronaut to drive the tread belt with variable mechanical resistance without the motor. The treadmill can be used as an ambulating trainer, endurance exercise of postural musculature, high impact skeletal loading for bone maintenance, and aerobic exercise for cardiac training.

The cycle ergometer provides a workload variable between 25 and 350 watts, driven by the hands or feet, which is controlled by manual or computer adjustment. It operates with the subject seated or supine, and provides time-synchronized data compatible with other complementary analysis tools. The cycle ergometer is used as an aerobic and anaerobic exercise countermeasure, for the maintenance of lower body musculature endurance, and for arm exercise training in preparation for extra-vehicular activity.

Figure 1-08. Left: An astronaut wearing squat harness pads performs knee-bends using the Interim Resistive Exercise Device *(IRED) on board the ISS. Right: He is using the "short bar" of the IRED to perform upper body strengthening pull-ups. Photos courtesy of NASA.*

The *Interim Resistive Exercise Device* (IRED) includes a series of human-machine interface devices (e.g., handgrips, straps, curl bars, ankle cuffs, and squat harness) that permit a variety of exercises to be performed by the astronauts (Figure 1-08). Cables on each side of shoulder straps are connected to two canisters, each containing a series of “flex packs” that can be dialed in sequentially to add greater resistance to the cables. The device provides eccentric and concentric contraction through a full range of motion of various exercises (Table 1-01). The IRED is used as training for muscle strength and endurance of all major muscle groups, to maintain skeletal muscle mass and volume, and to provide high-strain skeletal loading for bone maintenance.

Day 1	***Day 2***	***Day 3***
Dead lifts *Bent-over rows* *Straight leg dead lifts* *Heel raises*	*Shoulder presses* *Rear raises* *Front raises* *Hip abduction* *Hip adduction*	*Squats* *Heel raises* *Straight leg dead lifts* *Bent-over rows*

Table 1-01. Resistive exercise workout recommended daily for the ISS astronauts. Note that lower body exercises are performed every day.

While exercising, the Russian cosmonauts sometimes also use thigh constriction cuffs to decrease fluid shift, although data on the effectiveness of these cuffs are lacking (Herault *et al.* 2000). Further in-flight countermeasures include whole-body elastic loading suits, such as the Russian “Penguin” suit (Figure 1-09). Beside its effect on the cardiovascular system, the elastic bands in the suit also simulate some of the gravitational effects on the musculo-skeletal system. Expanders are also used occasionally.

5.2 Research on Countermeasures

The unusual environment of spaceflight imposes unique demands on the design of exercise protocols to maximize their efficiency. Designing exercise protocols requires striking a balance among several parameters. These include exercise efficacy, ease of performance, subject compliance, and the operational demands of the space vehicle. These demands comprise size and weight of equipment, operational time constraints, and minimal environmental disruption. A significant issue is that the workout procedures described in the previous section are strenuous, uncomfortable, and excessively time-consuming for many astronauts and cosmonauts.

It is well known that exercise has potential benefits on the cardiovascular, immune, and musculo-skeletal systems, and is therefore also potentially beneficial to the vestibular and thermoregulatory problems. However, despite an intensive in-flight exercise regime, the effectiveness of the current exercises for maintaining bone, muscle, and aerobic fitness has not been demonstrated. Furthermore, these routines manifest inconsistent effects on sensory-motor adaptive changes and postflight orthostatic hypotension. This is partly because of the fact that different types of exercises are required to build muscle strength and resistance to fatigue and injury, and maintain bone integrity. Ongoing studies continue to investigate how muscles and bones should be loaded in microgravity to prevent these changes (Baldwin *et al.* 1996).

In contrast with the extensive studies of the effects of exercise on muscle tissue, the possible bone tissue enhancing effects of exercise are a relatively recent topic. Indirect evidence is continually building up to suggest that there is a relationship between exercise and a decreased level of osteoporosis. Some scientists currently believe that bone mass is not only controlled by the high-magnitude, low-frequency strain resulting from the mechanical loads on bones associated with vigorous exercise, but also by low-magnitude and high-frequency strain that the musculature continuously places on bones while sitting or standing. Results of ground-based studies suggest that barely perceptible vibrations may generate enough strain to stimulate bone growth (Rubin *et al.* 2001). If proven valuable for humans, low-level vibrations during spaceflight may offer an alternative for the current, time-consuming astronaut exercise regimes for long-duration space missions.

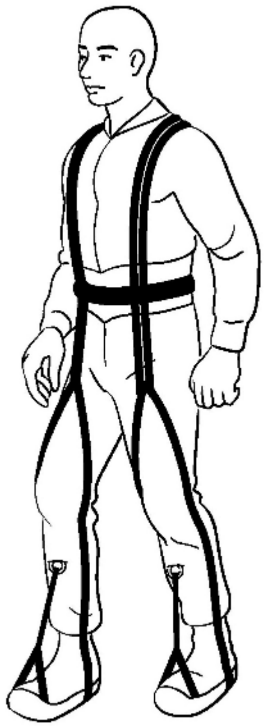

Figure 1-09. The "Penguin" suit. The inside of the suit contains a system of elastic, straps, and buckles that can be used to adjust the fit and tension of the suit. This suit forces the subjects to use his extensor muscles in microgravity to activate venous return. Drawing by Philippe Tauzin (SCOM, Toulouse) (Clément 2005).

Metabolic status can also have an effect on the physiological changes, such as bone demineralization and muscle atrophy. For this reason, nutritional countermeasures are believed to be an integral part of newer countermeasure programs (McCormick and Donald 2004). Caloric intake is an option, especially in relation to the energy expended in exercise. Obviously, the astronaut's diet has the potential for supplying enough calories so as to obviate the breakdown of body tissues to supply metabolic energy. However, it seems that increased caloric intake does not spare muscle tissue, and that spaceflight changes muscle metabolism through unknown mechanisms.

Hormones are also major factors in the control of synthesis and breakdown of tissue proteins. One hormone directly involved in tissue synthesis is *growth hormone*. Its presence is essential for the formation of muscle, bone, and other tissues during development. Other hormones that may be involved in maintaining muscle mass are insulin and testosterone. Reductions in growth hormone and testosterone during spaceflight worsen muscle health. If the opposite is true, augmenting selected hormones may maintain muscle mass in space and on Earth.

Other countermeasure projects are aimed at increasing muscle protein synthesis rates using supplements of amino acids. Bone studies are being conducted to investigate biphosphonate compounds that bind to bone crystal. These compounds tend to inhibit bone resorption, or the hormone glucose-dependent insulino-tropic peptide. This peptide is involved in bone cell insulin production.

Studies have so far indicated that drug efficacy may differ in weightlessness. Therefore, the pharmacokinetics of drugs must be examined during spaceflight. In addition, recent evidence of rapid degradation of pharmaceuticals used during long-duration missions, putatively due to radiation effects, raises concerns regarding the viability of this type of countermeasure.

A balance between nutrition, therapeutic measures, drugs, and exercise is likely to provide better protection. However, although improvements in exercise protocols, changes in diet, or pharmaceutical one-at-a-time treatments of single systems may be of value, they are unlikely to adequately eliminate the full range of physiological deconditioning induced by weightlessness. The urgency to develop countermeasures for exploration-class missions is compounded by the limited availability of in-flight resources to perform the validation of a large number of piece-meal countermeasure approaches. The surest countermeasure is clearly one that produces a gravito-inertial environment close to that on Earth, also known as artificial gravity.

6 ARTIFICIAL GRAVITY IS AN INTEGRATED COUNTERMEASURE

To realize the near-term goal of a human mission to Mars during the second quarter of this century, we must mitigate the human risks associated with prolonged weightlessness. At present, this goal is well beyond our current capabilities. Human spaceflight experience spans nearly 45 years. During that time, astronauts and cosmonauts have flown numerous long-duration missions. Yet with all of this experience, no completely effective single countermeasure, or combination of countermeasures, exists. In fact, the operational countermeasures currently employed have not been rigorously validated and have not been shown to fully protect crews executing long-duration missions, those of greater than three months, in low-Earth orbit. Thus, it seems unlikely that they will adequately protect crews journeying to Mars and back over a 30-month period (Figure 1-10).

If a crew of astronauts were to embark on a journey to Mars today, the suite of piece-meal countermeasures currently employed would leave them in a state of complete inoperability after their six-month exposure to weightlessness en route to their destination. Changes in the neurovestibular, cardiovascular, and musculo-skeletal systems are reversible upon return to normal Earth gravity. However, re-adaptation can take several weeks. It is not certain that the Mars gravity, which is 0.38 that of Earth in magnitude, will be sufficient for re-adapting these physiological functions while on Mars.

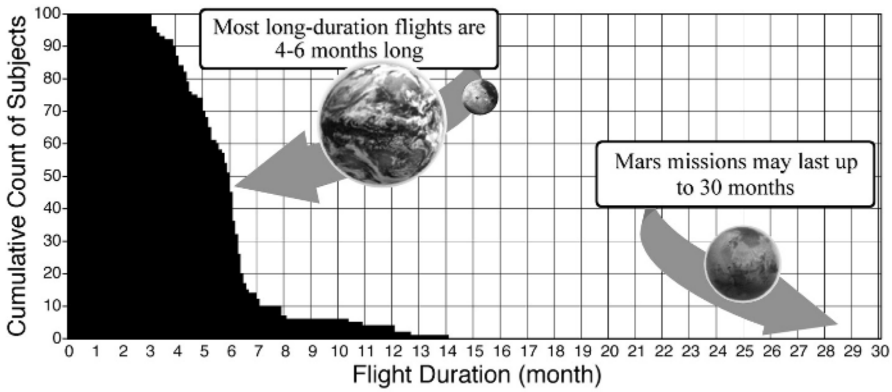

Figure 1-10. Current knowledge in space medicine is limited to space missions ranging from a few weeks to six months. Virtually nothing is known for missions lasting one year and beyond. Adapted from John Charles (NASA, Houston).

Artificial gravity represents a different and integrated approach to addressing the detrimental effects of microgravity, or even reduced gravity, on the human body. Artificial gravity mimics our natural 1-g environment. All body systems are challenged simultaneously by its application, not simply one physiological system at a time. Artificial gravity will not be a panacea for addressing all risks associated with human spaceflight. Obviously it cannot solve the critical problems associated with radiation exposure, isolation, confinement, and life support systems failures. However, it offers significant promise as an effective, efficient multi-system countermeasure against the physiological deconditioning effects associated with prolonged exposure to weightlessness. The appropriate application of artificial gravity might serve to address virtually all of the risks associated with bone loss, cardiovascular deconditioning, muscle weakening, neurovestibular disturbances, space anemia, and immune system deficiency.

In addition to the potential physiological benefits, artificial gravity might also greatly enhance habitability and personal hygiene maintenance during extended missions; hence, it would be easier for astronauts to carry out activities associated with everyday life. For example, if artificial were generated inside a space vehicle, liquids and particulate matter would “fall” to the floor rather than float around and get in people’s eyes or mouths. Toilets would actually flush and certainly better accommodate female astronauts. The galley for cooking and eating would be much simpler to design. No bungees would be required for exercise equipment. In fact, cots, treadmills, and weights could be used. A significant benefit is that artificial gravity would provide a better environment for medical procedures, especially emergencies like cardiopulmonary resuscitation, surgery, and for maintaining a sterile environment when and where it is needed.

To determine the best technique for implementing artificial gravity in space, a complex set of trade studies must be executed. The parameters that must be considered include, but are not limited to, vehicle design, engineering costs, mission constraints, countermeasure efficacy, reliability requirements, and vehicle environmental impacts.

From a physiological countermeasure perspective, a good solution is to provide artificial gravity continuously throughout the mission. This approach would most likely reduce or eliminate physiological deconditioning, improve human factors (e.g., spatial orientation, hygiene, food preparation, work efficiency), facilitate more efficient medical operations and equipment usage (e.g., countermeasure applications, surgery, cardio-pulmonary resuscitation), and provide a more habitable environment (e.g., management of liquids and contaminant). However, these benefits would need to be weighed against technical risks and uncertainties. These include engineering challenges such as system functional, performance and operational requirements; engineering and architectural designs; fluid management mechanisms; and propulsion system options. Furthermore, human factors and physiological issues will certainly result from the deactivation of artificial gravity once the space vehicle arrives in the vicinity of Mars. Considering that half of all astronauts require one to three days to adapt to microgravity, a similar period of adaptation is expected when artificial gravity is removed. Therefore, a complete set of trade studies cannot be fully executed and analyzed until after further physiological research is completed and vehicle design options are evaluated.

The design for a space habitat that could generate a continuous artificial gravity environment might resemble a torus or donut-shaped ring of several kilometers diameter (Figure 1-11). A rotational rate of one revolution per minute (rpm) would provide Earth-normal gravity on the inside of the outer ring via centrifugal force. Another way to achieve Earth-normal gravity is to linearly accelerate the vehicle at a constant 1 g, rather than rotating it (Figure 1-12).

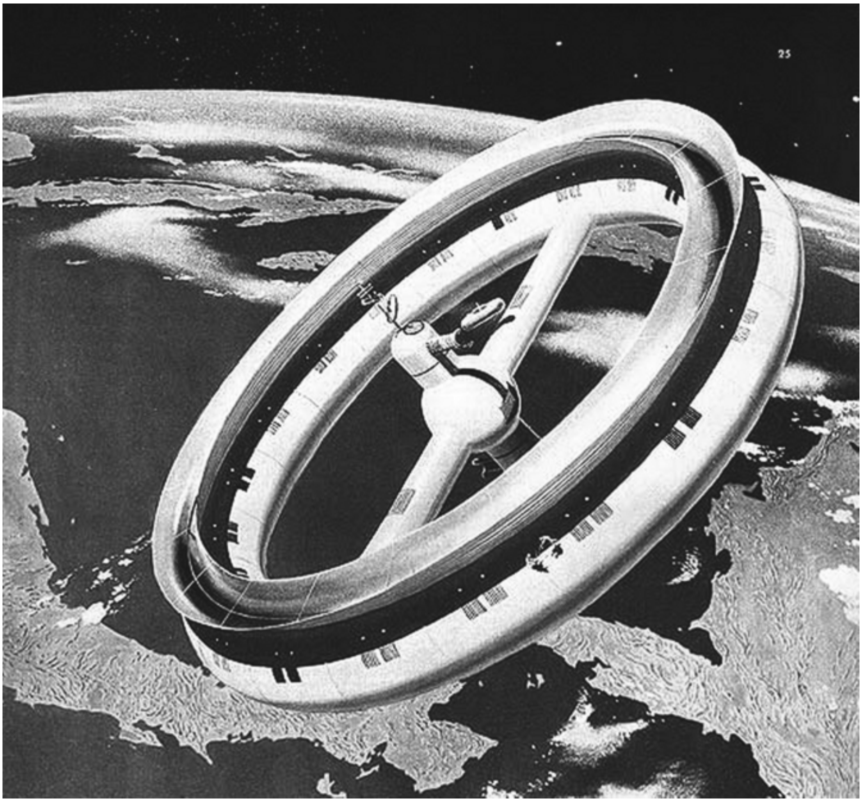

Figure 1-11. Illustration of Wernher von Braun's space station concept by artist Chesley Bonestell in the March 22nd, 1952 issue of Collier's *magazine. This station, made of flexible nylon, would be carried into space by a fully reusable three-stage launch vehicle. Once in space, the station's collapsible nylon body would be inflated much like an automobile tire. The 75-m-wide wheel would rotate to provide artificial gravity. Photo courtesy of NASA.*

However, there are a number of engineering challenges associated with generating artificial gravity through the use of very large rotating vehicles or the application of very high linear acceleration, given the engines required to accomplish this. Such designs are not likely to be realized in the near future. In the case of a crewed Mars spacecraft, the structure required would be prohibitively large, massive, and certainly not energy efficient. An alternative approach being explored is to provide astronauts with a small spinning bed. They would lie on their back with their head near the center of rotation and their feet pointing radially outward. Thus, their lower body could be loaded for a specified period of time each day in approximately the same way as under normal Earth gravity. While not expected to be as efficient a solution from a physiological standpoint, given the gravity gradient effects and intermittent exposure, this procedure may prove effective. The engineering costs and design risks would certainly be lower as compared to designing a rotating spacecraft.

The physiological responses to continuous Mars gravity exposure are unknown. In fact, the physiological responses to continuous exposure to anything other than 1 g are unknown. If it turns out that substantial physiological deconditioning occurs in Mars gravity, then the application of artificial gravity may be required to protect crews during long stays on the surface of Mars. The only feasible implementation on a planetary surface would be intermittent artificial gravity via a centrifuge.

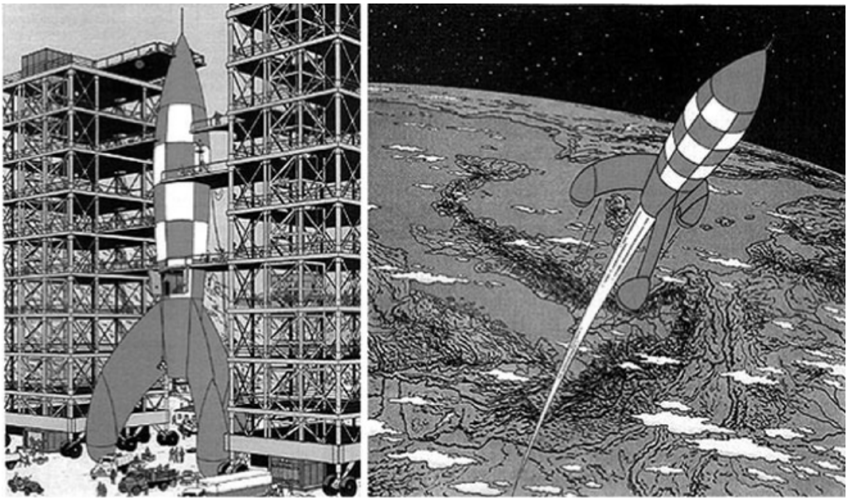

Figure 1-12. In the cartoon stories of "Tintin: Destination Moon" and "Tintin: Explorers on the Moon" (1953) by Hergé (Casterman, Paris), the nuclear-powered Moon rocket continuously accelerates at 1 g in a straight line, creating artificial gravity inside the spacecraft by a force in a direction opposite of the acceleration. At a distance half way between the Earth and the Moon, the rocket turns around and decelerates, still at 1 g, down to the Moon surface.

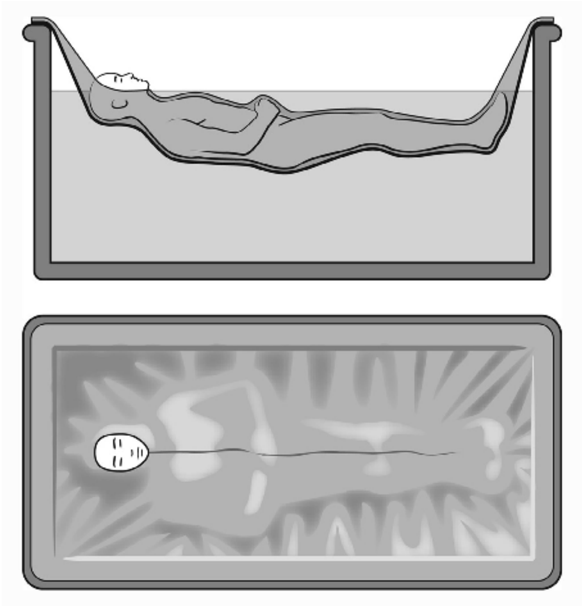

Figure 1-13. Water immersion has been used as an analog for weightlessness by a number of investigators primarily for studying renal and circulatory events. This technique produces rapid body fluid shifts by changes in hydrostatic forces and negative pressure breathing. Subjects in "dry immersion" are protected from water contact by a thin plastic sheet, thus avoiding the problem of skin maceration (Nicogossian and Parker 1982). Drawing Philippe Tauzin (SCOM, Toulouse).

Several research questions remain before artificial gravity can be effectively used on board space vehicles. The objective of this book is to review these questions and proposed research for finding the answers. For example, critical questions include the following. What is the minimum level of acceleration required to maintain normal physiological function? We are certain that a continuous 1 g is sufficient, but is it necessary? Will 0.5 g be adequate? Might we avoid deconditioning during transit to Mars by spinning the spacecraft continuously at a level of 0.38 g to match the gravity on Mars? Would intermittent exposure to artificial gravity levels of 1 g or lower be adequate?

We already know that rats that have been centrifuged during spaceflight don't manifest major deterioration in bone, muscle, and cardiovascular response as is observed in free-floating animals. However, the rats were only centrifuged at a level of 1 g. There is a plan to include short centrifuges in the ISS for fish, eggs, and other small animals. However, there is no plan for centrifuging mammals or primates, which many researchers feel is needed to adequately model human response.

Intermittent artificial gravity stimulation presents a number of potential advantages. As part of our normal circadian rhythm, the gravity-dependent processes that result in fluid loss and bone deconditioning are likely turned off during our normal sleeping hours (Vernikos 2004). On the other hand, extended periods of bed rest affect the skeleton, muscles, and cardiovascular system. These effects are similar to those that occur in space. Simulation of spaceflight by bed rest is more accurate if conducted with a six-degree head-down tilt to accelerate the shift of fluid toward the head. Accuracy is further enhanced if the subject lies partially immersed, although dry, in a high-tech waterbed (Figure 1-13).

A combination of short- and long-duration studies using ground centrifuges and slow rotating rooms could be useful in answering many of the key questions concerning the application period, frequency, and intensity of centrifugal force. They would also be useful in assessing whether dual adaptation to a rotating and a non-rotating environment is possible. Importantly, these studies might shed light on the physiological importance of a gravity gradient across the body. This is important if we are to proceed with centrifuges of radius comparable to the subject's height. These studies are essential to developing the artificial gravity prescription to be used during long-duration space missions (Young 1999).

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Artificial Gravity Encyclopedia:
http://www.daviddarling.info/encyclopedia/A/artgrav.html (Accessed 12 April 2006)
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Chapter 2

PHYSICS OF ARTIFICIAL GRAVITY

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Potential technologies for achieving artificial gravity in a space vehicle are now discussed. We begin with a series of definitions and a general description of the rotational dynamics responsible for the forces ultimately exerted on the human body during centrifugation. These include gravity level, gravity gradient, and the Coriolis force. Human factors considerations and comfort limits associated with a rotating environment are then discussed. Finally, engineering options for designing space vehicles with artificial gravity are presented.

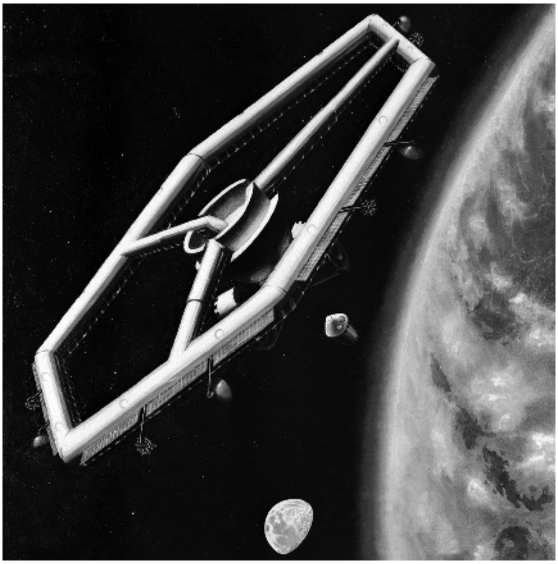

Figure 2-01. One of the NASA's early concepts, proposed in 1962, for a crewed space station with artificial gravity included a self-inflating rotating hexagon. Photo courtesy of NASA.

1 ARTIFICIAL GRAVITY: WHAT IS IT?

1.1 Definition

Artificial gravity is defined in this book as the simulation of gravitational forces aboard a space vehicle that is in orbit (free fall) or in transit to another planet. Throughout this book, the term *artificial gravity* is reserved for a spinning spacecraft or a centrifuge within the spacecraft such that a gravity-like force results. An important point is that artificial gravity is not gravity at all. Rather, it is an inertial force that is indistinguishable from the normal gravity experience on Earth in terms of its action on any mass. A centrifugal force proportional to the mass that is being accelerated centripetally in a rotating device is experienced rather than a gravitational pull. Although the effect of artificial gravity on a human body differs from that of true gravity, which will be discussed in some detail in subsequent sections, the effects are equivalent for any given mass. Therefore, one can think of artificial gravity as the imposition of accelerations on a body to compensate for the forces that are absent in the microgravity of spaceflight (Figure 2-02).

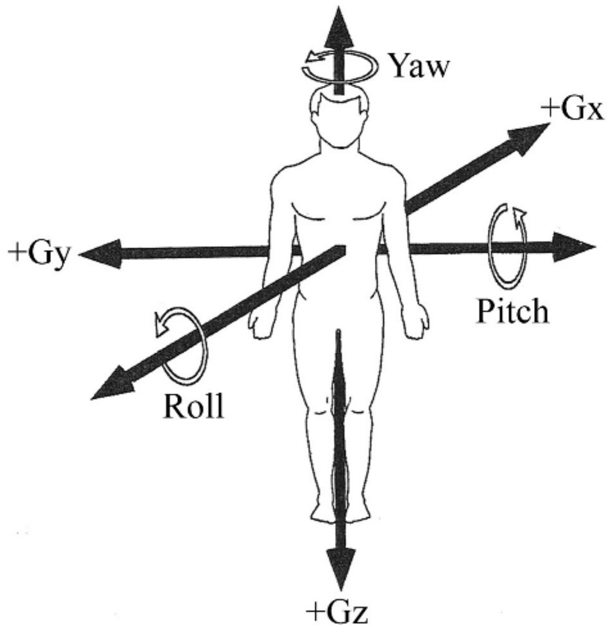

Figure 2-02. The cardinal axes of the human body are defined as x, y, and z. Rotation about these axes is roll, pitch, and yaw, respectively. The positive directions of the gravito-inertial forces (G) along these axes are chosen to be chest-to-back (+Gx), left-to-right (+Gy), and head-to-foot (+Gz), respectively. Note that the positive directions of the corresponding accelerations along these axes would be back-to-chest, right-to-left, and foot-to-head, respectively.

1.2 How to Generate Artificial Gravity

Artificial gravity can be produced in a number of ways. In the following sections, we discuss several interesting mechanisms that could, in theory, be used to develop artificial gravity. However, the practical limitations imposed on spacecraft mass, power, and cost means that achieving some of these designs must wait until technology catches up with our imagination.

These sections were compiled using information from http://en.wikipedia.org/wiki/Artificial_gravity.

1.2.1 Linear Acceleration

Linear acceleration is one means by which artificial gravity can be achieved in a spacecraft. By accelerating the spacecraft continuously in a straight line, objects inside the spacecraft are forced in the opposite direction of that of the applied acceleration. Astronauts routinely experience this phenomenon during orbital adjustments of the Space Shuttle and other orbital spacecraft when the thrusters are fired. Drivers also experience this as the force pushing them back into the seat when they step on the gas pedal after a traffic light turns green. The result is intermittent impulsive artificial gravity forces imposed on the astronauts, or car drivers, that is equal to the acceleration level achieved by the thrusters or automobile engines. However, the duration of this artificial gravity is only a few seconds and is too short to be considered as a potential countermeasure.

If, however, a continuously thrusting rocket could be constructed that would accelerate a spacecraft at a constant rate for the first half of the journey to Mars and then decelerate at that same constant rate for the second half of the journey, a constant artificial gravity situation would result (see Figure 1-12). Ideally, the acceleration level would be at 1 g during both phases of the flight so that the explorers would feel "normal" gravity loading throughout their trip and arrive on Mars ready to go to work[5]. But most rockets accelerate at a rate several times that of Earth's gravity. This acceleration can only be maintained for several minutes because of limits on the amount of fuel that can be carried on board the launch vehicle as well as the specific impulse of the fuel. Theoretically a propulsion system employing very high specific impulse fuel and the key characteristic of a high thrust-to-weight ratio could accelerate for long periods of time. The result would be the production of useful levels of artificial gravity over extended time periods, rather than very high gravity loads for a very short times. As an added bonus, such a constantly accelerating vehicle could provide relatively short flight times through the solar system. A spaceship accelerating (then decelerating) at 1 g could reach Mars in 2-5 days, depending on the relative distance[6]. In a

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[5] When they arrive, the gravitational level will only be 0.38 g and an adaptation period may be required. Some experts have proposed decreasing gravity levels during the final phases of the trip so that the astronauts will be already adapted to a 0.38 g environment when they get there.

[6] In the late 1950s, an experiment was conducted in in the centrifuge at the Aviation Medical Acceleration Laboratory (AMAL) in Johnsville, Pennsylvania (see Figure 11-06) to investigate whether or not humans could tolerate 2 g (+Gz) for 24 hours. It was calculated that at this acceleration level, Mars could be reached in this amount of time. The total travel time, however, would take about 30 hours because of the required deceleration time. The single subject of this experiment, Dr. C. Clark, was medically monitored. At the end of the run, he was still able to talk and move, but he was extremely fatigued (Chambers and Chambers 2005).

number of science fiction plots, acceleration is used to produce artificial gravity for interstellar spacecraft, propelled by as of yet theoretical or hypothetical means.

1.2.2 Mass

Mass is a key gravitational parameter. All masses have an associated gravitational field, be it ever so tiny for particles, or overwhelming as in the case of the gravitational field associated with an infinitely massive black hole. Hence, another way that artificial gravity might be achieved is to install an ultra-high density core into a spacecraft so that it would generate its own gravitational field and pull everything inside (and outside!) the spacecraft towards it. In reality, this is not artificial gravity because it *is* gravity! Many science fiction stories have played on this concept by implying that there are artificial gravity generators that can create a gravitational field based on a mass that does not exist. In a practical sense, the story is enhanced because an Earth-like environment is apparently present on the spaceship. This, of course, makes bringing a story to the big screen or television much more cost effective because it is significantly less expensive to produce a video in 1 g than it is to produce the special effects needed to simulate weightlessness.

An extremely huge amount of mass is required to produce even a tiny gravitational field. For example, fairly large asteroid[7] produces only several thousandths of a g. One could imagine that by attaching a propulsion system of some kind to this asteroid, it might loosely qualify as a space ship. The downside is that gravity at such a low level is not likely to have any practical value. In addition, the mass would obviously need to move with the spacecraft. Any significant acceleration required for such a craft would come with the penalty of vastly increased fuel consumption. The only pragmatic way to implement artificial gravity based on the principle of mass is to find as of yet undiscovered materials with very high densities such that significant mass is present in a low volume. However, engineers would still need to find a way to get so much mass into orbit in the first place.

1.2.3 Magnetism

If we again look to science fiction, we often see spacecraft in which artificial gravity, or the gravity cancellation, is clearly present. Yet the spacecraft is neither rotating nor accelerating. Current magnetic technologies have not yet been developed to the point that such an artificial gravity system can be created. Similar effects can certainly be created through the mechanism of diamagnetism. However, for this to work, it would involve avoiding any non-diamagnetic materials in or near the strong magnetic field that would be required for diamagnetism effects to be evident. Magnets of

[7] To achieve 1 g would require the mass of the Earth.

incredible strength would also be required for the implementation of such an artificial gravity system. Right now we can manage to levitate a frog using such devices, implying that up to 1 g can be produced. But this is accomplished using a magnet system that weighs thousands of kilograms and must be super cooled using very expensive cryogenics to keep it superconductive. This is hardly a practical device for implementation on a spacecraft.

1.2.4 Gravity Generator

No verified technique currently exists to produce gravity, apart from mass itself, even though there have been many claims over the years that such a device has been developed and exists. Eugene Podkletnov, a Russian engineer, has claimed since the early 1990s to build such a device consisting of a spinning superconductor that produces a powerful gravitomagnetic field. However, no verification has been provided and third parties have even purported negative results. In 2006 a research group from ESA claimed to have created a similar device that demonstrated positive results for the production of gravito-magnetism. The device produced only 10^{-4} g, hardly a usable level of gravity in any application (Tajmar *et al.* 2006).

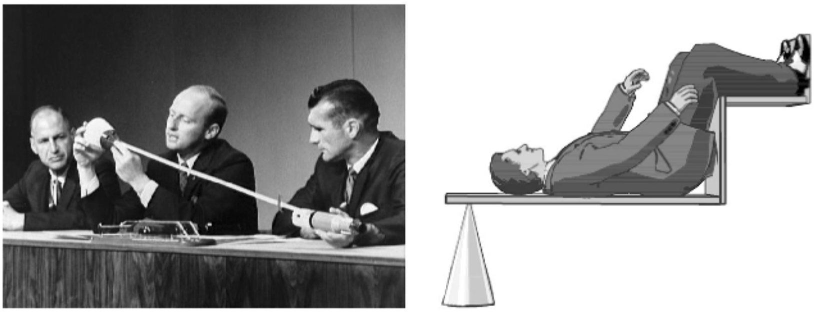

Figure 2-03. Left: In this NASA photograph, astronauts Charles Conrad (center) and Richard F. Gordon (right) use models of Gemini-11 spacecraft and the Agena Target Docking Vehicle to demonstrate tether procedures and maneuvers. Right: Schematic of an on-board short-radius centrifuge.

1.2.5 Centrifugal Force

Centrifugal force results from the centripetal acceleration generated by circular motion, or rotation. Examples of circular motion include artificial satellites in geosynchronous orbit, a racecar going around a curve on a racetrack, an aircraft executing a coordinated turn, or an object tied to the end of a rope and twirled about in circles. Most of us have experienced this phenomenon as the force that pushes us to the left (or right) as we make right (or left) hand turns in our cars or enjoy common amusement park rides.

Spinning motion or rotational motion is a special case of circular motion that occurs when an object rotates or spins about its own center of mass. An example of this kind of motion is a record spinning on a turntable, or indeed, the turntable itself. The spinning produces centripetal acceleration in a radial direction away from the center.

Centripetal force is the product of the centripetal acceleration times the mass of an object. Artificial gravity could therefore be generated in the following ways:

a. By spinning a spacecraft about its axis (Figure 2-01).
b. By rotating two spacecraft connected by a tether about the system center of mass (Figure 2-03, left).
c. By using a short-radius centrifuge on board a spacecraft (Figure 2-03, right).

In the case of a spinning spacecraft (a and b), anything inside would be forced toward the outside radius of spin by centripetal acceleration, which is the source of the artificial gravity. In the case of an internal short-radius centrifuge (c), only the subject and the objects on the centrifuge will be exposed to artificial gravity.

2 ARTIFICIAL GRAVITY GENERATED BY ROTATION

Throughout this book the term *artificial gravity* is used to describe the centrifugal force acting on masses in a spinning spacecraft or within a centrifuge inside the spacecraft. In a rotating system there are forces present other than the centrifugal force that influence how objects move in the rotating environment and, consequently, how humans feel in such a rotating frame. The parameters involved in centrifugation are now reviewed. Keep in mind that for the information presented in the following subsections, we are assuming that any movement by an astronaut or particle in a rotating coordinate frame is at a constant velocity. Furthermore, we will not consider accelerations in an inertial frame, but only in the rotating coordinate frame associated with the rotating centrifuge or spacecraft. This significantly simplifies the analysis and gets straight to the points we wish to make. For a full analysis of moving particles in a rotating coordinate frame in inertial space, see Greenwood (1965).

2.1 Gravity Level

Circular motion is characterized by a radius r and an angular velocity ω (in radians per second). The radius is measured from the center of gravity of the spinning object to its edge, which will henceforth be assumed to be circular with the center of mass exactly in the middle. The angular velocity is simply how fast the spacecraft or object is spinning. Most people are familiar with angular rate being expressed in revolutions per minute, or rpm. However, the units of radians per second, or r/s, are almost always used to express angular velocity because the radian is the SI[8] unit for the plane angle and using r/s greatly simplifies the mathemathics[9]. The magnitude of the resulting centrifugal force is the product of the mass *m* of the object moving in a circle times the centripetal acceleration. The centripetal acceleration is a vector quantity, having a magnitude and associated direction that is derived using vector multiplication by taking the cross product of the tangential velocity and the angular velocity. The magnitude of the tangential velocity is rω and it is oriented in the direction of the rotation of the rim of the spacecraft or object. The magnitude of the centripetal acceleration is simply the product of the magnitudes of the tangential and angular velocities ($r\ \omega^2$), and is always directed radially outward from the center of the rotating body. Therefore, the magnitude of the centripetal force is

$$F = m\,\omega^2\,r. \qquad [1]$$

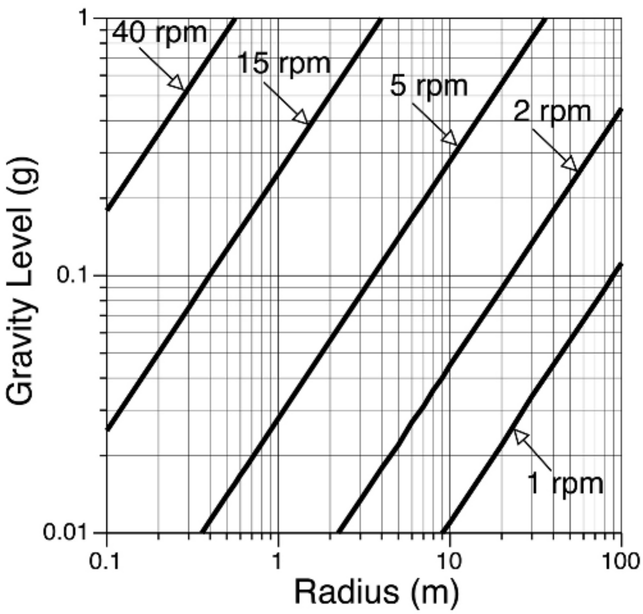

Figure 2-04. Gravity level generated during centrifugation as a function of angular rate (rpm) and distance from the center of rotation (radius) for four given rotation rates of the centrifuge. For a given rotation rate, the gravity level varies along the radius. It turns out that to generate 1-g artificial gravity, the radius needs to be very large with a slow rotation rate (e.g., 35 m for 5 rpm), or very small with a fast rotation rate (e.g., 4 m for 15 rpm).

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[8] International System of Units.

[9] 1 rpm is approximately equal to 0.10 rad/s.

In a reference frame that is fixed to the rotating body or centrifuge, that is, rotating along with the centrifuge, it appears as if an external force is pulling the subject toward the outer rim of the centrifuge. The centrifugal force is exerted on all objects in the rotating frame and is always directed away from the axis of rotation towards the rim. Every stationary object within the centrifuge is forced away from the axis of rotation and the magnitude of this force is a function of the object mass, distance from the center of rotation, and the square of the angular velocity of the device (Figure 2-04). In this book, the centripetal acceleration will be referred to as *the gravity level*. Accordingly, if an astronaut is standing on the rotating floor of a spinning vehicle, or is lying on an internal short-radius centrifuge with his feet outward, the artificial gravity level, A, at his feet is

$$A = \omega^2 r. \qquad [2]$$

2.2 Gravity Gradient

Because the gravity level varies along the radius of the centrifuge, an astronaut lying in a centrifuge along a radius with her feet positioned at the rim will have her head closer to the axis or rotation than her feet. The head will have a smaller radius of rotation. Consequently, the gravity level at her head will have a lesser magnitude than the gravity level at her feet. The variation in artificial gravity level as a function of distance from the center of rotation is referred to as the *gravity gradient.*

For an astronaut of height *h*, lying in a centrifuge along a radius with his feet positioned at the rim and his head pointing towards the center of rotation, his head has a radius of rotation equal to *r - h*. The ratio of head acceleration to foot acceleration can be simply expressed as

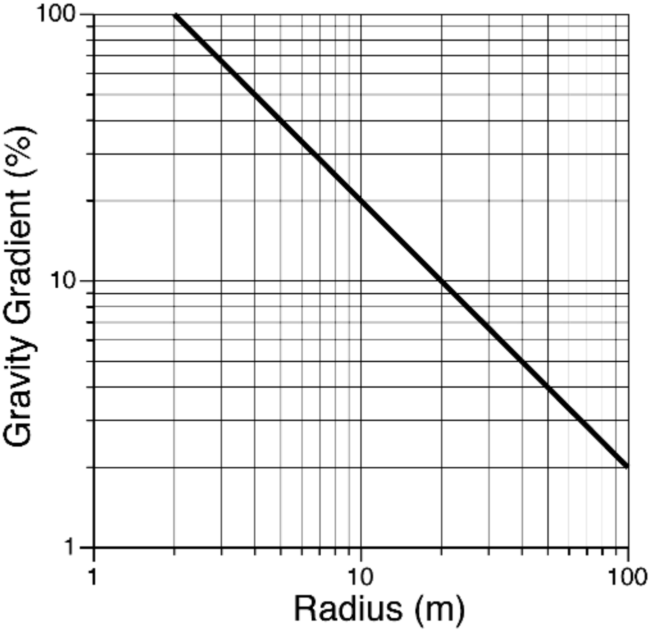
$$A_{head}/A_{foot} = \omega^2 r\,(r - h) / \omega^2 r = (r - h) / r. \qquad [3]$$

By way of example, for an astronaut of height h = 2 m in a rotating environment with a radius of 100 m, this ratio is 98%, which corresponds to a gravity gradient of 2%. An individual would not likely perceive a difference of only 2%. However, for radii of rotation less than 10 m, the gravity gradient ranges from 20 to 100% (Figure 2-05), which may be perceived as a bent posture.

Let us now consider the effects of a person moving inside a rotating vehicle. If an astronaut jogs around the rim of a spinning spacecraft in the same direction of rotation, as Frank Poole did in the movie *2001: A Space Odyssey* (see Figure 3-07), then his instantaneous linear velocity adds to the tangential velocity of the vehicle and the gravity level at his feet increases as a result. (Recall that the centripetal acceleration is the cross product of the angular and tangential velocities.) However, if an astronaut runs in the opposite direction to the rotation of the vehicle, then his instantaneous linear velocity would opposite that of the tangential velocity, thus decreasing the effective magnitude of the tangential velocity of the astronaut, and the apparent gravity level would be decreased. If the rim speed of the centrifuge were small enough, it would be theoretically possible for the astronaut to cancel out the artificial gravity by running in the opposite direction of rotation.

Another force is also playing a considerable role in this particular situation. The Coriolis force that results from the astronaut's velocity in the rotating frame as he runs along the rim is directed radially and either adds to or subtracts from the radial centrifugal force, depending on the direction of movement. This Coriolis force is described in the following section.

Figure 2-05. Gravity gradient as a function of radius of rotation for an astronaut height of 2 m standing on the floor of a spinning vehicle or lying on an internal centrifuge with his feet pointing outward towards the rim along a radius.



2.3 Coriolis Force

Although subjects at rest in a rotating system feel only the sensation of weight, that is, the gravity level generated by the centrifugal force, when they move, another force, called *Coriolis force*, is felt. The Coriolis acceleration is a direct result of any linear movement within the rotating reference frame and is equal to twice the cross product of the angular velocity vector ω and the linear velocity vector v of the moving object, person, or body part (Figure 2-06). The direction of the Coriolis acceleration is perpendicular to the plane formed by ω and v in a right-hand-rule sense in accordance with vector calculus. Of course, the resulting force is obtained by multiplying the mass of the moving object or person by the acceleration, so the magnitude of the Coriolis force is as shown in Equation [4].

$$F = 2m\,\omega\,v \qquad [4]$$

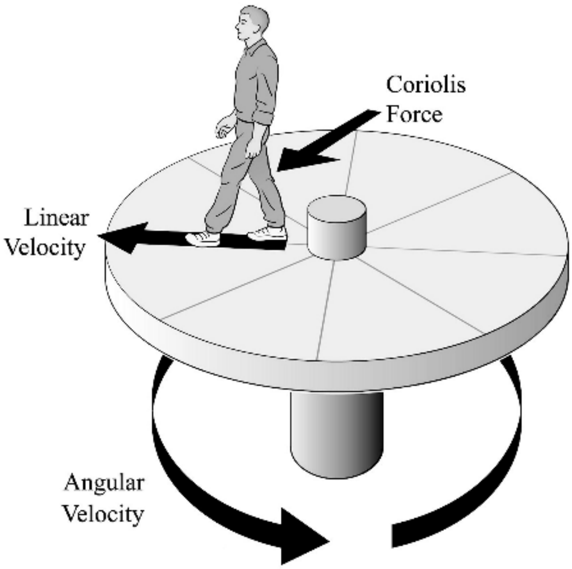


Figure 2-06. People trying to walk radially outward on a spinning carousel will feel a surprising force pushing them sideways, parallel to the circumference. The Coriolis force depends upon both the linear speed of motion, its direction relative to the axis of rotation (which together with the speed comprise velocity), and the angular velocity of rotation. Drawing Philippe Tauzin (SCOM, Toulouse).

Again, the Coriolis acceleration is derived by vector multiplication of ω and v. In non-vector terms, at a given angular velocity of the observer, the magnitude of the Coriolis force of the subject will be proportional to the linear velocity of the subject in the rotating frame as well as to the sine of the angle between the direction of movement of the subject and the axis of rotation. It is important to note that the Coriolis force is independent of the radius of centrifugation. That is, its magnitude is the same at all distances from the center of rotation (Figure 2-07).

The Coriolis acceleration acts in a direction that is perpendicular both to the direction of the velocity of the moving subject mass and to the axis of rotation. We can therefore make the following statements regarding the characteristics of the Coriolis force or acceleration:

a. When the velocity v (as always, in the rotating system) is zero, the Coriolis acceleration is zero.
b. When v is parallel to the rotation axis, the Coriolis acceleration is zero.
c. When v is directed radially inward (outward) towards (away from) the axis of rotation, the resulting Coriolis acceleration is aligned

with (opposed to) the direction of rotation (parallel to the tangential velocity).

d. If *v* is aligned with (opposed to) the direction the rotation (parallel to the tangential velocity), the Coriolis acceleration acts radially outward from (toward) the axis of rotation.

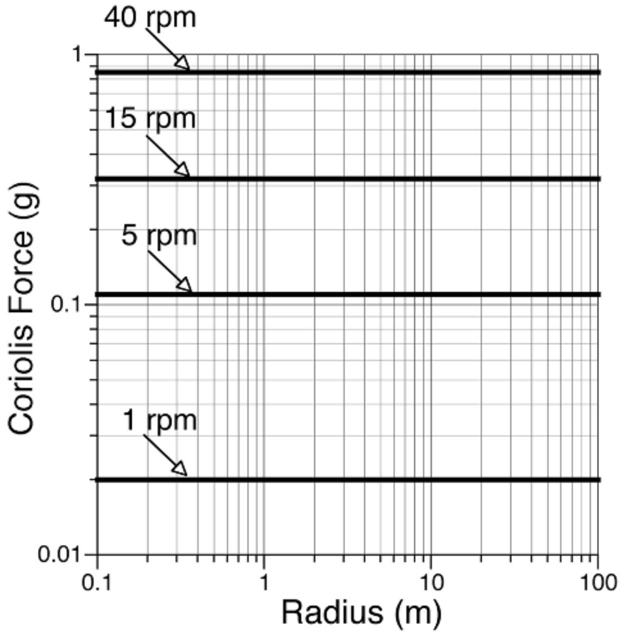


Figure 2-07. The Coriolis force generated during centrifugation is plotted as a function of radius for four different rotation rates of the centrifuge. Note that the Coriolis force is the same regardless of the distance from the center of rotation.

So, if a person is standing on the outside rim of a centrifuge or spinning vehicle and she jumps off the "floor" with a velocity directed radially inward towards the axis of rotation, she would not come straight "down". Rather, she would land a few centimeters to one side. Referring again to *2001: A Space Odyssey*, in the film we see scenes of the astronauts climbing ladders up and down from the rim of the spacecraft to the center. Because of the movie set used in the studio (see Chapter 3, Section 1.2), the Coriolis accelerations did not exist during the filming of these scenes. However, were those individuals to actually be on a spacecraft climbing and descending ladders as shown in the movie, they would feel the effects of the Coriolis acceleration in the form of a force that would tend to push them to one side or the other (Figure 2-08).

If the spacecraft was rotating in the counter-clockwise direction and the astronaut was climbing a ladder towards the center of the vehicle in the manner shown in the figure, he or she would feel a force pushing to the right. When descending the ladder, the force would seem to be pushing them to the left. As will be discussed in subsequent sections of this book, the Coriolis acceleration plays a significant role in causing the onset of motion sickness.

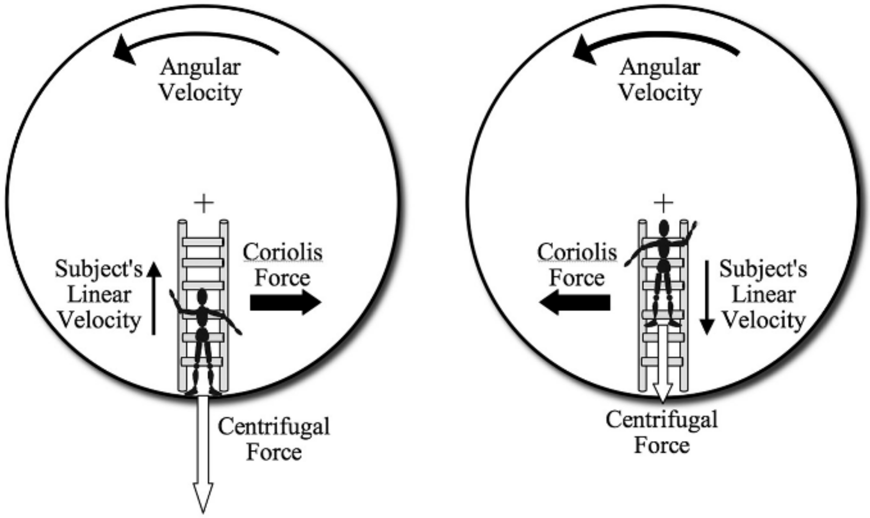


Figure 2-08. Coriolis and centrifugal forces exerted on a passenger climbing a ladder up (left) or down (right) in a rotating environment. The Coriolis force has the same amplitude in both conditions, but its direction is reversed. Note that the magnitude of the centrifugal force is greater when the space traveler is at the bottom of the ladder, due to the increased distance from the axis of rotation. Adapted from Stone (1973).

3 HUMAN FACTORS CONSIDERATIONS

Theoretical spacecraft designs that employ artificial gravity have a great number of variants, each with their own unique intrinsic problems and advantages. The parameters that most significantly influence the designs are now discussed.

3.1 Gravity Level

The minimum artificial gravity level, normally measured at the rim of a centrifuge, is the key parameter in the design of an artificial gravity system. Data from the limited animal tests executed in orbit suggest that continuous rotation generating 1 g at the feet of a small rodent is sufficient to maintain normal growth and development during spaceflight (see Chapter 3, Section 2.1). However, it remains to be determined whether or not a reduced magnitude gravity level will suffice. Based on long duration centrifuge studies on Earth, Russian scientists suggest that the minimum level of effective artificial gravity stimulation in humans is about 0.3 g. They further recommend that a level of 0.5 g be induced to increase a feeling of well-being and normal performance (Shipov *et al.* 1981). Perception studies have further shown that humans can detect artificial gravity levels of 0.5 g in orbit.

Astronauts, however, are not able to perceive artificial gravity levels of 0.22 g or less (Bukley *et al.* 2006).

As for the maximum level of artificial gravity in the +Gz direction, which is along the long body axis, ground-based bed rest studies suggest that gravity levels up to 2 g at the feet are probably useful, especially if combined with exercise (see Chapter 5). Passive hypergravity levels as high as 3-4 g at the feet are tolerable for more than 90 minutes in most subjects (Piemme *et al.* 1966). Active exercise, such as bicycling, on human powered centrifuges is also well tolerated from a hemodynamic perspective at gravity levels up to 3 g at the feet (Caiozzo et al 2004, see also Chapter 5). However, peripheral vision starts to decrease, a phenomenon known as *grey-out*, at 2-3 g at the head level, which would correspond to a rotation rate of 60 rpm at a radius of 0.5 m. These conditions would never be reached in an artificial gravity setting. However, it is well know that on Earth the tolerance to acceleration varies from day to day and is modified by body build, muscular tone, gender, and experience. Tolerance can be increased by continued exposure and experience. On the other hand, tolerance to higher gravity levels is decreased as a result of poor health, physical deconditioning, and fatigue (see Burton and Whinnery 2002 for review). Tolerance to acceleration is reduced after bed rest, but little is known about tolerance to acceleration after spaceflight. Also, most of the ground-based studies on the physiological effects of gravity levels have been performed with long-radius centrifuges. The effects of gravity gradient, for example, have not been investigated. Consequently, tolerance to acceleration during short-radius centrifugation must be further investigated.

It is not yet known if exposure to high gravity levels for intermittent, short periods of time, is as beneficial to health as continuous exposure to normal gravity. Another unknown is how effective gravity levels below 1 g are in countering the health effects of weightlessness. An artificial gravity level of 0.1 g can be achieved by the reasonably low rotation rate of 5 rpm at a radius of 4 m (see Figure 2-04). Likewise at a radius of 4 m, approximately 15 rpm is required to produce Earth gravity levels at the feet, although the gravity level would be 50% less at the head. A rotational rate of 21 rpm at the same 4-m radius is required to produce 2 g. If brief exposure to higher gravity levels could negate the health effects of weightlessness, then a small centrifuge could be used intermittently on board the space vehicle, as is the case now with muscle exercise devices. However, the on-board centrifuge would provide multiple physiological systems efficacy.

3.2 Rotation Rate

The maximum rotation rate of a centrifuge or spinning spacecraft is limited by the Coriolis force encountered when walking or when moving objects within the rotating environment. Coriolis forces are the result of real inertial accelerations that occur when moving within a rotating framework.

Any movement in a straight line with respect to the rotating frame, except for movements parallel to the axis of rotation, is in fact a curved motion in inertial space (see Figure 4-09). The curve reflects the effects of the Coriolis acceleration in the sideways direction and entails a sideways inertial reaction force.

At body motion or centrifuge rotation rates that are of low magnitude, the effects of the Coriolis force are negligible, as on Earth. However, in a centrifuge rotating at several rpm, there can be disconcerting effects. Simple limb movements become complex and eye-head movements are altered. For example, turning the head can make stationary objects appear to rotate and continue to move once the head is stopped. This is because Coriolis forces also create cross-coupled angular accelerations in the semicircular canals of the inner ear (see Figure 4-02) when the head is turned out of the plane of rotation. Consequently, motion sickness generally results even at low rotation rates, those less than 3 rpm, although people can eventually adapt to higher rates after incremented, prolonged exposure (see Chapter 3, Section 3.1).

Previous studies have suggested that the Coriolis force should be kept to less than a small fraction of the artificial gravity level. Stone (1973) suggests that this be no higher than 25%. However, in the light of recent ground-based data showing a rapid adaptation to the vestibular conflict generated by Coriolis force (Young *et al.* 2001), this limit seems overly conservative. Also, during an experiment performed on board Skylab, it was observed that head movements made during rotation after six days in microgravity failed to elicit motion sickness or disorientation (Graybiel *et al.* 1977). Lackner and DiZio (2000) performed parabolic flight experiments indicating that "the severity of side effects from Coriolis forces during head movements is gravitational force-dependent, raising the possibility that an artificial gravity level less than 1 g would reduce the motion sickness associated with a given rotation rate". Finally, restraining head movement during centrifugation also mitigates the nausea-inducing effects of Coriolis forces.

Finally, as mentioned above, the artificial gravity is constantly being distorted as the astronauts move about within the spacecraft, except when they move along an axis that is parallel to the axis of rotation. To reduce this effect, the rim speed needs to be much faster than the astronauts can walk or run. The minimum rim velocity is therefore limited only by the need to maintain enough friction for locomotion when they walk against the direction of spin. The normal forward velocity while walking is about 1 m/s. Therefore, the estimated minimum rim velocity is approximately 6 m/s.

3.3 Gravity Gradient

Because most studies of artificial gravity have involved long-radius centrifuges in which the gravity gradient is limited, there are no data available on the effects of gravity gradient on the subjects' comfort and well-being or on their physiological responses.

For a 2-m tall astronaut standing with his feet on the rim and his head towards the center of rotation, the centrifuge radius would need to be at least 4 m for a 50% maximum gravity gradient. For continuous rotation at smaller radii, comparable to the astronaut's height, the gravity gradient is more of a problem. In particular, this situation might make limb movement and changing body positions awkward, which can affect physiological functions. Furthermore, objects in the rotating environment have a different "weight", depending on their distance from the center of rotation. The larger the gravity gradient, the greater is this difference. This can greatly affect handling materials or moving objects. For example, for an astronaut standing on the rim of the centrifuge, objects become lighter as he "lifts" them toward the center of rotation. Furthermore, he becomes heavier when squatting down towards the rim and slightly lighter when he's standing on tiptoes.

3.4 Comfort Zone

With the beginning of manned spaceflight in the 1960s, there was a concerted effort to determine the comfort criteria for rotating habitats. In the U.S., much of this research took place in centrifuges, rotating rooms, and rotating space station simulators at the Aviation Medical Acceleration Laboratory in Johnsville, Pennsylvania, the Naval Aerospace Medical Research Laboratory in Pensacola, Florida, and the NASA Langley Research Center in Hampton, Virginia (Chambers and Chambers 2005).

Over the past four decades, several authors have published guidelines for comfort in artificial gravity (see Hall 1997 for review), including graphs of the hypothetical *comfort zone* bounded by values of gravity level, head-to-foot gravity gradient, rotation rate, and tangential velocity (Figure 2-09).

The results of these studies are often discordant. For example, Clark and Hardy (1960) performed centrifuge studies and concluded that a space station rotation rate should not exceed about 0.1 rpm to stay completely below the threshold of vestibular illusions and nausea due to cross-coupling accelerations when moving the head. At 0.1 rpm, a 1-g spinning station would require a radius of approximately 90 kilometers! Later, Stone (1973) assumed acceptable cross-coupling for up to three times the nausea threshold predicted by Clark and Hardy, giving a maximum station rotation rate of 6 rpm. This is 60 times the maximum rotation rate proposed by Clark and Hardy and brings the radius of a 1-g station down to only 25 meters. However, this solution could still only be achieved by a large spinning station or by a tether connecting two sections of a spaceship, possibly a habitat module and a counterweight consisting of every other part of the spacecraft.

Recent data indicate that these earlier limits on rotation rate for eliciting Coriolis motion sickness are overly conservative. For example, Young *et al.* (2001) have recently shown that subjects can quickly adapt to motion sickness induced by rotation of the head during centrifugation at 23 rpm. Higher rotation rates permit a shorter radius to obtain a specified gravity level.

The upper limit for the gravity level is fixed at 1 g, and the lower limit at 0.3 g. This lower limit was based upon results from Russian animal studies during spaceflight and from the performance of human subjects during the hypogravity phase of parabolic flight (Faget and Olling 1968). This limit also derives from the results of ground-based studies performed at NASA Langley using a circular platform of 12 m diameter with a 1.8-m vertical wall at the periphery. During rotation of the platform, subjects were suspended horizontally and allowed to "walk on the wall" (Letko and Spady 1970). Walking in the direction of rotation at a simulated gravity level of between 0.16 and 0.3 g at the feet (Gz) was found to be the most comfortable. At levels above 0.3 g, the subjects reported "sensations of leg and body heaviness", which became quite disturbing at 0.5 g. Consequently the lower limit of 0.3 g was chosen in most design studies for implementation of artificial gravity

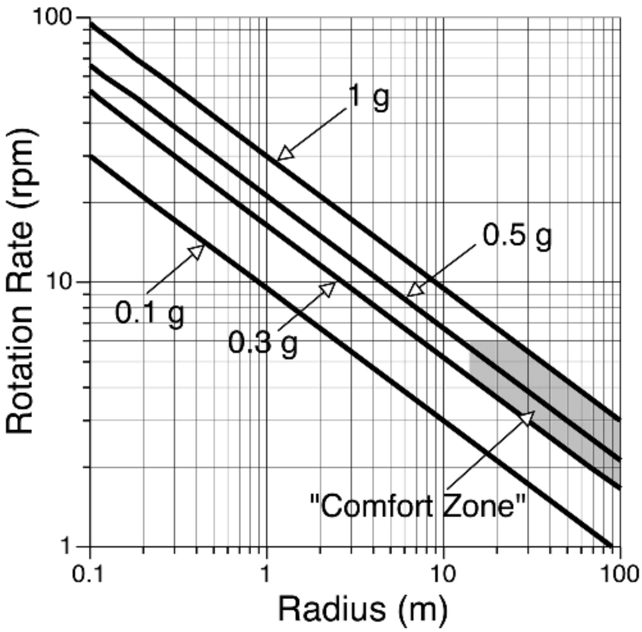


Figure 2-09. The rotation rate is plotted as a function of the radius of rotation for four gravity levels. Previous studies performed in the 1960s referred to the "comfort zone" as the area in grey delimited by a minimum radius of 12 m, maximum and minimum gravity levels of 1 g and 0.3 g, respectively, and a maximum rotation rate of 6 rpm. However, recent data indicate that these limits are overly conservative.

A minimum radius of 12 m has been specified to limit the gravity gradient to approximately 15% (see Figure 2-05). This limit is imposed taking into account the human factors consideration of work efficiency. As previously mentioned, for a person standing on the rim of a spinning space station, an object will get heavier when it is lowered from head to foot level.

Despite the virtual absence of data on the effects of gravity gradient (because most the studies were performed on a large-radius centrifuge that minimized the gravity gradient), the 15% upper limit was obviously a conservative value aimed at easing materials handling and reducing the potential risk of musculo-skeletal injuries.

It is important to note that the limits for comfort criteria mentioned above address the issues of humans *walking* and *moving objects* in a rotating environment. Indeed, these limits were proposed at a time where large rotating stations were foreseen for space missions, as described in the next section. These comfort limits must obviously be re-evaluated for the case of on-board short-radius centrifuges, where body, limb, and head movements will be more restricted.

4 DESIGN OPTIONS

The choice of artificial gravity design depends on a basic decision concerning whether the crew is to be transported with continuous artificial gravity, requiring a large-radius spinning vehicle, or exposed to intermittent artificial gravity, in which case a small centrifuge can be employed. These two design options are reviewed in the following subsections. Their content is based to a great extent on material contained in the final report of the International Academy of Astronautics Study Group 2.2 entitled "Artificial Gravity as a Tool in Biology and Medicine" (Paloski 2006).

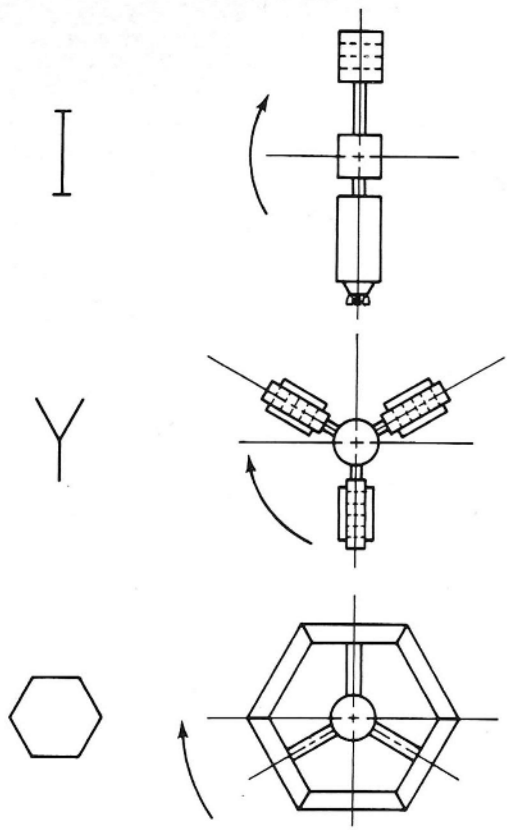


Figure 2-10. The three basic rotating space station configuration concepts are the 'I', the 'Y', and the 'toroidal' configurations, in reference to their basic shape. Adapted from Faget and Olling (1968).

4.1 Continuous Artificial Gravity: Spinning the Vehicle

The classical large spinning space station, as proposed by von Braun, was the basis for early designs in the Apollo era. The three basic rotating space station configuration concepts are the 'I', the 'Y', and the 'toroidal' configurations, in reference to their basic shape (Figure 2-10). The 'Y' and the 'toroidal' configurations have a better rotational stability, because the greatest moment of inertia is about the axis of rotation. The 'I' configuration, however, has a large moment of inertia in two axes. Therefore, a stabilizing device such as a momentum wheel is required. However, the 'I' configuration is less complicated to transport and deploy in orbit (Loret 1963) (Figure 2-11).

The large mass and volume of such designs motivated engineers to consider methods of generating centrifugal forces at large radii. The two concepts that emerged are the rigid truss or boom, and the tether concept, which are detailed below. Another engineering issue is the design of a propulsion system to spin up or spin down the vehicle. If parts of the spaceship are by design not spinning, friction and torque between the spinning and non-spinning sections will cause the rotational rate to decrease and possibly cause the otherwise-stationary parts to spin. Flywheels and thrusters are required to keep the appropriate sections of a spacecraft spinning and the other parts relatively stationary. Angular momentum resulting from the spinning spacecraft can also complicate propulsion with regard to orbital maneuvers, but could simplify attitude control.

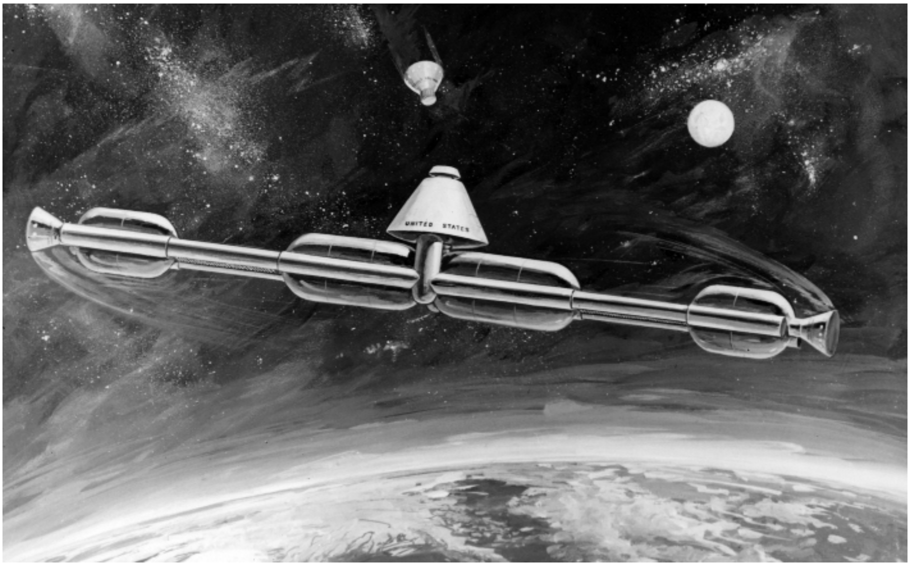


Figure 2-11. In this NASA 1969 space station concept, the vehicle was to rotate on its central axis to produce artificial gravity. It was to be assembled on-orbit from spent Apollo program stages. Photo courtesy of NASA.

4.1.1 Rigid Truss

A rigid truss design typically would have the crew quarters and operations module at one end and a large counterweight at the other end. The counterweight might be an expended fuel tank or an active element such as a nuclear power source. In most cases a counter-rotating hub is present at the center of rotation to provide both a non-spinning docking port and to allow for a zero-g workspace for experiments.

A variation on the rigid truss is the extendable or telescoped boom concept, in which the radius of the artificial gravity systems could be varied more easily than with a fixed truss and slider. However, both of these designs imply considerably more mass and power requirements than a tether system.

In a recent NASA architecture study to support a manned mission to Mars, Joosten (2002) developed a truss-based vehicle design capable of meeting typical Mars mission requirements while providing acceptable artificial gravity parameters. The architecture includes a reactor power module near the center of rotation, a crew vehicle at the end of a truss to distance the crew from the reactor's radiations, and radiators at the other end. Rotation of the structure at 4 rpm would generate 1-g of artificial gravity in the crew compartment located at a radius of 56 meters from the rotation axis (Figure 2-12).

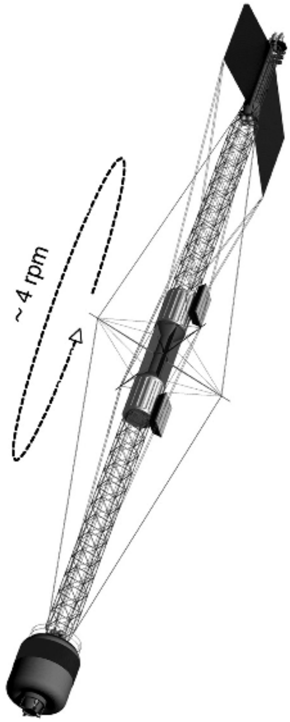


Figure 2-12. In this NASA design, a high-power nuclear electric propulsion (NEP) system based on high-temperature liquid-metal cooled fission is used to generate thrust and rotation of the structure, providing a continuous 1-g artificial gravity level in the crew compartment. Photo courtesy of NASA.

The NEP vehicle mass associated with the mission is consistent with previous design solutions, and steering strategies were identified consistent with mission requirements without excessive propellant expenditure. The vehicle mass penalties associated with artificial gravity were minimal, only a few percent. Joosten noted that providing an artificial gravity environment by crew centrifugation aboard deep-space human exploration vehicles has received surprisingly limited engineering assessment. He stated that this is most likely due to the lack of definitive design requirements, especially acceptable artificial gravity levels and rotation rates; the perception of high vehicle mass and performance penalties; the incompatibility of resulting vehicle configurations with space propulsion options (i.e., aerocapture); the perception of complications associated with de-spun components such as antennae and photovoltaic arrays; and the expectation of effective crew micro-gravity countermeasures. He concluded that these perceptions and concerns may have been overstated.

4.1.2 Tether

The Gemini-11 mission demonstrated basic tethered spacecraft technology in 1966 when the crew connected their capsule to the Agena booster with a 30-m tether (see Figure 2-03) and put the assembly into a slow rotation to produce a minuscule amount of artificial gravity. A longer tether or faster rotation, or both, would be needed to produce artificial gravity at useful levels. The Gemini-11 tethered vehicle exercise revealed some unexpected tether dynamics that will need to be considered in designing an artificial-gravity space habitat (Wade 2005), should tether options be pursued.

A variable length tether that can be unreeled in orbit and used to connect a spacecraft to a counterweight has emerged as the most acceptable design for a large artificial gravity system. As envisioned for a Mars mission (Schultz *et al.* 1989), it would consist of an 80,000 kg habitat module 225 m from the center of mass, with a 44,000 kg counterweight 400 m beyond. A tether, weighing 2,400 kg, reeled out by a deployment mechanism weighing 1,700 kg, connects the two. All told, the additional weight for accommodating a tethered artificial gravity mechanism for a human Mars mission is about 4,100 kg, or about 3% of the total system mass, plus about 1,400 kg of propellant.

One of the obvious concerns about a tethered artificial gravity system is its vulnerability to tether breakage. For the Mars mission design, a tether in the form of a band 0.5 cm x 46 cm x 750 m would provide a dynamic load safety factor of 7, offering a working strength of 630,000 N. That concern has otherwise been addressed by using webbing or braided cable to maintain tether integrity, even in the event of a meteoroid collision. The probability of tether impact with a micrometeoroid of mass greater than 0.1 gm was calculated as 0.001 for a mission of 420 days. A second concern about a tethered system lies in its dynamic stability, especially during unreeling and during spin up and spin down. The interaction with orbital maneuvers is complex, whether the spin axis is inertially fixed or tracking the Sun to facilitate the use of solar panels.

4.1.3 Spinning the Vehicle about an Eccentric Axis

In a recent study, Bukley *et al.* (2006) investigated two scenarios wherein artificial gravity levels ranging from 0.2 to 0.5 g could be created on board the Space Shuttle (Figure 2-13). One possible means of accomplishing this is by rotating the vehicle about an eccentric roll axis[10] (in this case, the baseline orbital trajectory of the vehicle) at a constant angular velocity. This roll maneuver would create artificial gravity in the +Gz direction of the vehicle, such as when the vehicle is on Earth. The other means is by rotating the vehicle in pitch about its center of gravity. This pitch maneuver would create artificial gravity in the +Gx direction of the vehicle, so that astronauts could "stand" on the middeck lockers.

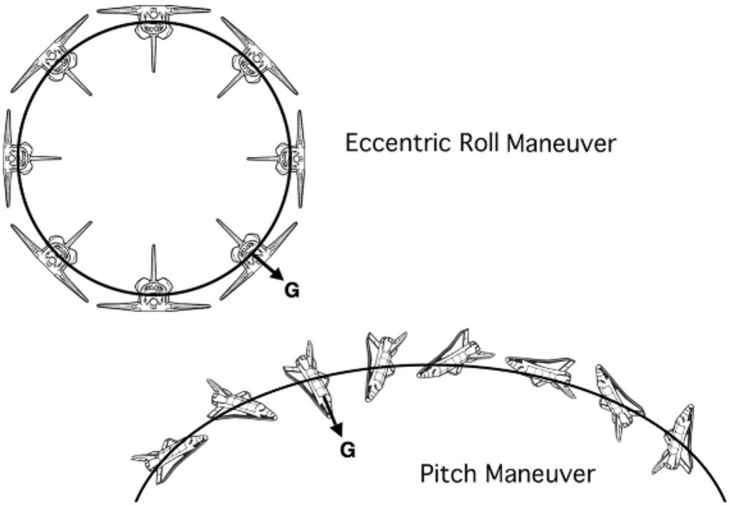


Figure 2-13. Two possibilities of spinning the Space Shuttle for creating artificial gravity: the eccentric roll (toroidal) maneuver (above) and the pitch maneuver (below). The eccentric roll maneuver, however, is beyond the capabilities of the Space Shuttle orbital control system. Adapted from Bukley et al. *(2006).*

A feasibility analysis of the eccentric roll maneuver was executed beginning with the simple dynamics of a point mass in a central gravitational field to ascertain the force levels required to execute the proposed maneuver. Once the force levels were determined, they were then compared to the capability of the Space Shuttle orbital control system, which includes the *Orbital Maneuvering System* (OMS) and the *Reaction Control System* (RCS). The former controls the spacecraft orbital altitude, and the latter its attitude. Assuming that the force levels were within the capability of the orbital control system, they could then be translated from inertial coordinates to vehicle coordinates and ultimately distributed amongst the various thrusters in accordance with an appropriate control law.

[10] John Charles (NASA) originally proposed this maneuver during the NASA/NSBRI Artificial Gravity Workshop held in League City, Texas, in January 1999 (Paloski and Young 1999).

The eccentric roll maneuver analysis was executed assuming that the orbital altitude was 400 km, which is typical for Space Shuttle missions. The Shuttle mass was assumed to be 99,117 kg, which is also the typical vehicle mass near the end of a mission (Joels and Kennedy 1992). Results of the point mass dynamic analysis indicated that the force levels needed to generate an artificial gravity environment in the +Gz direction of the Space Shuttle vehicle exceed the capability of its orbital control system (Table 2-01). While the OMS engines have a thrust capability of 26,700 N, which would appear to be sufficient for the 0.2-g artificial gravity maneuver, there is only enough OMS fuel for about 21 minutes total of operation. Furthermore, to execute the eccentric roll maneuver, a thrust in the –Gz direction in the Space Shuttle coordinate frame must also be generated.

The Space Shuttle has no capability to generate a thrust in this direction. However, designers of future space vehicles, e.g., the *Crew Exploration Vehicle*, may wish to keep the results of this analysis in mind when designing that vehicle in the event that it may be desired to execute such a maneuver. The mass of the Shuttle dictates the required thruster force; therefore, a lighter vehicle with a more robust thruster system may have the capability to fly such a trajectory.

Analysis of the pitch maneuver is considerably simpler. Rather than altering the orbital trajectory of the Space Shuttle center of gravity, the vehicle is simply pitched about the center of gravity, nose-over-tail, at a rate sufficient to generate a centrifugal acceleration at the desired gravity level. Figure 2-14 shows the rotation rate required to generate varying levels of artificial gravity at the forward bulkhead of the middeck, which would be now be used as the “floor” by the astronauts. It is interesting to note that the Space Shuttle actually flew this rotational pitch maneuver during the return-to-flight missions STS-114 and STS-121 prior to docking with the ISS. This maneuver allowed the crew on board ISS to capture photographs of the heat shield on the belly of the Shuttle. However, the rotation rate during this 360-degree back-flip maneuver was 0.125 rpm, thus generating artificial gravity in the Space Shuttle crew compartment of 0.0003 g, a level far too low to be perceived as artificial gravity by its passengers.

Gravity Level	***Max Force Level***
0.2 g	*19,440 N*
0.3 g	*29,150 N*
0.4 g	*38,900 N*
0.5 g	*48,600 N*

Table 2-01. Maximum thrust force levels required in both the Gx and Gz axes of the vehicle to execute the eccentric roll maneuver for artificial gravity levels of 0.2, 0.3, 0.4, and 0.5 g. Forces required in the Gy direction are significantly smaller. Adapted from Bukley et al. *(2006).*

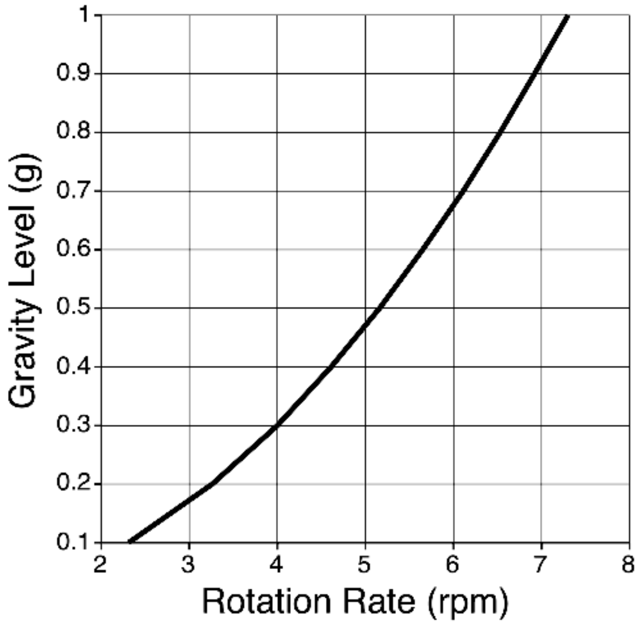


Figure 2-14. Artificial gravity level generated at a distance of 16.8 m from the center of rotation, which corresponds to the middeck forward bulkhead in the Space Shuttle, plotted as a function of rotation rate of the vehicle in pitch. Adapted from Bukley et al. *(2006).*

4.2 Intermittent Artificial Gravity: Internal Centrifuge

The alternative approach to continuous, rotating vehicle generated artificial gravity is to use an on-board short-radius centrifuge intermittently. In this case, the exposure would not necessarily be limited to 1 g or less, but could be as high as 2 or 3 g to deliver adequate acceleration in exposures of perhaps 1 hour daily or several times per week. Of course, such a short-radius device would need to spin much faster than the 6-rpm limit envisioned for a large continuous system, and would produce significant Coriolis forces and motion sickness stimuli with head movement, at least until adaptation occurs. However, recent work on adaptation indicates a high likelihood of successful adaptation by most subjects to head movements, even at high angular rates (Young *et al.* 2001).

The short-radius centrifuge becomes particularly attractive when its dimensions shrink to the point that intermittent centrifugation could be carried out within the confines of a contemporary spacecraft. Rather than requiring the rotation of an entire complex, a 2-m-radius artificial gravity device permits subjects to stand upright and even walk within its limited confines. Of course, the head is then close to the center of rotation and a significant gravity gradient from head to toe is manifested. Many of the ground studies conducted with intermittent short-radius centrifugation have been conducted with centrifuges of radii from 1.8-2.0 m. As the radius decreases even further to less than 1.5 m, taller subjects can no longer stand erect and must assume a squatting or crouching posture. For many such designs, the subject would also provide the power to turn the device and perform valuable exercise by bicycling the centrifuge into rotation. Indeed, from the engineering point of view, a shorter radius centrifuge permits less mass and less kinetic energy for any particular centripetal acceleration, or artificial gravity level. Although the power savings may be trivial, or not even significant, the importance of active exercise while exposed to intermittent centrifugation might lie in its protection against syncope, or fainting, as the body is exposed to the unfamiliar footward forces that tend to pool blood in the lower extremities. Also, if the head can be placed far enough off-axis to allow sufficient vestibular otolith stimulation, vestibulo-spinal reflexes might be protected, resulting in increased neuro-motor activation and improved motor tone. The on-board short-radius centrifuge has implications for mass and momentum balance, pressurized volume, and crew scheduling. The intensity and duration of the required therapeutic dose of artificial gravity remains unknown and is a worthy research topic (Clément and Pavy-Le Traon 2004, Hall 2004).

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Chapter 3

HISTORY OF ARTIFICIAL GRAVITY

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In this chapter we review past and current projects on artificial gravity conducted during space missions. The idea of a rotating wheel-like space station providing artificial gravity goes back in the writings of Tsiolkovsky, Noordung, and Wernher von Braun. The most famous fictional representation of this concept is in the film *2001: A Space Odyssey*, which also depicts spin-generated artificial gravity aboard a space station and on a spaceship bound for Jupiter. The O'Neill-type space colony provides another classic illustration of this technique. A more realistic approach is to provide astronauts with a smaller centrifuge contained within a spacecraft as opposed to rotating an entire space station. The astronauts would climb into it for their workout and to get their therapeutic dose of gravity for a certain period of time daily or a few times a week. This simple concept is currently undergoing analysis in ground-based studies underway in several laboratories around the world.

Figure 3-01. A short-radius human centrifuge. "Artificial gravity is an idea whose time has come around, ...and around, ...and around, ..." --Pr. Laurence R. Young, Department of Aeronautics and Astronautics, Massachusetts Institute of Technology.

1 CONCEPTS

1.1 History of Space Travel and Artificial Gravity

The idea of creating a substitute for gravity by using centrifugation was introduced early in the conception of human space travel. In fact, schemes for achieving artificial gravity in space preceded actual human spaceflight by many decades. Konstantin Tsiolkovsky, the influential Russian space visionary, discussed the idea in his manuscript *Free Space* that he wrote in 1883. This manuscript was first published in 1956. In it he sketched out the primitive design of a true spacecraft, which moved in space with the help of reactive forces, described the life and ways of motion in zero gravity, and discussed the possibility of a spinning space vehicle for creating artificial gravity (Figure 3-02).

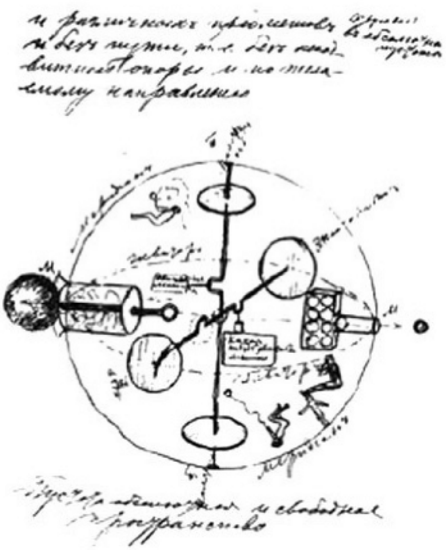

Figure 3-02. This was the first drawing of Tsiolkovsky's of a space vehicle, from his monograph Free Space *(1883). It shows cosmonauts in weightlessness inside the vehicle, and in artificial gravity when running along the internal walls.*

Tsiolkovsky never saw his designs materialize. However, 50 years later a younger generation of Russian engineers and scientists began to make his visionary concepts into reality. Among those engineers was Sergey Korolev, who would become the "Chief Designer" of the Soviet space program, and who launched humanity into space with Laika on Sputnik and Yuri Gagarin on Vostok (for a detailed chronology of the space missions involving humans and animals, see *Fundamentals of Space Biology*, in this *Space Technology Library* series).

As early as 1959, a team of enthusiasts led by Sergey Korolev was already working on a concept, fantastic at the time, for a manned mission to Mars. Gradually, the concept was taking on the form of a design, which became the basis for defining specifications of the advanced N1 rocket, which was then in its initial design phase. The N1 rocket was designed to put a spacecraft into a circular orbit using an upper stage, which was then to be injected into a Mars fly-by trajectory. Assisted by the Martian gravitational field the spacecraft was to return to the vicinity of Earth. The descent vehicle would then land back on Earth. The *Heavy Interplanetary Manned Vehicle* (HIMV) had a mass of 75 tons, a length of 12 meters, and a pressurized cabin of six meters in diameter, which was designed for a crew of three. The total expected mission duration was two to three years. The craft was to have an instrumentation compartment that doubled as a radiation shelter for the crew during solar flare activity. In addition, a biological reactor would provide food for the crew. In flight, HIMV was to revolve about its long axis to create artificial gravity.

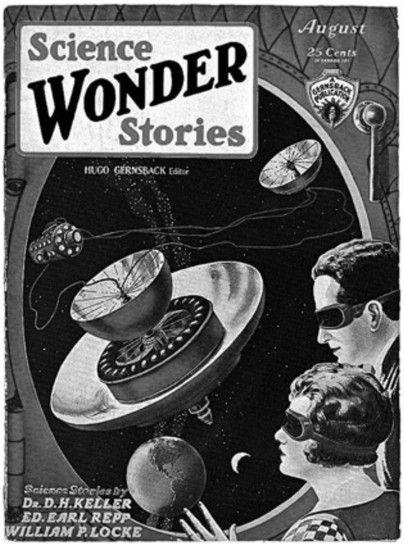

Figure 3-03. The Austrian writer Hermann Noordung's space station was a 30-m diameter rotating station called "Wohnrad" (Living Wheel) that he placed in geostationary orbit. This cover of the August 1929 edition of the Science Wonder Stories *magazine by well-known science fiction illustrator Frank R. Paul illustrates Noordung's space station array.*

The HIMV was to have been developed in the 1962-1965 timeframe (Vetrov 1998). In the following decade, however, the Soviet rocket industry concentrated its efforts mostly on matching NASA's Apollo program and toward the full-scale deployment of intercontinental ballistic missiles. Korolev always retained his interest in using artificial gravity on board large space stations and interplanetary spacecraft. He proposed to test the concept in orbit from the early days of the Voskhod program by connecting two modules by a tether (Harford 1973). Separation of the two components would first produce 0.03 g of artificial gravity. When the distance between the two modules reached 300 m, a rotation rate of 1 rpm would produce 0.16 g. The two-module scheme was attractive because nose-to-nose tethering meant that the living module would be in the correct vertical orientation for sustained experiments. Because the solar cells could not be kept in the proper orientation with respect to the sun during the artificial gravity-producing maneuver, the batteries on board the spacecraft would run down after about three days, thus limiting experiment time. After Korolev's sudden death in 1966, the project was terminated.

In 1928, inspired by the pioneering projections of Hermann Oberth, Hermann Noordung introduced a detailed engineering proposal for a space station that employed artificial gravity. Noordung's proposed design consisted of a wheel-shaped structure for living quarters, a power generating station attached to one end of the central hub, and an astronomical observation station. The latter two components were connected to the habitat by an umbilical. Collecting sunlight through a concave mirror in the center generated power. This power allowed the habitat wheel to rotate, thus creating artificial gravity inside the space station (Figure 3-03).

In his vision of space exploration in the *Collier's Weekly* space magazine, Wernher von Braun proposed an updated version of Noordung's rotating wheel having a diameter of 76 m (von Braun 1953). Orbiting at an altitude of 1730 km[11], his inflated three-deck space station would be built of reinforced nylon fiber covered with protective plates and rotate at three revolutions per minute (rpm) to provide the occupants with 0.3 g, a suitable platform for Mars expeditions. Later, Wernher von Braun worked with Walt Disney Studios to present space travel concepts to the public. The spinning station in the Disney television series *Man in Space* (1955-1957) was an update to the *Collier's* station that von Braun had designed a few years earlier with the main difference being that instead of being solar powered, the updated station included a nuclear reactor on its axis (Figure 3-04).

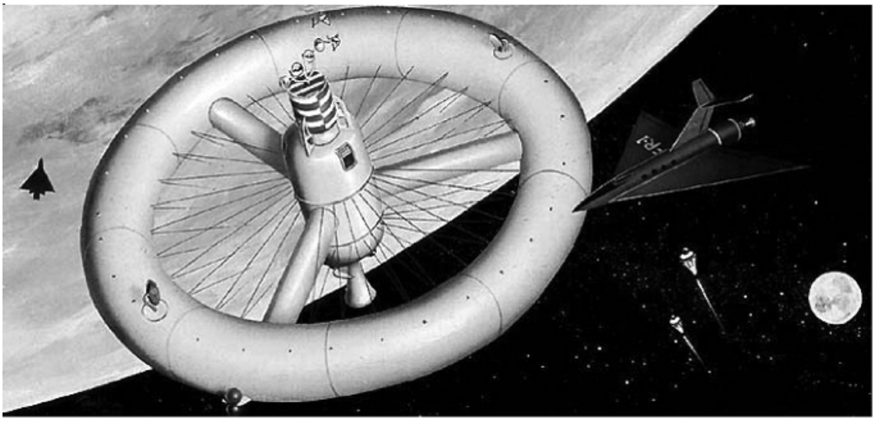

Figure 3-04. The Wernher Von Braun spinning station as shown in the Disney television series Man in Space *aired on ABC in 1955.*

[11] This orbit was later found to be within the then-unknown Van Allen radiation belts and therefore unusable by a human inhabited spacecraft.

1.2 Science Fiction

The popularization of artificial gravity, however, is attributable to the science fiction community. The large rotating space station image in the second episode (TMA-1) of the movie *2001: A Space Odyssey*, directed by Stanley Kubrick in 1968 (Figure 3-05) is also based on Wernher Von Braun's concept. The movie script was based on Arthur C. Clarke's short story *The Sentinel*, written two decades earlier (Clarke 1948). The Earth-orbiting space station in the second episode of the movie was 300 m in diameter and was home to an international contingent of scientists, passengers, and bureaucrats. It rotated around its center to provide artificial gravity to its inhabitants.

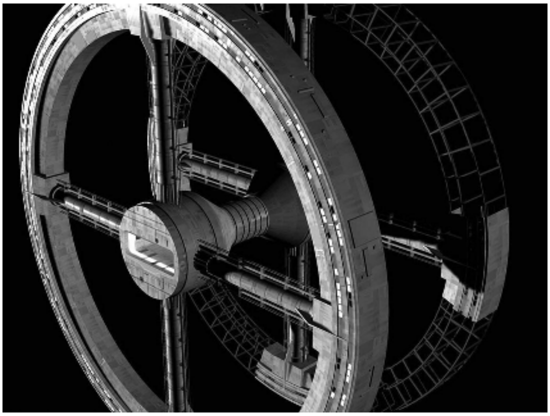

Figure 3-05. The gigantic space station in Earth orbit in the movie 2001: A Space Odyssey *produced and directed by Stanley Kubrick (1968). The station is shaped like a pair of four-spoked wheels on a common axis, about which it rotates to provide artificial gravity. It had not yet been completed: one of the wheels consisted primarily of a bare "wire" frame, with "skin" only at the points of intersection with the spokes.*

In the third episode of Kubrick's *2001: A Space Odyssey* (Jupiter mission), the *Discovery One* spacecraft used for interplanetary travel included another means for providing artificial gravity. *Discovery One* consisted of a large sphere as its fore end, then a long segmented spine with a communications dish, and a matrix of hexagonal exhaust nozzles on the aft end (Figure 3-06). The equatorial region of the sphere comprised a slowly rotating carousel, 11 m in diameter. By rotating at a rate slightly faster than five rpm, this internal centrifuge produced an artificial gravity level equal to that of the Moon. According to Clarke and Kubrick, this was enough to prevent the physical atrophy that would result from weightlessness, and it also allowed the routine functions of living to be carried out under nearly normal conditions.

The *Discovery One* internal centrifuge provided an idealized version of life in space that was free of health problems and the negative effects usually associated with transiting from the rotating to the stationary parts of the station. The carousel contained the kitchen, dining area, and washing and toilet facilities. Around the rim of the carousel were five tiny cubicles, decorated by each astronaut according to personal taste and containing their belongings (Figure 3-07).

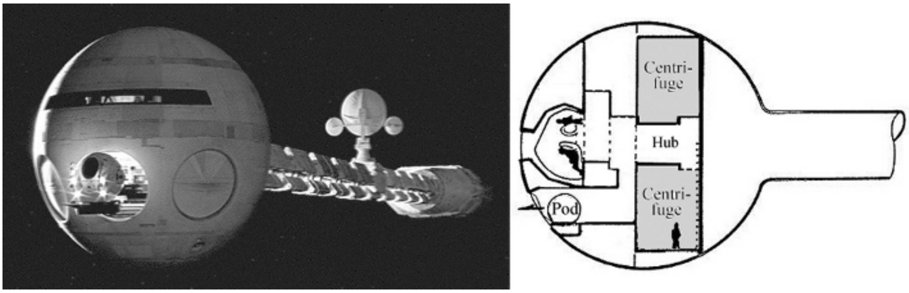

Figure 3-06. External view of the interplanetary Discovery One *spaceship in the movie* 2001: A Space Odyssey*, and cross-section showing the location of the internal centrifuge.*

The spin of the carousel could be stopped if necessary. When this happened, its angular momentum had to be stored in a flywheel, and switched back again when rotation was restarted. Under normal circumstances, it was left running at a constant speed. In the movie, it was easy enough to enter the large and slowly turning drum by going hand-over-hand along a pole through the 0-g region at its center. According to Clarke's story, "transferring to the moving section was as easy and automatic, after a little experience, as stepping onto a moving escalator"[12] (Figure 3-08).

Figure 3-07. In this scene of the movie 2001: A Space Odyssey *Astronaut Frank Poole is jogging around the rim of the internal centrifuge in* Discovery One*. In a real spinning space station, a jogger running along the rim of the station in the direction of the spin would increase his tangential velocity, thereby creating a slight increase in the centrifugal pull he would experience, and giving him the impression of running uphill. Running in a direction opposite that of the spin would decrease the pull slightly and create the impression of running downhill (see Chapter 2 for a description of the physics behind this phenomenon).*

[12] In reality, adaptation to the changes in gravity level and to Coriolis forces when crewmembers were passing from artificial gravity to weightlessness and back might take much more than just "a little experience", as suggested by the ground-based studies in slow rotating rooms (see this Chapter, Section 3.1).

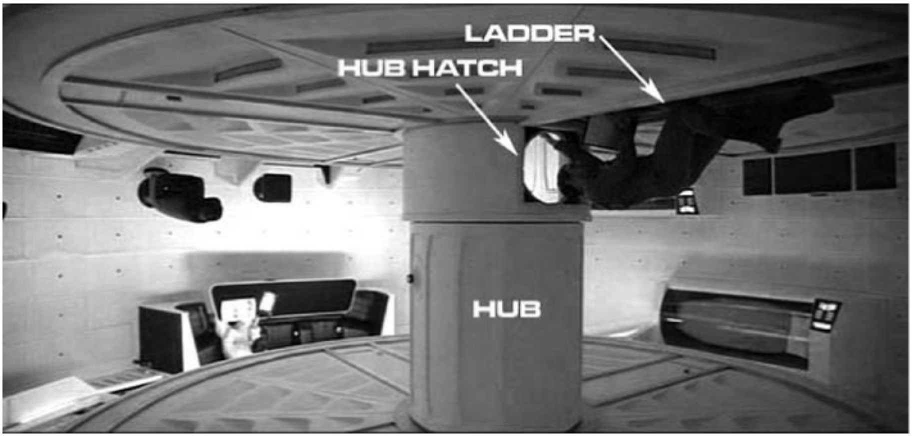

Figure 3-08. In another scene of the movie, an astronaut is emerging from an access panel at the hub of the Discovery One *centrifuge. The access way (hub hatch) is at the hub of the centrifuge and is stationary while the centrifuge rotates about it. The bottom of the ladder leads to the rim of the centrifuge, where the astronaut walks to join the first astronaut. In a real spinning centrifuge, moving along the ladder and transitioning from the ladder to the rim of the centrifuge would significantly challenge the vestibular and balance systems (see Chapter 4).*

For filming the scene involving the astronauts walking and jogging inside the spinning carousel, Kubrick had an 11-m diameter circular set constructed, at the cost of $750,000, which was a considerable portion of his budget for the film. The circular set could spin on its axis at a rotation rate of less than 1 rpm, corresponding to a speed of 0.5 km/h at the rim. The actors were always at the bottom of the set. As they walked, the set would be turned beneath them to maintain their position and prevent them from falling over, like the hamsters in an exercise wheel. The camera and the operator were installed on a wheeled dolly allowing it to also sit at the bottom. From the point of view of the camera and audience, the astronauts appeared to be walking around the walls while the set stood rock steady. Earlier shots of a stewardess climbing around the walls in the *Aries* kitchen module were achieved in a similar way (Bizony 2000).

A similar technique was first used in the movie *Royal Wedding* (Director Stanley Donen, 1951, MGM) where Fred Astaire, in one of his best-known solos, dances on the walls and ceilings of his hotel room (Figure 3-09). The number was filmed by mounting the camera and operator in a cage that rotated with the room, while Fred Astaire was dancing in a normal orientation relative to gravity.

Von Braun and Kubrick's "space wheels" kept the attention of the popular press and science alike. In 1956 Darrell Romick advanced an ambitious proposal for an on-orbit rotating cylinder that was one km long and 300 m in diameter. It would have the capacity to house 20,000 people. Then in 1964, Dandridge Cole and Donald Cox suggested the hollowing out of an ellipsoidal asteroid approximately 30-km long, rotating it about its major axis to generate artificial gravity, reflecting sunlight inside with mirrors, and creating on the inner shell a pastoral setting as a permanent habitat for a colony. And in 1971, Henry Gray proposed expanding the hub of a Kubrick-type station into a cylindrical habitat, which he called a *Vivarium* and patented under that name.

Figure 3-09. In this scene from the movie Royal Wedding *(1951), Fred Astaire performs a tap dance on the walls and ceiling of his hotel room. In fact, the furnishings were anchored and the room was built inside a rotating carousel that turned simultaneously with the camera, permitting the impressive special effects. Even knowing how this cinematic legendary scene was accomplished does not detract from its brilliance and virtuosity. The movie has slipped into public domain and this particular scene is accessible at the following URL:* http://www.youtube.com/watch?v=ac6o8PXthzQ

In his novel *Rendez-Vous With Rama* (1973) Arthur C. Clarke took Romick's kilometer-long cylindrical habitat and increased its size by an order of magnitude, combining it with the concept of the "generation ship" as a vehicle for interstellar travel at an achievable velocity. The vehicle called *Rama* was a dome-ended cylinder 50-km long and 16 km in diameter, rotating about its primary axis at 0.25 rpm to produce a near-terrestrial gravity level on the interior of its hull. Huge banks of lights in three vast trenches running the length the cylinder, 120 degrees apart, provided light for the interior. A ten-km-wide "Cylindrical Sea" at its equator divided the structure into two sections.

Gerard K. O'Neill is another futurist thinker who has considered space stations with artificial gravity. He is an American physicist at the Institute for Advanced Studies, Princeton. In 1969, O'Neill began to work out a strategy for the future expansion of the human race into space. He championed the idea of orbital settlements in several papers (O'Neill 1974) and in his book *The High Frontier* (1972). O'Neill first envisaged the construction of a space colony within a self-sufficient sphere, some 500 m in diameter. His *Island One* space sphere, rotating at two rpm, would generate an Earth-normal artificial gravity at its equator. An advantage of the sphere is that it has the smallest surface area for a given internal volume, so minimizing the amount of radiation shielding required.

O'Neill later contrived plans to orbit permanent colonies at the L4 and L5 Lagrange points in near-Earth space, culminating in a structure 32-km long and 3.2 km in radius, and capable of permanently supporting hundreds of thousands (*Island Two*) or even millions of inhabitants (*Island Three*). Normal Earth gravity would be achieved by rotating the colony at a rate of 0.53 rpm. The interior of the wheel would have three inhabited "valleys" each containing lakes, forests, and towns (Figure 3-10). Three large mirrors, capable of being opened and closed on a regular day/night basis, would shine sunlight into the valleys, and a large parabolic collector at one end of the cylinder would focus solar energy onto steam-driven generators to provide the colony's electricity needs. His large orbiting space colony consisted of an immense rotating aluminum wheel, the structure of which would be built of material mined from the Moon or asteroids.

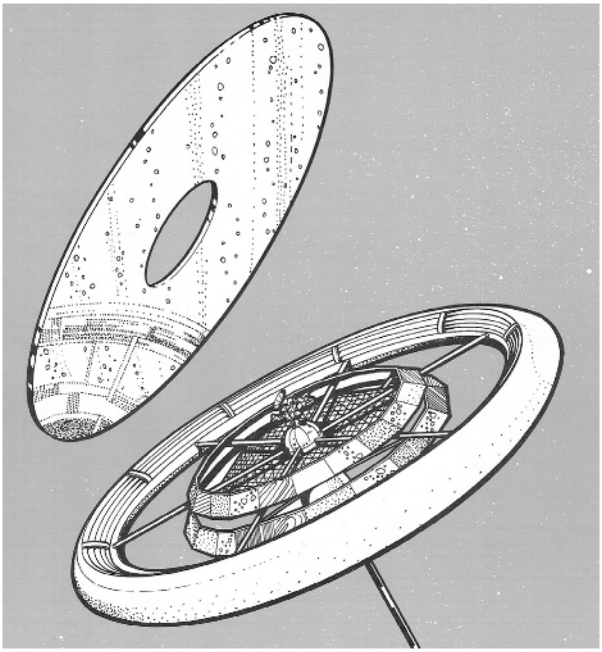

Figure 3-10. Gerard O'Neill's vision of a space colony with artificial gravity. Artificial gravity is generated on the inner rim of the wheel. Visiting spaceships dock at the center of the hub. There is zero gravity at the axis, so this area could be used for human powered flight, acrobatic sports or microgravity research. Also shown is one of the large mirrors for energy collection. Photo courtesy of NASA.

1.3 Formal Studies

The "space arks" proposed by Clarke and O'Neill's sparked a fire in both the science-fiction readership and the scientific community. All of a sudden, mere space stations like the NASA Skylab were no longer enough. Once-conservative scientists began setting their sights higher and their goals loftier. Artificial worlds were now the order of the day.

In 1975, NASA and the American Society for Engineering Education conducted the first formal investigations into the feasibility of man-made worlds in a 10-week systems engineering design program. The output of the study was a 185-page report called *Space Settlements: A Design Study* (Johnson and Holbrow 1977). Several types of space habitats were proposed. These included an updated version of the O'Neill *Island One* sphere, a domed cylindrical design inspired by Clarke's *Rama* and a ring-shaped design that expanded Von Braun's space wheel into a self-sufficient "space island."

NASA selected the new space wheel or "toroidal habitat" design, submitted by Stanford University students and later named the *Stanford torus* to recognize their contribution, as the most feasible of the proposed designs, making it the focus of the study. Deemed both ambitious and achievable, the *Stanford torus* was a cylindrical tube 130 m in diameter and 5.6-km long, bent into a circle and joined end-to-end to form a wheel 1.8 km across. The shape and design of the *Stanford torus* is perfect for creating artificial gravity. Spinning the torus like a giant centrifuge at exactly one rpm generates centripetal acceleration toward the exterior that feels just like Earth gravity to the inhabitants of the colony. The *Stanford torus* would accommodate 80,000 people in a near-Terrestrial environment complete with suburban villages, parks, and woodlands with free-running streams (Figure 3-11).

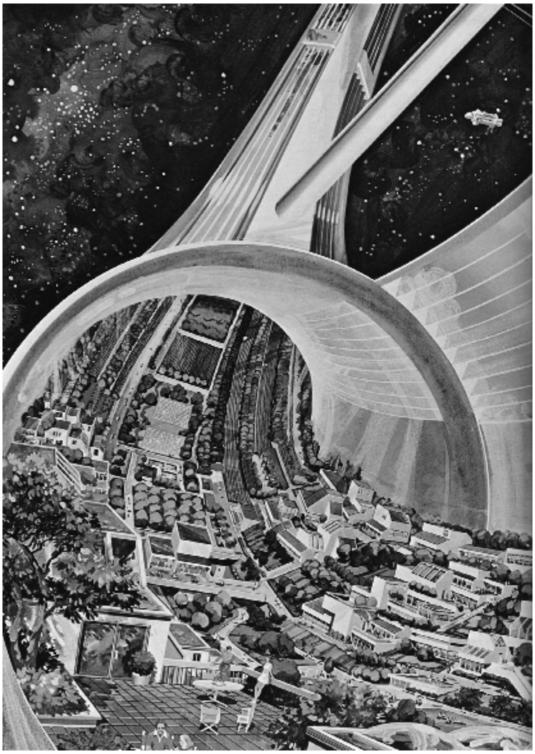

Figure 3-11. Artist conception of the inside of a Stanford torus, with a radius of 1.8 km and spinning at one rpm to produce a 1-g artificial gravity environment. Photo courtesy of NASA.

Following these pioneering ideas, the majority of early space station concepts involved the creation of artificial gravity in one way or another (see Figure 2-10) to simulate a more natural environment for the inhabitants. During the Mercury and Gemini program, astronauts had no trouble executing routine activities as long as they were inside the spacecraft. However, they experienced considerable difficulty when carrying out a spacewalk or *extra-vehicular activity* (EVA). It was later discovered that EVA training could be achieved with reasonably fidelity through neutral buoyancy simulations carried out in huge water tanks. At the time, artificial gravity in an orbital station was seen as a situation "where we [NASA] do not have to train the people, where we would be able to accommodate a greater variety of experimenters and not to have to end up training for every task prior to flight" (Faget and Olling 1968).

However, the concept of a rotating spacecraft or two spacecrafts connected by a tether presents serious design, financial, and operational challenges. In more recent studies, emphasis has been placed on reducing the artificial gravity level, reducing the radius, and increasing the rotation rate (Loret 1963, Shea 1992). However, all these trends introduce new problems. First, the surest artificial gravity solution is clearly one that produces a gravito-inertial environment close to that experienced on Earth. It remains to be determined whether a lesser gravity level will suffice. Second, reducing the radius and increasing the rotation rate introduce potential problems associated with gravity gradient and Coriolis forces (see Chapter 2, Section 2), such as disorientation, and impaired movement and locomotion. These problems might in turn compromise the living and working conditions in the rotating environment.

An alternative to a rotating vehicle is in-flight exposure to artificial gravity using a small centrifuge inside the spacecraft. A centrifuge with a radius of 2 m permits subjects to stand upright and even walk within its limited confines. Of course, the head is then very close to the center of rotation and a significant gravity gradient in the head-to-foot direction results. As the radius shrinks even further to less than 1.5 m, taller subjects can no longer stand erect but must assume a squatting or crouching posture. To generate 1 g at the subject's feet, such a short-radius device would be required to spin at a much higher rate than a larger system. The small centrifuge would also produce significant Coriolis forces and motion sickness stimuli if the head is moved, at least until adaptation occurs.

However, as for all other physical stimuli, there is certainly a dose-response relationship between the amplitude and duration of the gravity level and the physiological body functions, which remains to be determined (Young 1999). Although our current knowledge is limited, it is very likely that humans do not need a continuous exposure to 1 g to remain healthy. As part of our normal circadian rhythm, the gravity dependent processes that result in body fluid loss and bone deconditioning are probably turned off during normal sleeping hours (Diamandis 1997, Vernikos 2004). Furthermore, with the use of a centrifuge for short periods, there is no reason to be restricted to only 1 g. Rather, the exposure might be as high as 2 or 3 g in periods of perhaps one hour daily or several times per week which might be just enough to deliver adequate stresses on the bone, muscle, cardiovascular, and sensory-motor systems. An on-board human periodic or intermittent small centrifuge therefore presents a realistic near-term opportunity for providing artificial gravity during planetary missions. Note that the physiological responses to continuous Mars gravity exposure, which is 0.38 g, are unknown. If it turns out that substantial physiological deconditioning occurs at Mars gravity, then intermittent artificial gravity exposure may be required to protect crews during long stays on the surface of Mars as well.

The potential use of 1.5 to 2-m-radius centrifuges for intermittent artificial exposure to astronauts has been validated in numerous ground-based studies as an effective way to overcome the deconditioning of bed rest. The main results of these studies are reviewed in the following section.

2 EXPERIENCE WITH ARTIFICIAL GRAVITY

Despite the long-standing interest in artificial gravity, experimental results obtained in space are quite limited. There were a few space missions early on that were devoted to animal studies. Rats were centrifuged continuously at 1 g for several days and showed no signs of physiological deconditioning. A 2.5-m-radius centrifuge was planned for installation on board the ISS to afford the opportunity to examine the adequacy of various levels of artificial gravity in protecting rodents during spaceflight. However, this project was cancelled. Human experiments with artificial gravity are even more limited. They include anecdotal reports of the crew on the lunar surface, during space missions with tethered and spinning vehicles, during orbital maneuvering systems burn, or when riding eccentric rotating chairs and sleds used by scientists for investigations of the vestibular system in orbit.

2.1 Flight Animal Experiments

The Soviet space research community expressed an early and intense interest in artificial gravity. In 1961 Soviet scientists began testing rats and mice in parabolic flights, in which 25 seconds of weightless are provided for each parabola flown. The posture and locomotion of the animals appeared normal during brief periods of 0.3 g exposure, thus setting this as a minimum gravity level requirement for locomotion (Yuganov *et al.* 1962, 1964).

The first animals to be centrifuged in space were flown on the 20-day Cosmos-782 mission in 1975, when fish and turtles housed in containers were centrifuged at 1 g. The center of the containers was placed at 37.5 cm from the center of a platform rotating at 52 rpm. After the flight, the physiology and behavior of the centrifuged animals was indistinguishable from their 1-g ground and 0-g flight controls. Furthermore, turtles centrifuged at levels as low as 0.3 g showed none of the muscle wasting that is typically associated with exposure to weightlessness (Ilyin and Parfenov 1979).

In 1977, a significantly more extensive investigation was executed using rats that were centrifuged during the 19-day mission of Cosmos-936. The rats were kept in individual cages and were not restrained. Their cages were placed in a centrifuge with a radius of 32 cm. An artificial gravity level of 1g was obtained by spinning the centrifuge at 53.5 rpm (Figure 3-12).

Results revealed that in-flight centrifugation had a protective effect on the myocardium and the musculo-skeletal system, as compared to the animals that were exposed to microgravity and not centrifuged. However, there were some adverse effects of the in-flight centrifugation that were noted in the visual, vestibular, and motor coordination functions, such as equilibrium, the righting reflex, and orientation disorders. These deficits may have been the result of the high rotation rate of the centrifuge and the large magnitude of the gravity gradient (Adamovich *et al.* 1980).

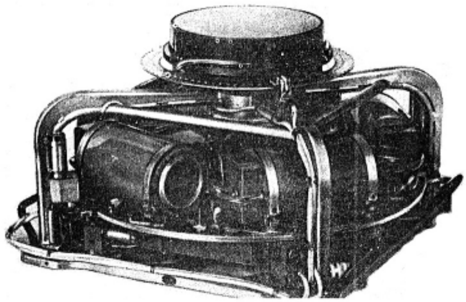

Figure 3-12. Centrifuge for housing rats on board the biosatellite Cosmos missions. Adapted from Adamovich et al. (1980).

Another series of experiments involved rotating four rats on suborbital rockets during a 5-min period of free fall. The rocket was rotated about its longitudinal axis using a special motor at a rate of 45 rpm. The rotation created a variable artificial gravity field of from 0.3 to 1.5 g along the boxes that housed the rats. The movements of the rats were recorded on film and showed than one rat stayed in a position where the artificial gravity level was about 0.4 g, whereas the other three settled down where the artificial gravity level was 1 g (Lange *et al.* 1975).

Small radius high rotation-rate centrifuges have been flown in the Spacelab of the Space Shuttle and in the Skylab, Salyut, and Mir space stations to conduct experiments on bacteria, cells, and other biological specimens. Results indicate that microgravity effects, especially at the cellular level, may be eliminated by artificial gravity (see Clément and Slenzka 2006 for review).

As mentioned previously, plans to install a 2.5-m-radius centrifuge on the ISS to carry up to eight modules for rodents, fish, and eggs (Figure 3-13) have been cancelled. This variable gravity animal centrifuge would not only have provided a 1-g control for the 0-g experiments, but would also have allowed exploring the entire range from 0.01 g to 1 g for a variety of species. Such a device would have afforded the opportunity to examine the adequacy of various levels of artificial gravity in protecting rodents during spaceflight. It is unfortunate that this centrifuge, which was the heart of the gravitational biology flight program, was eliminated from the ISS program. Not only was it essential for basic research, but it also formed the basis for understanding the physiological effects of short radius artificial gravity in a manner needed for effective human artificial gravity prescription.

Finally, it is worth to mention the efforts of the students from the Massachusetts Institute of Technology (MIT), and the Georgia Institute of Technology (Georgia Tech) who have proposed to study the effects of Mars gravity on mice on board an unmanned biosatellite. Their project, the *Mars Gravity Biosatellite,* is a 400-kg biosatellite that will carry 15 mice housed in individual life support systems that will rotate about its central axis, providing 0.38 g outwards against a curved floor. After 5 weeks in low Earth orbit, the re-entry capsule will separate from the primary spacecraft to return the mice safely to a landing zone in the Australian desert. The biosatellite provides autonomous life support capabilities and data telemetry or storage from on-board experiments. The comparison between the deconditioning of the mice in the Mars Gravity Biosatellite and in previous microgravity space missions should provide valuable data about the effects of partial gravity on physiological functions.

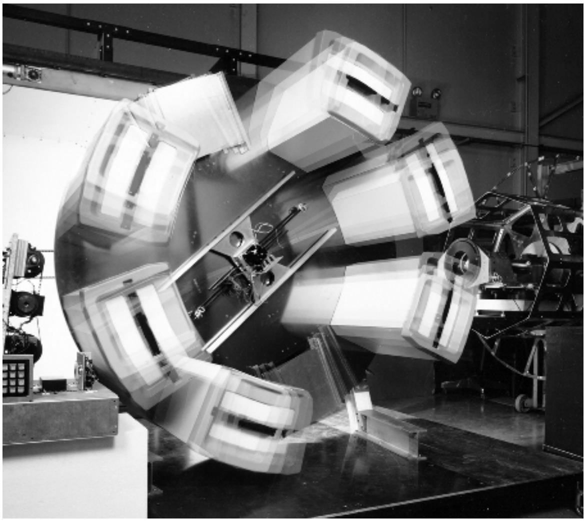

Figure 3-13. A 2.5-m centrifuge was originally planned for the Centrifugation Accommodation Module developed jointly by JAXA and NASA for the ISS. This photograph shows a ground test of this centrifuge at the NASA Ames Research Center. Habitats mounted on the centrifuge were to house various biological specimens, from cells to large plants and rodents. Unfortunately this ISS centrifuge project got cancelled. Photo courtesy of NASA.

2.2 Human Space Experience

During the first 40 years of the space age, no formal human artificial experiments were performed in space. In the early years of human spaceflight, the only major physiological disturbance involved space motion sickness and this was of concern only for the first few days in orbit. After the Apollo missions, the NASA flight surgeon position was, "The magnitude of the motion-sickness problem experienced by astronauts to date does not appear to suggest clearly the need for design and incorporation of artificial gravity system in near-future space vehicles" (Berry 1973). The debilitating effects of weightlessness on the bone, muscle, and cardiovascular system were demonstrated on the longer Skylab missions in the early 1970s and later on the long-duration Salyut and Mir flights. However, it was believed that in-flight exercise, augmented by resistance training and fluid loading, would solve the problem. As time passed, the opportunities for human centrifuges or rotating spacecraft in orbit disappeared.

The Gemini-11 mission in 1966 offered the first chance to turn artificial gravity science fiction into fact. The Gemini program was, however, halfway completed before NASA got around to planning tethered vehicle flights. When tethered flight was identified as a mission objective, NASA planners first thought of it as a way of evaluating the tether as an aid to station keeping. However, tethering might also be a means of inducing some degree of artificial gravity. The minimum rotation rate depended on whether the tethered activity was intended primarily for formation flying or for achieving gravity. NASA decided to attempt both, although it would settle for "an economical and feasible method of long-term, unattended station keeping", and chose a 36-meter Dacron line (Wade 2005).

An astronaut connected a tether to an orbiting Agena rocket casing and to the Gemini-11 spacecraft during a spacewalk. The two vehicles were then put into a slow spin (see Figure 2-03, left). The rotation rate was about 0.15 rpm. At a distance of about 19 m from the center of rotation, the Gemini cabin and its crew (astronauts Gordon and Conrad) experienced 0.0005 g of artificial gravity. When the astronauts put a camera against the instrument panel and then let it go, it moved in a straight line to the rear of the cockpit and parallel to the direction of the tether. However, the crew, themselves, did not sense any physiological effect of gravity. After they had been rotated for 2½ orbits around the Earth (about four hours), the pilots ended the exercise by jettisoning the spacecraft's docking bar. All in all, they reported it had been "an interesting and puzzling experience" (Wade 2005).

It is now known that Sergey Korolev also had a project for an artificial gravity experiment in 1965-1966 (Harford 1973). As mentioned above, his plan was to deploy a tether between a Voskhod vehicle and the spent last stage of its booster, and rotate both vehicles, thus providing artificial gravity in the crew compartment. The flight was supposed to last for 20 days and clearly upstage the Americans. The crew would have included a pilot and a physician (Volynov and Katys), and artificial gravity experiments would have been conducted for 3-4 days during the flight. However, after the unexpected death of Korolev in January 1966, the Soviet space program was in crisis. This mission was postponed to February 1966, with the deletion of the artificial gravity experiment, before being finally cancelled outright (Wade 2005).

No further artificial gravity tests involving spacecraft have been conducted. Since Gemini-11, the only opportunities for artificial gravity human experiments in weightlessness have come from anecdotal reports by the crew, and from neurovestibular system investigations using controlled, although short-lasting, linear accelerations.

As an example, during the Skylab missions the crew took advantage of the large open compartment to run around the curved circumference, imitating the jogger in Stanley Kubrick's film. The astronauts produced self-generated artificial gravity by running (see the video at the following URL site: http://www.artificial-gravity.com/Skylab-clip2.mpg). They reported no difficulty with either locomotion or motion sickness during this exercise (Conrad and Klausner 2005).

In late 1960s, tests were also conducted in parabolic flights to define artificial gravity requirements for a space station and to assure that the crew could perform well in reduced gravity. Parabolas were flown at 0.1, 0.2, 0.3, and 0.5 g during about one-half minute each. The tests subjects, who had previously flown several hundreds of parabolas in reduced gravity, carried out certain predefined tasks. These tasks included walking while carrying small and large containers, tightening bolts, connecting and disconnecting electrical equipment, and pouring water back and forth between two containers. These tests, although preliminary in nature, indicated that 0.2 g provided a much better environment for such tasks than did 0.1 g. At gravity levels greater than 0.2 g, very little gain in performance was indicated. Furthermore, the test subjects reported that at 0.5 g they felt as sure of themselves and as comfortable as they did at 1 g (Faget and Olling 1968).

In a *European Space Agency* (ESA) linear acceleration experiment on board the Spacelab D-1 mission in 1985, subjects were oscillated in a sinusoidal fashion on a linear sled at frequencies between 0.18 Hz and 0.8 Hz generating a peak linear acceleration of 0.2 g (Figure 3-14). The acceleration could be in either the interaural (Gy) or the longitudinal (Gz) direction, with ±Gy directed to the right or left shoulder, respectively, and the ±Gz directed head-to-foot or foot-to-head, respectively (for a graphic definition of axis and direction, see Figure 2-02). The fundamental result was that the test subjects in microgravity did not perceive linear Gz accelerations of less than 0.2 g in magnitude as artificial gravity (Arrott *et al.* 1990).

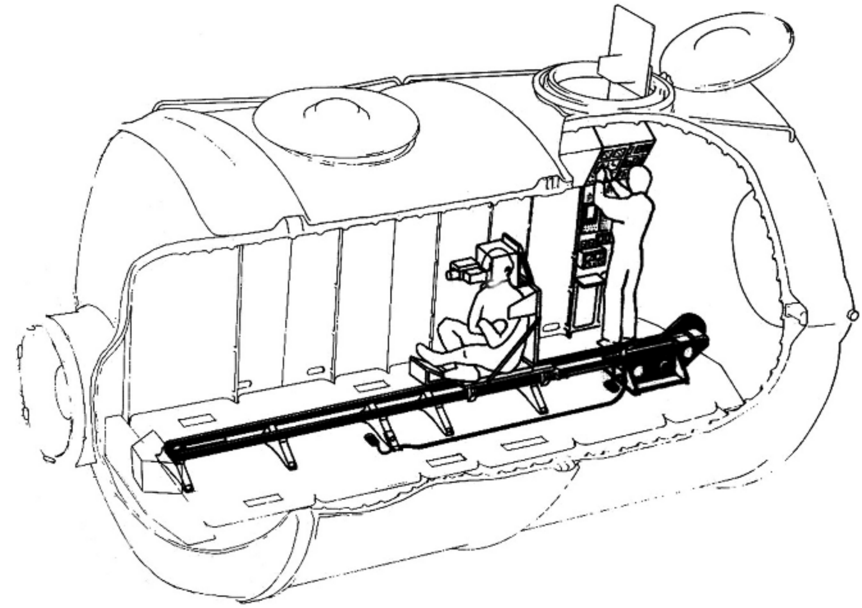

Figure 3-14. The ESA linear sled on board the Spacelab D-1 mission could generate linear accelerations ranging from 0.2 g to 1 g. Due to the limited track length (2.5 m), sustained constant exposure was only possible for very low acceleration levels of less than 0.05 g. Perception studies involved sinusoidal profiles with the subjects being accelerated back and forth in either the interaural (sideways) or longitudinal (forward-backward) directions. Photo courtesy of ESA.

In another experiment conducted during the Spacelab International Microgravity Laboratory (IML-1) mission that was flown on STS-42 in 1992, four subjects were spun on a rotator in pitch and in roll (Figure 3-15). The head of the subjects was 0.5 m off-center and experienced an acceleration of 0.22 g in the –Gz direction, while the feet were on the other side of the rotation axis, experiencing an acceleration of 0.36 g in the +Gz direction. No unusual inversion phenomena were reported, indicating that the artificial gravity stimulus of –0.22 g at the head did not provide a vertical reference in any of the test subjects (Benson *et al.* 1997).

During the Neurolab mission frown on STS-90 in 1998, a systematic evaluation of the effects of artificial gravity in humans was conducted using the ESA off-axis rotator, a short-radius centrifuge with a variable radius of 0.5 to 0.65 m that was capable of generating artificial gravity levels of 0.5 and 1 g. The artificial gravity forces were applied through the subject's ±Gy or –Gz axis for seven minutes at a time (Figure 3-16). Eye movements and perception recorded during the artificial gravity events provided both objective and subjective data. The experiment indicated that the test subjects perceived sustained levels of 0.5 g and 1 g as artificial gravity (Clément *et al.* 2001).

Although the threshold for perception of linear acceleration in humans is on the order of 0.007 g (Benson *et al.* 1986) the threshold for perception of artificial gravity by astronauts in space is, based on the data we have so far, somewhere[13] between 0.22 and 0.5 g. Perhaps it is not necessary to *perceive* artificial gravity at the cognitive level for it to be effective as a countermeasure. However, for purposes of defining the comfort zone of astronauts in an artificial gravity environment (whether it's a rotating spacecraft or on-board centrifuge), it would indeed be useful to determine the threshold value of perceived artificial gravity. Unfortunately, there are no plans to put a human centrifuge on board the ISS, at least in the near term.

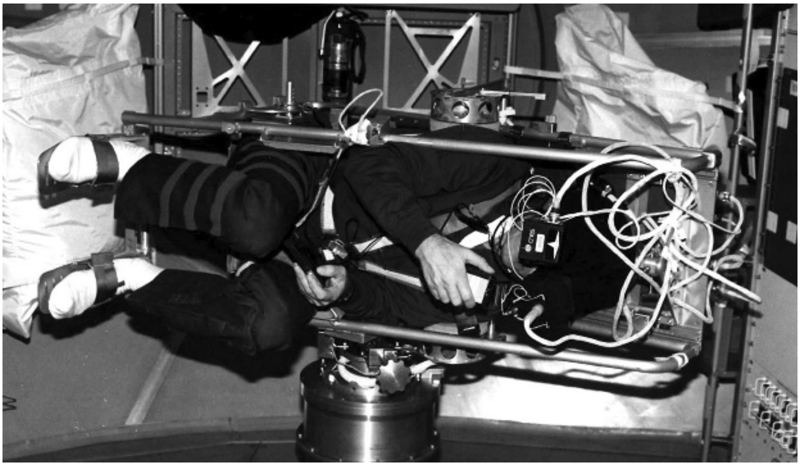

Figure 3-15. The Microgravity Vestibular Investigations *rotator flown on STS-42. The subjects were spun in pitch, as seen here, or in roll. Because the axis of rotation was at about the center of mass, a centrifugal force of 0.22 g was exerted at the head and was directed foot-to-head, or the –Gz direction. The centripetal acceleration exerted at the feet was directed head-to-foot. Photo courtesy of NASA.*

The astronauts who visited the lunar surface were exposed to a reduced gravity level of 0.16 g on the Moon for several hours or days during their 12-day space missions. They reported having "difficulty in determining just what straight up and down was". During Apollo-11, the lunar module floor on the Moon surface was, in fact, tilted 4.5 deg from the horizontal. The crew did not perceive this tilt. During their spacewalks on the Moon, the astronauts lost their balance several times, in most cases because they could not evaluate the slope of the terrain. They also reported this problem "caused

[13] It is interesting to note that the human factor design envelope derived from rotating studies also suggests a lower limit of 0.3 g (see Chapter 2, Section 3.4).

our cameras and scientific experiments sometimes not maintaining a level attitude we expected" (Godwin 1999).

Interestingly, less decrease in heart size and less increase in heart rate were found postflight in the Apollo astronauts compared with Skylab and Shuttle astronauts (Johnston *et al.* 1975, Johnston and Dietlein 1977, Nicogossian *et al.* 1994). Unfortunately, there was no comparison between the results obtained on those astronauts staying on the Moon and those who stayed in orbit around the Moon. Therefore, it cannot be concluded that the exposure to lunar gravity during the course of their exploration missions was helpful in reducing cardiovascular deconditioning. All of the Apollo astronauts were highly trained jet fighter pilots in exemplary physical condition. Their long hours flying high-g maneuvers in jet aircraft may have increased their orthostatic tolerance and promoted the development of adaptive protection in these individuals, as compared to other Skylab and Space Shuttle astronauts (Clément and Pavy-LeTraon 2004).

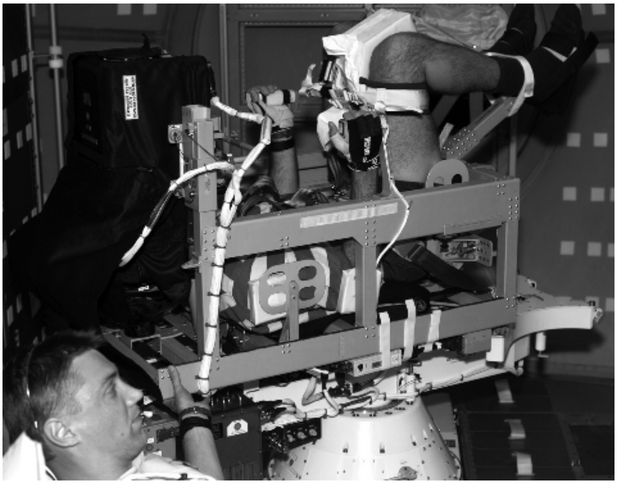

Figure 3-16. The off-axis rotator developed by ESA for the Neurolab mission. In this orientation, the rotation axis is at hip level. During centrifugation at 0.5 and 1 g on Earth, the four subjects had the sensation of a head-down tilt of 27 or 45 deg, respectively. In microgravity, the centripetal acceleration was the only acceleration stimulus and the subjects had the illusion of standing on their head. Photo courtesy of NASA.

Interestingly, the four subjects tested intermittently in the on-board centrifuge during the Neurolab Spacelab mission mentioned above (see Figure 3-16), seemed to have achieved some measure of resistance to postflight orthostatic instability and did not show the usual decrease in vestibular sensitivity to tilt. The other three crewmembers on that mission had orthostatic intolerance. Based on the result that about 64% of astronauts experience profound postflight orthostatic intolerance (Buckey *et al.* 1996), the probability that four crewmembers on the same flight do not exhibit orthostatic intolerance by chance is approximately 1 in 60 (0.364) (Moore *et al.* 2000). During the flight, the centrifuge runs were executed during about 10 min at 0.5 g or 1 g every other day, for a total duration ranging from 45-60 min during the 16-day mission. Obviously, more experiments are needed to validate these results.

3 GROUND-BASED CENTRIFUGE EXPERIMENTS

Despite the absence of flight-test opportunities, several laboratories worldwide have continued ground-based studies of the efficacy and acceptability of large scale rotating artificial gravity environment. Of course, all of these investigations are hampered by the presence of the steady gravitational pull. On Earth, gravity adds to the centrifugal force vectorially and produces a net specific *gravito-inertial force* (GIF) that is tilted relative to the horizontal. In weightlessness, the artificial gravity level is equivalent to the centrifugal force (Figure 3-17).

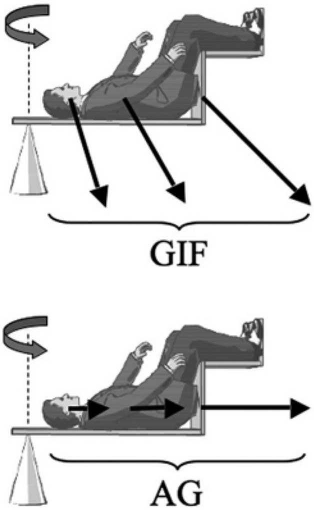

Figure 3-17. These drawings illustrate the difference between the physical effects of centrifugation on Earth (top figure) and in space (bottom figure). On Earth, the gravito-inertial force (GIF is tilted relative to the plane of rotation. In space, artificial gravity (AG) is aligned with the plane of rotation. Also shown is the gravity gradient in both conditions. For example, in the lower figure, the AG level is 1 g at the feet and 0.38 g at the head for a rotation rate of 20.8 rpm.

Ground simulations have shown that humans are extremely sensitive to rotation. Although few adverse effects are present for a rotation rate less than 1 rpm, because of the unusual pattern of vestibular stimulation under ground-based conditions, higher rotation rates produce motion sickness that is similar to that occurring during the acute period of adaptation to weightlessness. The Coriolis effects on inner ear endolymph flow and on moving limbs create disorientation, nausea, vomiting, and loss of coordination. Unless the head motion are restrained or a dual-adaptation to both microgravity and artificial gravity environment occurs, motion sickness can be a serious problem.

There is not a clear consensus in the definition of short- and long-radius centrifuges in the literature. Distinction can be made on radius length, gravity gradient, or subject mobility. The latter parameter will be used in this book. By *long-radius centrifuge*, we mean a device in which a subject is completely free to move about, whereas a *short-radius centrifuge* is one where the subject is immobile, i.e., either strapped in or otherwise constrained.

3.1 Long-Radius Centrifugation

The earliest of the extensive tests in sustained rotation were conducted in the *Naval Medical Research Laboratory* (NAMRL) in Pensacola, beginning in 1958. The *Slow Rotating Room* (SRR) had a 5-m-radius with complete living facilities, in which subjects could live for periods ranging from one day to three weeks. Rotation rates ranged from 1 to 10 rpm, with the floor of the SRR staying horizontal. Initially, most subjects developed motion sickness symptoms when they made head movements at room rotation rates in excess of 3 rpm and, through that experience, learned to restrict these movements. The rate of the room rotation rate was increased incrementally. After several days, most subjects were able to make head movements without nausea at rotation rate up to 6 rpm. Only a subset of the subjects progressed to the point that they could move around comfortably at 10 rpm.

Research was also performed to examine the problem of adapting the postural system to a 3-rpm run. As is the case for motion sickness, the subjects' balance control was initially disrupted on entering the SRR, but recovered within three to four days. Subsequently, most subjects were able to walk on thin rails about as well as in the Earth-normal environment, throw darts, and pour coffee without having to think about motor control. They also performed watch-keeping tasks within normal limits (Guedry *et al.* 1964).

When the SRR was stopped after 12 days, subjects experienced after-effects and erroneous motion sensations during head movements. Their balance control was again disrupted for three to four days. These effects were stronger after runs at 10 rpm than after runs at 3 rpm (Graybiel *et al.* 1965).

The investigators concluded from these studies that humans can adapt to rotation rate of 3 rpm and that a 14-day period of rotation at this velocity causes no significant changes in general condition or performance. In contrast, no adaptation took place when subjects were rotated at 10 rpm for 12 days, implying that a 10-rpm rotation rate is close to the upper threshold of endurance.

As a next step, ways of adapting humans to rotation at 10 rpm were investigated through incremental increases in rotation rate over time. Increasing the rotation rate in nine stages of approximately two days each over the course of 16 days mitigated the symptoms of motion sickness and generated less balance problems even at 10 rpm (Graybiel *et al.* 1969). Results also indicated that executing a series of specific head movements could significantly shorten the time needed to adapt. The higher rotation rate, the more difficult the adaptation, but adaptation to 10 rpm was possible as long as the rate-increase increments were held to 1-2 rpm with a period of 12-24 hour at each increment (Faget and Olling 1968). The time needed for this adaptation might therefore prove to be too long for practical use during spaceflight. However, anti-motion sickness drugs could then be used to attenuate motion sickness while the terminal velocity is more rapidly achieved (Lackner and DiZio 2000b).

Periodic stops of 10 to 15 min were required during the long-duration SRR runs for re-provisioning. Over time, the on-board experimenters who helped in this activity made transitions between the stationary and SRR rotation without experiencing motion sickness or disruptions of movement control. They manifested perfect *dual-adaptation* (Cohn *et al.* 2000, Lackner and Graybiel 1982, Bob Kennedy's personal communication), thus indicating that is possible to be simultaneously adapted to rotating and non-rotating environments. Furthermore, there was retention of the adaptation to the SRR for several days in all the subjects, which implies that transitions from weightlessness to rotation should be acceptable under certain conditions (Graybiel and Knepton 1972).

The *Institute for Biomedical Problems* (IBMP) in Moscow conducted a major ground-based research program on artificial gravity beginning in the 1960s. Their earliest tests in the *MVK-1* small rotating chamber were executed at speeds up to 6.6 rpm and involved the rotating of one or two subjects for up to a week. The *MVK-1* was followed up by the roomier 10-m radius *Orbita* centrifuge, capable of rotating two to three people for several weeks at speeds up to 12 rpm. The longest tests executed during this program were for 25 days at 6 rpm.

The initial rotation exposures produced the expected disturbances in dizziness, equilibrium, and coordination. Within an hour, the usual pattern of motion sickness symptoms occurred, including vomiting in some cases. In four to five hours, subjects also complained of drowsiness and headache. Three periods of vestibular adaptation were distinguished for these long-duration exposures. The first one or two days were characterized by severe motion sickness. This was followed by a week during which the nausea and related acute symptoms disappeared, but drowsiness and headache remained. Finally, after the first 7 to 10 days, subjects showed immunity to motion sickness, even when additional vestibular stimulation was provided.

As found in Graybiel's SRR studies in Pensacola, the severity of motion sickness symptoms and the time to adapt to prolonged rotation on the Russian small rotating room *MVK-1* were related mostly to rotation rate. There was an absence of any motion sickness symptoms at 1 rpm, moderate symptoms at 1.8 rpm, and marked symptoms at 3.5 rpm. On the larger *Orbita* centrifuge, however, symptoms appeared only above 1.8 rpm. Head movements brought on discomfort in all cases (Kotovskaya *et al.* 1981).

The authors also report the following: "cardiovascular function remained within normal limits, […] no significant sleep disturbances were noted in the long-rotation environment, […] all assignments were completed even in the presence of pronounced illness, and no decline was noted in short-term verbal memory" (Shipov 1977).

These experiments employing long-radius centrifugation suggest that all of the undesirable sensations are proportional to the rotation rate. Almost all subjects can adapt quickly to work in a 3-rpm rotating environment. With higher rotation rates, however, the subjects will all experience symptoms of motion sickness and disturbances in postural equilibrium, the extent of which are a function of the rotation rate. Nevertheless, adaptation can be achieved under these conditions in six to eight days, and the remainder of the stay in a rotating environment is characterized by normal health and performance.

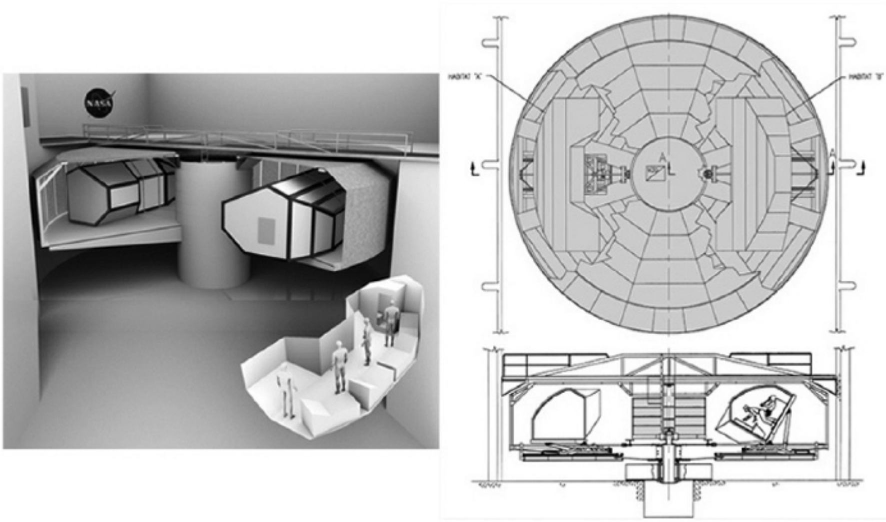

Figure 3-18. These drawings illustrate a joint project by NASA and the U.S. Air Force for long-duration studies of exposure to rotating environment and hypergravity. It comprises a large-radius centrifuge with two manned habitats. The habitats are mounted on actuators to align the passengers' body axis when standing with the resultant of the centrifugal and gravitational forces. A central hub connecting the two habitats and the outside is used for re-supply and service without interrupting rotation. Photo courtesy of NASA.

The studies conducted in the 1960s were actually quite preliminary and involved a limited number of subjects. A total of only 30 subjects were exposed to the rotating environment in the SRR in Pensacola. At the time, there was no attempt to identify optimum exposure and training strategies for adapting people to rotating environments. Furthermore, subjects in the SRR tended to avoid making any movements, especially at higher rates of rotation. Recent experiments have demonstrated that complete adaptation to rotation rates as high as 10 rpm can be achieved within minutes if repeated voluntary movements are made, so that the central nervous system can anticipate the forthcoming Coriolis forces (see Lackner and DiZio 2000b for a review). The subjects in the SRR did not make movements that would have provided experience with Coriolis forces. Consequently, it is not surprising that these subjects failed to fully adapt at high rotation rates. In fact, Lackner and DiZio (2000b) conclude their review by expressing a need for a re-evaluation of these earlier SRR studies. In particular they state, "Concerns that it would be difficult if not impossible to adapt to Coriolis forces generated by movements made in a vehicle rotating at more than 3 or 4 rpm have turned out to be unfounded. Everyday reaching and walking movements typically involve simultaneous body turning and generate higher levels of Coriolis forces than would be elicited by body movements in an artificial gravity environment rotating at 10 rpm".

Research on this important issue is currently in progress using the slow rotating rooms at Brandeis University and in Pensacola. These apparatus expose subjects to rotating environment up to a few days. For longer exposure studies, lasting weeks or months, a joint project NASA-U.S. Air Force also envisions the construction of two habitats installed diametrically opposed at the end of the arm of a large-radius centrifuge (Figure 3-18). Each habitat could house four persons. The habitats are mounted on actuators, allowing the longitudinal body axis of standing subjects to be aligned with the direction of the centrifugal force. A rotation rate of 10 rpm would generate 1.16 g along the subjects Gz axis. This value is particularly interesting, since it correspond to Earth gravity plus Moon gravity.

3.2 Short-Radius Centrifugation

More recent investigations have assessed the ability of subjects to avoid motion sickness during head movements while rotating at the high velocities associated with short-radius centrifugation. Antonutto *et al.* (1993) in Udine found that subjects who were pedaling on a bicycle-powered short-arm centrifuge were able to make head movements without acute motion sickness while rotating at 19-21 rpm. Young, Hecht, and colleagues used the 2-m radius centrifuge at MIT (see Figure 3-01) to show that most subjects could adapt both their eye movements and motion sickness symptoms by rotating at 23 rpm (Young *et al.* 2001). Both the Udine and the MIT studies were conducted at rotation rate sufficient to produce 1 g of horizontal centrifugal force or a net GIF of 1.4 g. In the Udine centrifuge, the GIF was aligned with the subject's, head-to-foot (Gz) axis, whereas in the more provocative MIT studies, the subject remained horizontal.

The Coriolis forces associated with limb and head movements as well as walking in a rotating environment are initially both surprising and disturbing. In almost all cases, subjects develop appropriate new motor control strategies to adapt to the new environment and, in fact, are no longer aware of the unusual forces. Extensive experiments in the Brandeis University slow rotating room demonstrated the remarkable ability to adapt to unusual environments (Lackner and DiZio 2000a). A measure of dual-adaptation apparently exists so that subjects can switch from the rotating to the non-rotating environment with minimal re-learning (see Chapter 4, section 5.2).

The adequacy of artificial gravity in stimulating the cardiovascular system has been investigated in ground studies. In most of these studies, the detrimental effects of weightlessness are simulated by sustained bed rest, often with the 6 deg of head-down tilt and occasionally by partial submersion in water to better emulate the fluid shift that occurs in space. In a pioneering study in 1966, White and his colleagues at Douglas (Figure 3-19) showed that intermittent exposure to 1 g or 4 g on a 1.8-m-radius centrifuge was effective in alleviating the usual decrease in tolerance to standing (orthostatic intolerance). Exercise produced little additional benefit (White *et al.* 1965).

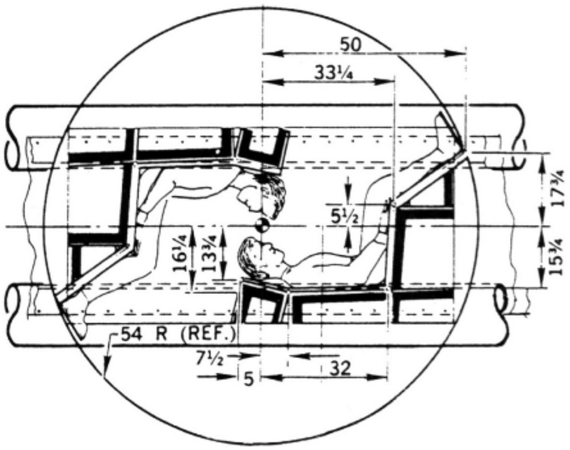

Figure 3-19. Short-radius centrifuge used during the Douglas Aircraft Co.'s studies. Two subjects were tested simultaneously. The subjects were lying on their sides and their heads were very slightly off-center. Measurements are in inches (White et al. *1965). Photo courtesy of NASA.*

The baroreflex regulation, blood pressure, and venous tone, especially in the legs, are the principal cardiovascular reactions of interest for centrifugation studies. For a short-radius centrifuge small enough to accommodate a subject only in a squatting position, the centrifugation does little to encourage venous return by stimulating the muscles. However, tests in a ground centrifuge at the IBMP in Moscow (Shulzhenko *et al.* 1979) demonstrated that subjects who were deconditioned by 2 weeks of water immersion could increase their post-immersion tolerance to 3 g in the +Gz direction by intermittent exposure to acceleration on a 7-m-radius centrifuge.

It was debated for quite some time as to whether intermittent centrifugation conditioned only the passive motor tone or whether the body's active baroreflex, that counters the effects of gravity on blood pressure, was also affected. Burton and Meeker (1992) use a 1.5-m-radius centrifuge intermittently to show that the baroreceptors are adequately stimulated by the centrifugal force. Their slow compensation for the hydrostatic pressure drop during rotation permits the tolerance to gradual onset acceleration to exceed that to rapid onset acceleration.

Beyond the benefits derived from intermittent acceleration on cardiovascular responses, positive effects on blood volume are also seen. Normally, weightlessness or head-down bed rest produces a fluid shift toward the head that in turn leads to fluid loss, including plasma, and a resulting increase in hematocrit. However, Yajima and his colleagues from Nihon University School of Medicine in Tokyo (Yajima *et al.* 2000) showed that exposures of their subjects to one hour per day of 2 g in the +Gz direction, using a 1.8-m-radius centrifuge, was sufficient to prevent hematocrit from increasing during a 4-day bed rest period. In other studies, they confirmed the effectiveness of intermittent centrifugation on maintaining baroreflex and parasympathetic activity (Iwasaki *et al.* 1998). To prevent motion sickness, the Nihon investigators stabilized the subjects' heads during these centrifuge runs.

The interaction between the cardiovascular fitness enhancement of regular exercise and the tolerance built up during centrifugation has also been studied. For example, Katayama *et al.* (2004) showed that cardiovascular fitness could be protected by intermittent artificial gravity exposure in individuals exposed to 20 days of head down bed rest. More ground-based studies evaluating the efficacy and acceptability of human horizontal centrifugation on long-duration cardiovascular deconditioning are detailed in the following chapter. There is, however, a lack of studies on the cardiovascular implications of gravity gradient.

3.3 Human Powered Centrifuge

Only recently have several research groups begun to explore the potential benefits of artificial gravity generated by a human powered centrifuge. With respect to skeletal muscle, data suggest that muscles must be mechanically loaded to maintain or increase muscle mass. Similarly, mechanical loading (e.g., microstrain) of bone is essential for maintaining or increasing bone density (see Clément 2005 for review). Given these perspectives, several authors suggest that passive centrifugation on a short-radius centrifuge will not be effective in maintaining skeletal muscle mass and bone density during long exposures to microgravity. Hence, as a complement for passive centrifugation, they have pursued the development of active centrifugation, where the subjects exercise while being centrifuged, as potential multipurpose countermeasures to microgravity. This system has the capacity for studying the effects of centrifugation on muscle mass, bone density, and orthostatic tolerance.

Currently, two general types of ground-based designs have been described in the literature. The first of these designs has been referred to as a *human powered centrifuge*. Both the NASA Ames Research Center and the

University of California Irvine groups have been actively pursuing research on this concept. The second approach has been described as a *Twin Bike System*, and was proposed by Di Prampero and his colleagues at the University of Udine, Italy (see Chapter 5, Section 7).

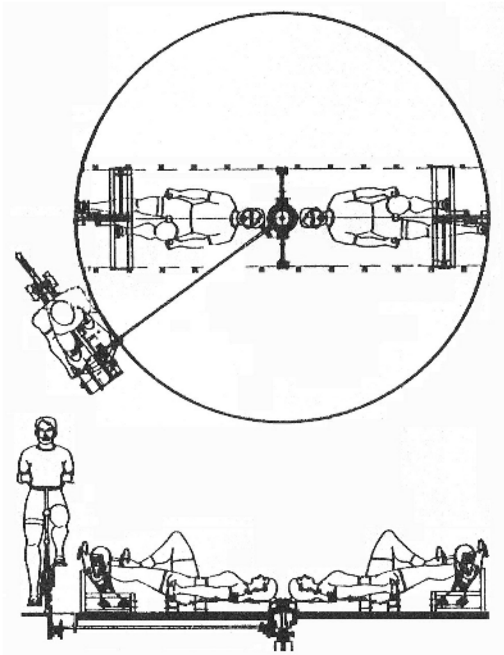

Figure 3-20. In the Human Powered Centrifuge *designed by NASA Ames Research Center, the motion of the platform can be powered by the two supine subjects on the centrifuge using a cycle mechanism or by an off-board operator using an upright off-centrifuge bicycle. Adapted from Greenleaf* et al. *(1996).*

The *Human Powered Centrifuge* developed by Greenleaf *et al.* (1996) is a 1.9-m-radius centrifuge fitted with two recumbent rider seats, and can carry one or two subjects in the seated supine position with their heads near the centrifuge hub. The configuration allows for one active on-board subject to power the centrifuge using a modified cycle mechanism (Figure 3-20). The cycling activity of the rider is coupled to the rotation of the platform and, hence, the development of various gravity levels along the Gz axis. An additional passive rider can be carried on the centrifuge at the same time. Alternatively, an off-board operator can power the centrifuge by using an upright off-centrifuge bicycle. Centrifugal force up to 5 g at the subject's feet (Gz) is obtained during rotation at 50 rpm.

Similarly, in the *Space Cycle* concept, developed by the Irvine Medical Center at the University of California, subjects ride opposite one another, one on a bike and one on a platform (Caiozzo *et al.* 2004). However, both the bike and the platform are free to tilt. As one individual pedals, the cycle moves in a circular motion around a central pole. The motion generates a gravito-inertial force aligned with the riders along their long body axis. The rider on the platform can perform various types of resistance training exercises, such as running on a treadmill or performing squats (Figure 3-21).

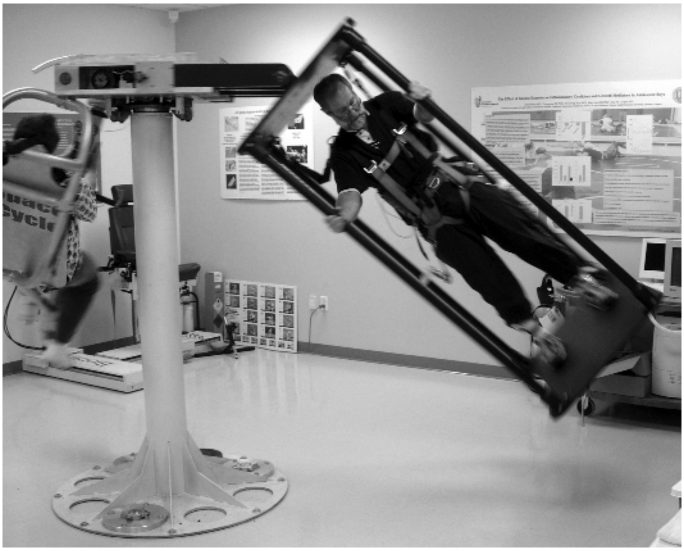

Figure 3-21. The Space Cycle *at the of the University of California Irvine Center generates artificial gravity levels ranging from 1 to 5 g on both the rider who powers the cycle and the rider who performs the squats or other types of exercise. The riders shown in this picture experience approximately 3 g. Photo courtesy of NASA.*

The *Twin Bike System* proposed by Antonutto and Di Prampero (1994, 2000) envisions two bicycles mechanically coupled to one another in a counter-rotating fashion. Astronauts would ride the bicycles along the inner wall of a cylindrically shaped space module (see Figure 5-06). The angular velocity of cycling would then determine the amplitude of the centrifugal vector along the main body axis of the rider. Like the human powered centrifuge designs developed by Greenleaf and Caiozzo, the *Twin Bike System* approach also has the potential for overcoming the deconditioning effects of microgravity on the musculo-skeletal and cardiovascular systems.

In the past few years, following the impetus given by the new Vision for Space Exploration program, dedicated centrifuges for investigating the effects on centrifugation on physiological deconditioning during bed rest studies have been developed at NASA (Figure 3-22) and ESA (Figure 3-23). Similar centrifuge designs are also being used in Russia and Japan (Table 3-01). The objective of these studies is to place test subjects in a 6-deg head-down bed-rest position for duration lasting up to 60 days, which simulates the long-term effects of weightlessness on the cardiovascular, muscle, and bone function. Typically, one group of test subjects is placed in the supine position on these ~3-m-radius centrifuges and subjected to various gravity levels and duration along their longitudinal axis throughout the bed rest to periodically simulate a +Gz gravitational environment. Another group of subjects is not exposed to centrifugation. After the bed rest, comparison between the deconditioning of both subject groups allows to determine the effectiveness of centrifugation as a countermeasure. These studies help to develop appropriate prescriptions for using a centrifuge to protect crews and to understand the side effects of artificial gravity.

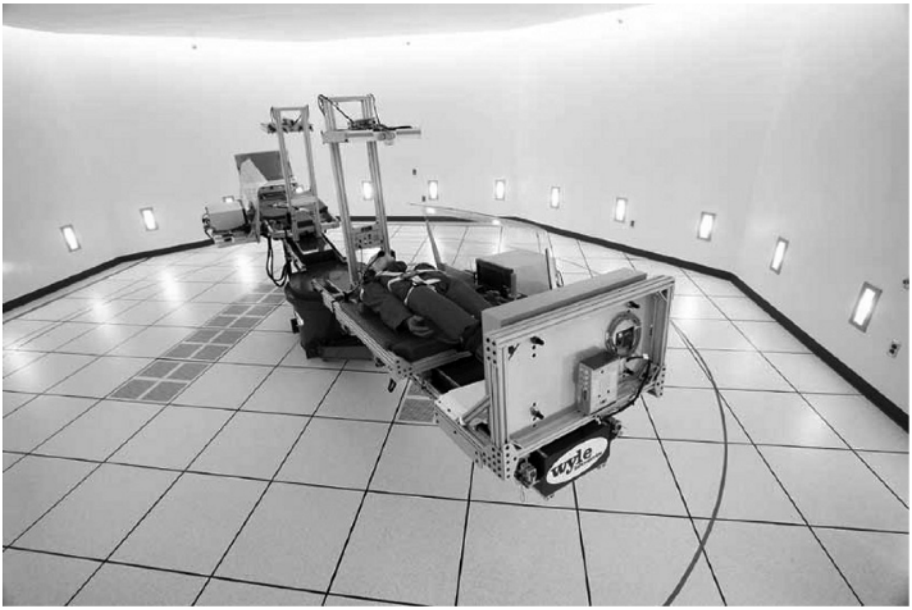

Figure 3-22. The NASA/Wyle Laboratories bed rest centrifuge at the University of Texas Medical Branch in Galveston, Texas, USA. During the on-going initial study, 32 test subjects are placed in a six-degree, head-down, bed rest position for 21 days to simulate the effects of microgravity on the body. Half that group spins once a day on the centrifuge to determine how much protection it provides from the bed rest deconditioning. Subjects are oriented radially in the supine position so that the centrifugal force is aligned with their long body axis, and while spinning, they "stand" on a force plate, supporting the centrifugal loading (2.5 g at the feet, 1.0 g at the heart). The subject station allows free translation over approximately 10 cm to ensure full loading of the lower extremities and to allow for anti-orthostatic muscle contractions. Control subjects are positioned on the centrifuge but do not spin. Photo courtesy of NASA.

Other types of human-rated centrifuges are also used worldwide in aeronautics or clinical environments for aircrew training or for physiological and medical research. Short-radius centrifuges, or rotators, are used in laboratory or in clinics for the investigation of the vestibular system in normal subjects and in patients (see Table 3-01). Large-radius human-rated centrifuges are used to simulate the acceleration stress encountered by pilots flying high-performance jets (see Figure 12-01). These centrifuges have usually a radius ranging from 6-12 m, and can generate a centripetal acceleration of up to 30 g at an onset rate ranging from 5-8 g/s, depending on the drive motor used. These centrifuges are primarily used to investigate the physiological effects experienced by a pilot exposed to a rapid onset, high-g environment and to investigate methods to provide the pilot protection thus maintaining his performance in this environment. Other uses include testing equipment designed to provide aircrew g-protection, medical evaluation of flight personnel, training aircrew for improving their tolerance to high-g environment, and acceleration physiology research.

Name	Location	Radius	Max g	Axes
Unilateral Centrifuge	*Antwerp U, B*	*0.4 m*	*0.2 g*	*±Gy*
Unilateral Centrifuge	*Charite Campus, Berlin, D*	*0.4 m*	*0.2 g*	*±Gy*
NASA JSC centrifuge	*NASA, Houston, USA*	*0.5 m*	*1.0 g*	*–Gz*
ESA Neurolab Off-Axis Rotator	*Antwerp U, B*	*1.0 m*	*1.0 g*	*±Gy, –Gz*
Short-Radius Centrifuge	*Mt Sinai School of Med, New York, USA*	*1.0 m*	*1.0 g*	*±Gx, ±Gy*
Human Centrifuge	*Brandeis U, Waltham, USA*	*1.2 m*	*3.0 g*	*±Gy*
Short-Arm Human Centrifuge	*Nihon U, Nishi-Funabashi, Japan*	*1.8 m*	*3.0 g*	*+Gz*
Artificial Gravity Sleeper	*MIT Cambridge, USA*	*2.0 m*	*1.8 g*	*+Gz*
Short-Radius Human Centrifuge	*Nagoya U, Japan*	*2.0 m*	*2.0 g*	*+Gz*
Short-Radius Centrifuge	*IBMP, Moscow, Russia*	*2.0 m*	*2.0 g*	*+Gz*
NASA Ames Human Powered Centrifuge	*Moffet Field, USA*	*2.0 m*	*5.0 g*	*+Gz*
Space Cycle	*UC Davis, USA*	*2.0 m*	*3.0 g*	*+Gz*
ESA Short-Arm Centrifuge	*MEDES, Toulouse F*	*2.9 m*	*3.5 g*	*+Gz*
Twin-Bike System	*University Udine, I*	*3.0 m*	*1.0 g*	*+Gz*
NASA Short-Arm Centrifuge	*UTMB, Galveston, USA*	*3.0 m*	*3.5 g*	*+Gz*
TNO Desdemona	*Soesterberg, NL*	*4.0 m*	*3.0 g*	*±Gx, ±Gy, ±Gz*
Slow Rotation Room	*Brandeis U, Waltham, USA*	*6.7 m*	*4.0 g*	*±Gx, ±Gy, ±Gz*
Slow Rotation Room	*NAMRL, Pensacola, USA*	*7.0 m*	*3.0 g*	*±Gx, ±Gy, ±Gz*

Table 3-01. Short-radius centrifuge facilities used worldwide in research projects on artificial gravity, with their radius, the maximum gravity level (usually at the subject's feet) and the direction in which this level is exerted. This list is not exhaustive.

4 SUMMARY

While many studies have suggested the production of artificial gravity through rotation to counteract the detrimental effects of weightlessness, knowledge of the ability for humans to live and work in a large scale rotating artificial gravity environment is limited. The few observations conducted on humans in space suggest that the sustained application of a centrifugal force above 0.3 g is perceived as artificial gravity by the crewmembers. However, in these instances, the artificial gravity exposure was limited to a few minutes and subjects were restrained from moving their head or body.

Research conducted in slow rotating rooms on Earth has concluded that humans can adapt and live for extended periods of time (up to 25 days) to rotation rate as high as 10 rpm. Adaptation to continuous rotation has also been achieved with shorter exposure duration and higher rotation rates (up to 23 rpm) by using short-radius centrifugation in which subjects are supine and only able to perform head movements.

Several human centrifuges, with either long- or short-radii and either passive or human powered capabilities, are currently being used to assess the sensory-motor, cardiovascular, and musculo-skeletal responses under hypergravity conditions. One practical objective of these studies is to determine the limits for centrifugation as an effective countermeasure. It is important to stress, however, that ground-based tests are made with the deficiencies associated with Earth-bound environment. In particular, there are notable differences between a centrifuge on Earth and in space. Both conditions generate a centrifugal force in the plane of rotation, but gravity is always present and perpendicular to the plane of rotation in the centrifuge on Earth, while the artificial gravity vector is in the plane of rotation in the centrifuge in space (see Figure 3-17). Head and body motion will yield a different pattern of stimulation on Earth and in space. Given these differences, it is clear that the *final* assessment of artificial gravity prescription by centrifugation can only be carried out in space.

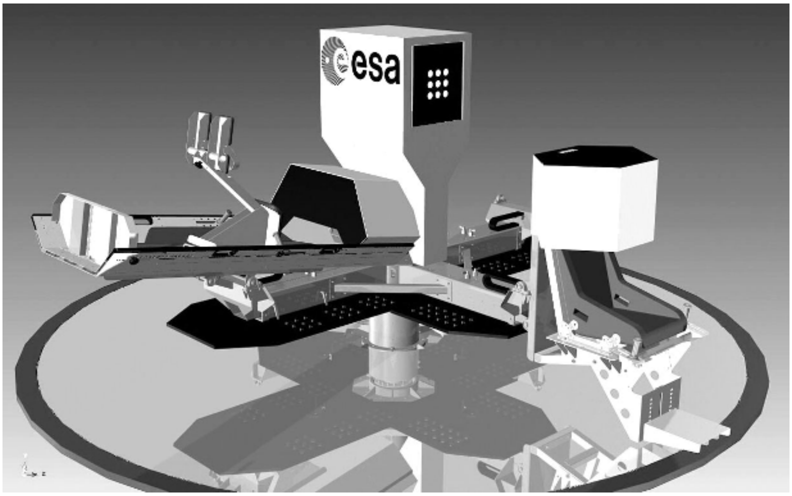

Figure 3-23. The ESA bed rest centrifuge. The centrifuge has two arms with a radius of 2.9 m each. The centrifuge can accommodate one subject on each arm. The arms can be equipped with supine beds or recumbent seats. The seats allow placing the subjects in a semi-flexed position, a less cumbersome and a more natural position in weightlessness. Photo courtesy of ESA & Verhaert Space, Kruibeke, Belgium.

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Chapter 4

PHYSIOLOGICAL TARGETS OF ARTIFICIAL GRAVITY: THE SENSORY-MOTOR SYSTEM

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This chapter describes the pros and cons of artificial gravity applications in relation to human sensory-motor functioning in space. Spaceflight creates a challenge for sensory-motor functions that depend on gravity, which include postural balance, locomotion, eye-hand coordination, and spatial orientation. The sensory systems, and in particular the vestibular system, must adapt to weightlessness on entering orbit, and again to normal gravity upon return to Earth. During this period of adaptation, which persists beyond the actual gravity-level transition itself the sensory-motor systems are disturbed. Although artificial gravity may prove to be beneficial for the musculo-skeletal and cardiovascular systems, it may well have negative side effects for the neurovestibular system, such as spatial disorientation, malcoordination, and nausea.

Figure 4-01. Astronauts during extra-vehicular activities have experienced acrophobia, or "fear of height", in which vision and vestibular cues clearly play a major role. Photo courtesy of NASA.

1 STRUCTURE AND FUNCTION OF THE SENSORY-MOTOR SYSTEM

The human *sensory-motor system* allows us to ascertain the status of our body, sense our environment, make relevant adjustments in relation to this environment, or move around in our environment to achieve various goals. The *sensory* part, relying on our body's numerous physiological sensors, detects the motion or position of body parts relative to each other, our spatial awareness, or to the environment, our spatial orientation. The *motor* part refers to our movement within and relative to our environment. Sensing and moving around in the environment cannot be regarded as separate entities: any movement will stimulate the sensors, and immediately alter their afferent information to the *central nervous system* (CNS). For example, a rapid head movement is sensed by the vestibular organs, which in turn signal to the extraocular muscles to generate a compensatory eye movement. If this were not the case, blurred vision would occur. In addition to eye-head coordination, the vestibular system is involved in various other human sensory-motor functions, including maintenance of posture, gait stabilization, general coordination of limb movement, and spatial orientation.

As is the case for all species we have evolved a sensory apparatus that is optimally matched to our natural behavioral repertoire under terrestrial gravity conditions. Thus we achieve upright bipedal posture, maintain attention to the world around us, and move within our habitat.

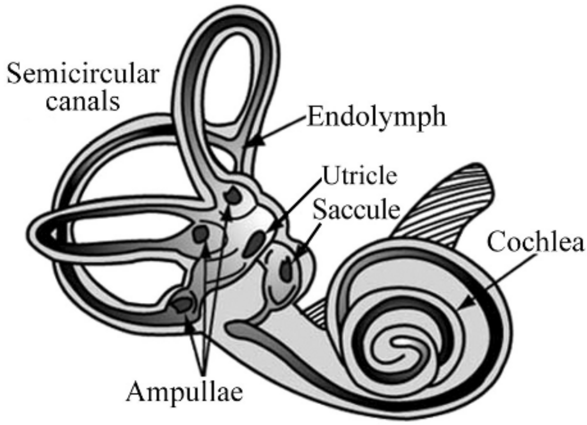

Figure 4-02. The labyrinth or vestibular apparatus is the organ of balance. Located in the inner ear, it consists of three semicircular canals and the otolith organs (utricle and saccule).

The afferent signals from the vestibular organs converge in the *central vestibular system* situated in the brainstem, and are integrated with visual inputs from the peripheral retina and proprioceptive and tactile inputs from skin, muscles, and joints. This convergence allows sensory integration that is essential for maintaining balance and spatial orientation. Resultant motor outputs primarily contribute to the regulation of our eye movements to ensure gaze stabilization and to the anti-gravity muscle apparatus that keeps us upright. Signals from the vestibular system are also transmitted to the cerebellum and to higher centers in the thalamus, hippocampus, and cortex, which are involved in subjective perception of motion and spatial orientation. This perception involves synthesis and assignment of some meaning to sensory input, taking into account our expectations in the behavioral context, and our prior experience and culture. These areas are also involved in related processes, including learning, adaptation, and habituation.

The vestibular organs in the inner ear comprise the *semicircular canals*, which transduce rotation, and the *otolith organs*, which transduce linear translation of the head and head tilt relative to gravity (Figure 4-02). To maintain clear vision during head movement, the afferent signals from the semicircular canals drive the extraocular muscles via a three-neuron arc, the so-called *vestibulo-ocular reflex (VOR*), to facilitate compensatory eye movements, With a transmission time of approximately 10 ms, this represents perhaps the fastest reflex in the human body.

In contrast to the semicircular canals, which respond to angular acceleration of the head, the otolith organs sense linear accelerations of the head. Each of the otolith organs, the utricle and the saccule, possesses a sensory epithelium populated by several thousand hair cells whose sensory hairs, or *cilia*, project into a gelatinous membrane. Embedded in this membrane are a multitude of densely packed, small crystals of calcium carbonate, the *otoconia* (Figure 4-03). The otoconial mass, which has a specific density 2.7 times greater than the surrounding endolymph, functions as an inertial mass that is displaced proportionally to the linear acceleration of the head during any movement. In turn, the movement of the otoconial membrane shears the cilia of the hair cells. It follows that during any constant velocity translation the otolith afferences do not signal movement. The otolith afferences, however, continuously monitor the gravito-inertial force generated by head tilt relative to gravity.

Each hair cell possesses a preferred polarization direction in which it responds maximally. The cell population is distributed across the maculae of the utricle and saccule, so as to encompass head accelerations in any direction. While the utricles are orientated approximately in the horizontal plane, and the saccules in the vertical planes of the head, i.e., each covering the corresponding two dimensions of movement, the macular form is by no means planar, a feature which introduces redundancy and ensures omnidirectional sensing of linear acceleration.

A major role of the otolith organs is to provide information about head orientation to gravity. If the head and body begin to tilt, the vestibular nuclei in the brainstem will automatically relay the information from the otolith organs via the vestibulo-spinal pathways to activate the muscles necessary to correct our posture. In such a situation, the interpretation of otolith signals involves the problem of distinguishing between *tilt* relative to gravity, which is equivalent to a constant linear acceleration, and linear acceleration due to *translation.* The general explanation is that, over the course of ontogenesis, the CNS learns to understand that gravity is constant in direction and magnitude, whereas linear accelerations caused by locomotion are usually variable. With this knowledge, the CNS is able to separate out gravity as the low-frequency component. The remaining high-frequency component of the sensed accelerations can subsequently be ascribed to self-motion. Although this scheme has been successfully described by various mathematical models (Merfeld *et al.* 1993, Bos and Bles 2002), the neural mechanisms underlying this separation are not yet fully understood.

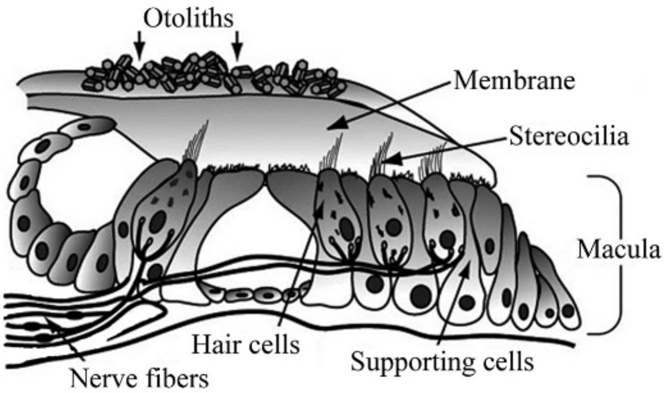

Figure 4-03. Otoliths are small particles of calcium carbonate in the gel-like membrane layer situated over the sensory hairs (cilia) of the utricles and saccules. When the head moves or is tilted relative to gravity, the inertia of this layer causes it to exert a shear force on the cilia, which in turn stimulates the hair cells. The hair cells signal the corresponding information via the nerve fibers to the central nervous system, where the sensation of motion or tilt results.

Besides its involvement in reflex behavior the vestibular system also plays a role in spatial cognition and navigation, i.e., the knowledge of directional heading and location in the environment. Furthermore, recent research has demonstrated that information from the vestibular system also influences heart rate, blood pressure, immune responses, circadian rhythms, and arousal (see Chapter 8). Accordingly, any dysfunction of the vestibular system can potentially induce a number of symptoms including spatial disorientation, postural instability and vertigo, often accompanied by vegetative symptoms such as nausea. It can also involve psychogenic anxiety or panic attacks (Highstein *et al.* 2004).

Astronauts very often experience such sensations of dizziness and disorientation during their first few days in weightlessness. Furthermore, upon returning to Earth after spaceflight, they frequently have difficulty maintaining stable stance and gait, e.g., walking or turning corners in a coordinated manner, and stabilizing their gaze, and (see Clément and Reschke 1996 for review). Their sense of balance and spatial orientation require a period of re-adaptation to terrestrial one-g conditions.

In this respect, their behavior is comparable to that of patients with vestibular disorders, i.e., a pathological condition. In the acute stage of disease, such patients suffer from vertigo and disorientation. In many cases the patients will adapt over a period of several days and vertigo will decrease. Depending on the original cause of the disease, responses may return to normal, or a continuous handicap might remain. Thus, the examination of the adaptive behavior of the healthy vestibular system to altered gravito-inertial conditions has provided, and should continue to provide, basic knowledge that is relevant to the clinical situation.

Numerous experiments have demonstrated that the function of the semicircular canals is largely unaltered in prolonged microgravity. Those aspects that are altered are understood to involve the interaction with the input signals from the otolith organs (Clarke *et al.* 2000). Surprisingly, only small disturbances in the control of posture and limb or body movements were observed during spaceflight (see Lackner and DiZio 2000 for review). Given that only few individuals have spent more than six months in space (see Figure 1-10), which corresponds to the current predicted duration of a one-way trip to Mars (see Figure 1-03), there is no conclusive evidence to indicate that prolonged exposure to weightlessness might produce changes to the vestibular system that cannot be reversed. However, we need to refine our diagnostic tools and techniques to examine and even detect those changes that occur over the course of in-flight and postflight adaptation.

There is a limited amount of data on very young rats indicating that the otoconia are irregular in size and distribution following extended periods of weightlessness. These animal studies also suggest plastic CNS reorganizations of motor units and their response characteristics, and of cortical maps during spaceflight (Ross *et al.* 1992, 1993, 1994). It would be very adventurous to transfer these observations to the human species. Until long-duration studies are conducted using higher primates in microgravity, the hypothesis of such changes occurring in humans during spaceflight remains speculative.

2 SPATIAL ORIENTATION

Our natural behavior includes sitting, standing, walking, or running, where we are continuously re-orienting ourselves with respect to gravity. Via the vestibulo-spinal reflex mechanisms, the CNS detects such changes in body orientation and initiates the necessary compensatory muscle activity to maintain posture. The brainstem centers involved in this process operate primarily at the reflex level. This process involves integration of information from all contributing sensors: the eyes, the vestibular organs, and the proprioceptive sensors distributed throughout the body. Whereas information from the vestibular and proprioceptive sensors is coded in internal head and body coordinates, the visual system provides information about our motion and orientation relative to the environment. Hence, visual information is used to match, or "calibrate" the internal with the external frames of reference, i.e., the egocentric information with the exocentric, or external world. At the basic reflex level this calibration is illustrated by the coordination between vestibular and optokinetic reflexes.

2.1 Visual Orientation

The terrestrial environment is rich in horizontally and vertically oriented visual cues (e.g., floors, ceilings walls, buildings, trees). Such horizontal and vertical contours together define a visual frame. The world around us is also polarized, defining perceptual "up" and "down". Visual polarity may be surmised from objects with recognisable "tops" and "bottoms", such as people and trees. Other, more indirect cues reveal the direction of gravity: objects are perceived as lying on the floor, or hanging from a ceiling. Visual frame and polarity together offer a reference frame that strongly influences our sense of orientation (Asch and Witkin 1948, Howard and Childerson 1994). Because we are bound to the Earth, we normally see the environment from a limited range of perspectives. For example, we enter a room through the door in an upright stance, and view the interior from normal eye level.

Accordingly, during their ground-based training, astronauts always view the interior of the spacecraft mock-up from this same perspective. Yet, in space they can assume any body orientation, and view the spacecraft from unfamiliar perspectives (Figure 4-01). This frequently results in strong visual orientation illusions, especially during the early phase of spaceflight (Oman *et al.* 1986, 1988). Such subjective re-orientations may be sudden, and can be triggered by watching a crewmember floating in an inverted position. This view may instantly produce a sensation of being upside-down, a sensation which can be highly nauseating due to the missing vestibular cues for the orientation change.

Visual orientation illusions are aggravated by the complex and inherently ambiguous interior configurations of spacecraft such as the ISS and Mir (Figure 4-04). This has caused significant incidences of spatial disorientation, reference frame issues, and navigation problems among the astronauts and cosmonauts (Young 2000). When Shuttle crewmembers visited the Mir space station, they often became disoriented or lost. This was due to the size and the labyrinth-like nature of the station, and self-rotation of the astronauts producing unexpected visual orientation when floating from one module to another. In fact, the Mir crew's response to the collision with the

Progress spacecraft in 1997 was hampered by the fact that they were experiencing cognitive reference frame problems (Linenger 2001). There are also numerous anecdotal reports of operational errors associated with disorientation during ISS crew debriefings. In particular, multiple frames of reference and visual reorientation illusions have caused numerous robotic tele-operation problems for the crew (Young 2000).

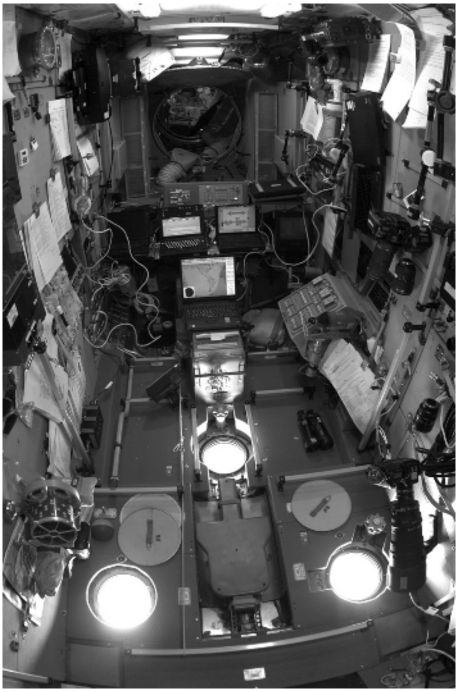

Figure 4-04. Photograph of the interior of the Russian module of the ISS, showing the lack of clear orientation cues. The standard facilities, computers, and spreadsheets are all oriented uniformly. However, the lighting comes from light sources and windows located on both the "floor" and the "ceiling" of the module. Photo courtesy of NASA.

Countermeasures directed at spatial orientation problems, as well as training techniques, are clearly required. One promising approach is the use of virtual reality, which offers the possibility to present the spacecraft interior from unusual visual perspectives. It is argued that this facilitates the development of improved spatial memory for the situation (Lackner 1992, Lackner and DiZio 1998a). However, current virtual reality imagery is not powerful enough to override vestibular gravity information and reproduce those visual illusions that occur in flight. It has been demonstrated, for example, that placing the test subject in a supine position, where the vestibular reference to gravity is indifferent with respect to the visually presented orientation, enhances the effectiveness of virtual reality. In this situation, subjects experience compelling re-orientation illusions, including a sensation of weightlessness, when watching a visually tilted scene (Howard *et al.* 1997, Howard and Hu 2001, Groen *et al.* 2002). The effectiveness of these methods for familiarization with weightless conditions has not yet been fully explored.

Other mitigating approaches would include evidence-based human factors standards applied to spacecraft architecture and interior configuration as well as signs directing the occupants to exits (Marquez *et al.* 2004). More research is required to understand the extra-vehicular activities and tele-operational issues. Astronauts operating the robotic arm on board the Shuttle have indicated that it is difficult to relate the three-dimensional information that is concurrently presented to them in several reference frames. Crewmembers from both Mir and the ISS have reported height vertigo (acrophobia) when the Earth appears lower in their field of view, which has proven temporarily disabling for some[14]. There is also concern over the lack of visual reference cues for ISS astronauts performing extra-vehicular activity operations while the space station is passing through the dark portion of its orbit (Oman *et al.* 1988).

2.2 Sensory Reinterpretation

Apart from these visual inconsistencies, spatial orientation during the flight is further challenged by weightlessness itself. For example, after a couple of angular displacements, free-floating, blindfolded astronauts on the ISS are completely guessing as to what is "up" and "down" (Clément *et al.* 1987, Glasauer and Mittelstaedt 1998, van Erp and van Veen 2006). Without the pull of gravity, the usual contact forces and tactile cues between the body and the supporting surface are absent. Body fluid and internal organs shift toward the head, resembling a prone or supine body orientation (Vernikos 1996). The otolith organs no longer have to detect linear orientations against the prevailing 1-g bias. Deprived of the natural 1-g reference for the definition of head upright, the concept of head tilt becomes meaningless. On the other hand, the semicircular canals continue to code head rotations correctly. Consequently, the normal multi-sensory synergism, above all between gravity sensing and rotation, is no longer operative during head and body movement. Adaptive modification of the related sensory integration in the CNS, or *sensory reinterpretation*, is required to cope with the altered configuration. It can be surmised that visual information becomes more heavily weighted during this process, as evidenced by the increased effectiveness of moving visual scenes to induce sensations of self-motion, or *vection* (Young *et al.* 1986). On Earth, upright observers experience illusions of self-tilt when viewing visual patterns that rotate about a horizontal roll axis (Held *et al.*

[14] While many astronauts say they've been wowed by the experience of an EVA (extra-vehicular activity, or spacewalk), a few, such as American Jerry Linenger, have confessed to terrible feelings of disorientation. In his memoir, "Off the Planet" (Mcgraw-Hill, 2001) Linenger described a "dreadful and persistent sensation" of falling. "White-knuckled, I gripped the handrail on the end of the pole, holding on for dear life."

1975). However, the effect is limited due to the missing otolith stimulation that would normally accompany the visual tilt. Without the one-g stimulation of the otolith organs, moving visual scenes produce larger effects with shorter latency (Young and Shelhamer 1990).

Another element of sensory rearrangement is that the CNS must consider any otolith input in weightlessness as translation of the head rather than tilt. Given that this so-called *tilt-translation reinterpretation* occurs in space, it would follow that a misinterpretation should arise after return to 1-g conditions on Earth. Earlier findings indicated that dynamic body tilt is underestimated postflight, and could even lead to strong sensations of translation (Parker *et al.* 1985). Astronauts report the sensation of being accelerated sideways or forward/backward when they tilt their head in pitch or in roll, respectively, during re-entry and immediately after landing. In general, prolonged exposure to weightlessness affects the sensitivity to linear accelerations, and increases the variability in the detection of accelerations (Young *et al.* 1986, Merfeld *et al.* 1994). This is certainly a contributing factor to the increased postural imbalance and gaze instability observed postflight (Kenyon and Young 1986, Paloski *et al.* 1993).

2.3 Perception of the "Vertical"

Remarkably, weightlessness does not induce a continuous sensation of falling. Nor does the absence of the gravitational vertical completely take away a sense of "upright". Astronauts basically perceive some orientation, which is largely determined by the remaining cues for vertical. As mentioned above, the visual environment strongly influences spatial orientation in space. In addition, astronauts often report a tendency to perceive the surface below their feet as "floor", and the surface above their head as "ceiling", irrespective their actual orientation in the spacecraft. This observation indicates that the main body axis also provides a subjective reference for vertical (Mittelstaedt 1983). Hence, subjective orientation in space results from a weighted sum of the visual vertical and an internal body vertical. Astronauts show differences in the relative weighing between both reference frames, as reflected in individual styles of orientation (Harm and Parker 1993). Moreover, studies in parabolic flight have shown that subjective orientation in microgravity can be modified by visual and tactile cues, cognitive factors, and even by gaze shifts (Lackner and Graybiel 1983, Lackner 1992, Lackner and DiZio 1993). Apparently, the relative contribution of different reference frames is not rigid, but depends on the situation.

An interesting question regarding the issue of spatial orientation is whether artificial gravity can be used to retain some "memory" of gravity. This may preserve basic orientation reflexes that support postural balance after landing on Earth or another planet. Spatially oriented oculomotor and sympathetic functions would also benefit from such approach (see this

Chapter, Sections 4 and Chapter 8, Section 2, respectively). To be effective, the artificial gravity stimulus should essentially be perceived as vertical reference, and hence produce tilt responses. Data from the IML-1 Spacelab mission showed that sustained linear acceleration with a gravity gradient ranging from –0.22 g at the head to +0.36 g at the feet (Gz) did not result in sensations of tilt (Benson *et al.* 1997). According to experiments with a short-radius centrifuge on Neurolab, centrifugation at 0.5 g along the Gy or Gz axes did produce considerable tilt sensations of, respectively, lying on a side, and hanging upside-down (Clément *et al.* 2001). Thus we may conclude that the threshold for the perception of the gravitational vertical lies somewhere in between 0.22 g and 0.5 g. Further research should focus on the exact threshold value, and also look into related questions, such as how to orient the astronaut on the short-radius centrifuge and where to place the rotation axis. In order to achieve otolith stimulation, it would be preferable to place the head substantially off-center. Based on the observed variation in visual-vestibular weighting, it can be assumed that the threshold for perceived vertical is also individually determined. Consequently, individual tailoring of the artificial gravity stimulus should be considered.

2.4 Spatial Disorientation during Piloting

Special attention should be paid to the commander who controls the spacecraft during docking or landing phases. It is well known that the human sensory apparatus is principally not suitable to adequately monitor aircraft motions. This creates the risk of spatial disorientation in pilots, which can be described as a false sensation of aircraft motion or attitude with respect to the earth. Spatial disorientation is a common human factor in aviation accidents, such as those designated “controlled-flight-into-terrain” (see Benson 1988, Previc and Ercoline 2004 for review). There is evidence that adaptation to weightlessness makes the commander more prone to spatial disorientation upon re-entry. Flight errors in Space Shuttle landings, including height over threshold, distance, and airspeed, were found to correlate with the intensity of postflight neurological symptoms (McCluskey *et al.* 2001). Shuttle pilots recognize the risk that head movements are disorienting, but vehicle accelerations may still lead to vertigo or eye movements (nystagmus) that interfere with instrument readings. In a centrifuge study, pilots refused to fly a real aircraft after exposure to 3 g in the Gx direction for 1.5 hours (Bles *et al.* 1997).

Clearly, countermeasures should specifically address spatial disorientation problems during phases of piloting the spacecraft. In this respect, there is an interesting development in the field of ground-based spatial disorientation devices. One of such devices features an instrumented cockpit on a six degrees-of-freedom motion-base that can also be centrifuged (Figure 4-05). This facility allows for ground-based studies of the relation between vestibular adaptation to increased gravity levels and the pilots' control behavior in flight maneuvers that induce spatial disorientation. This approach may be used to train pilots in how to deal with spatial disorientation illusions, and adopt strategies to maintain adequate control of the aircraft despite distracting vestibular sensations. Other systems relate to the use of tactile information to give additional orientation cues to pilots and astronauts (Rupert 2000, Van Erp and Van Veen 2006). In addition, new medications may be tested that suppress vestibular hyper-reactivity as a facilitating factor for spatial disorientation.

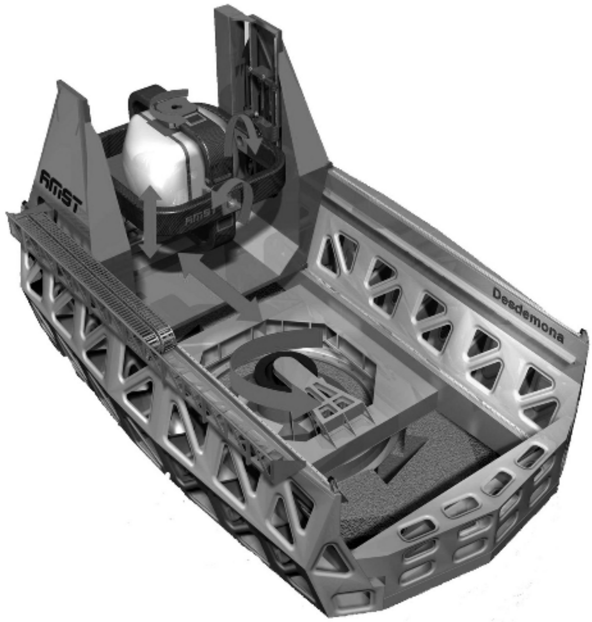

Figure 4-05. Desdemona is a sophisticated demonstration, simulation, training, and research facility specified by TNO Human Factors and developed by AMST Systemtechnik in The Netherlands. The subject is sitting in a fully gimbaled cockpit with four cascaded degrees of freedom (360 deg of yaw, pitch and roll rotation, and 2m heave), placed on a longitudinal track (8 m) that is rotated around the vertical axis, adding two synergistic degrees of freedom. Rotation of the track allows centrifugation up to 3 g. Photo courtesy of TNO.

3 MOTION SICKNESS

In association with the above-mentioned motion and orientation illusions, more than 50% of space travelers also experience symptoms of motion sickness during the first two to three days in space. Because of the similarity with other forms of motion sickness, it has been designated *space motion sickness*, or *space sickness* (Benson 1977). The cardinal symptoms of motion sickness are stomach discomfort, nausea, and vomiting (Reason and Brand 1975). Other signs include dizziness, increased perspiration, pallor, hyperventilation, decreased appetite, increased salivation, vague discomfort (malaise), fatigue (Sopite syndrome), and depression. Individual responses to the same situation are quite variable. From our comprehensive knowledge with seafarers, we know that in severe situation, however, even the most seasoned sailor will get seasick.

Motion sickness arises in conditions of simulated motion, called simulator sickness, and passive exposure to actual motion, e.g., carsickness, airsickness, and seasickness. It may also occur in the absence of real motion, for example when watching moving visual scenes in a cinema, a condition dubbed cinerama sickness, or computer games, which of course is referred to as cyber sickness. In addition, motion sickness occurs in situations where the normal regularities between self-motion and sensory feedback are disturbed, such as when looking through left-right reversing prisms.

3.1 Sensory Conflict Model

The vestibular organs play an essential role in the etiology, because people lacking vestibular functioning do not get motion sick. As a general rule, the onset of motion sickness is triggered by situations where the normal relationship between body movement and accompanying sensory feedback deviates from what the brain would predict based on previous experience. This is the essence of the widely accepted *sensory conflict model*, according to which motion sickness arises as a result of a conflict between sensory inputs about self-motion, and expected sensations (Reason 1978). Illustrative is the observation that carsickness rarely occurs in the driver, but rather the passenger, who is less likely to anticipate the accelerations and turns of the car, especially when there is no view on the road ahead (Griffin and Newman 2004). The driver, however, controls the car motion, and is therefore able to anticipate the sensory feedback. Interestingly, drivers do suffer from simulator sickness when driving in a fixed-base simulator that does not reproduce the corresponding motion feedback. In this case, the sensed motion differs from what the driver anticipates based on his experience in the actual vehicle.

Space motion sickness is often elicited by active head movements in space, in particular pitch and roll (Oman *et al.* 1986). This fits in with the sensory conflict model, because without the 1-g bias the otolith response to head tilt differs radically from the usual response in a 1-g environment. It thus makes sense that roll and pitch movements are more provocative than yaw movements, because the former two would normally involve concomitant otolith stimulation due to the change in head orientation relative to gravity. After several days in weightlessness, head movements are no longer provocative because the CNS has adapted, or recalibrated the vestibular response to account for the absence of gravity. Upon return to Earth, however, astronauts often develop transient motion sickness, much like the *mal de débarquement* experienced by sea travelers on going ashore. Such passengers may have a persistent sensation of motion after return to the stable environment, accompanied by symptoms similar to those of seasickness. This again points out the essential role played by CNS adaptation to altered sensory environments. Thus motion sickness, including space motion sickness, can be considered an "adaptation problem", i.e., it remains until the vestibular system recalibrates to the new motion environment.

3.2 Centrifuge Induced Sickness

Although the symptoms of space sickness closely resemble those of terrestrial motion sickness, it is remarkable that the commonly used acute motion sickness tests, including cross-coupled Coriolis stimulation and parabolic flight, show no correlation with in-flight incidence (von Baumgarten 1986, Oman *et al.* 1986). Apparently, these short-term tests do not trigger the same causal mechanism that is involved in transitions from 1 g to 0 g. However, there is some indication that space motion sickness can be simulated on Earth by means of prolonged exposure to hypergravity in a human centrifuge. Although the one-hour centrifuge run producing a constant gravity level of 3 g in the +Gx direction was not experienced as uncomfortable, head movements were found to provoke nausea and motion illusions for several hours afterwards. Symptoms of this *centrifuge-induced sickness* (SIC) were rated the same rank-order as during the flight (Ockels *et al.* 1990, Albery and Martin 1994, Bles *et al.* 1997). Furthermore, after the SIC centrifuge run, postural instability was observed similar to the effects observed in astronauts during the first days postflight (Bles and Van Raaij 1988, Bles and de Graaf 1993).

After the SIC centrifuge run, visual motion illusions and motion sickness symptoms are induced by head movements. Similar to in-flight experiences, the intensity of the effects depends on the orientation of the head rotation axis: moving the head out of the vertical, that is, pitch and roll movements, is more provocative than moving the head about an Earth-vertical (yaw) axis (Bles and de Graaf 1993, Groen 1997, Nooij *et al.* 2004). Furthermore, the effects are more pronounced with the eyes open than with the eyes closed, which also agrees with in-flight reports (Oman *et al.* 1986).

Based on these observations, a refined version of the sensory conflict theory was proposed stating that motion sickness does not arise from any sensory conflict, but only when the conflict concerns the internal representation of the vertical, i.e., the *subjective vertical*. In this sense, the subjective vertical is determined by integration of sensory afferent information from the visual, the vestibular, and the somatosensory systems on the one hand, and efferent information on planned body movements. The subjective vertical theory for motion sickness has been implemented in a mathematical model based on the control of postural balance (Oman 1982, Bles *et al.* 1998, Bos and Bles 2002). The relation with postural balance is understandable because it obviously also requires accurate information of body orientation relative to gravity. The subjective vertical model contains an "internal model" that generates the individual's expectation of sensory feedback on self-motion and orientation. Current research into the "g-adaptation parameter" in the internal model is in on going.

The apparent success of the SIC centrifugation paradigm in mimicking space motion sickness makes it suitable to test individual susceptibility of astronauts. It may also be useful for preflight training. It is assumed that it is the gravity-level *transition*, rather than the microgravity environment itself, which causes problems. The idea is that the otolith organs and other, non-vestibular, graviceptors are adapted to the prevailing gravity level. Transition to another gravitational environment, being from 1 g to 0 g or from 3 g to 1 g, brings the system in a mal-adapted state. Until new adaptation is established the orienting responses are inaccurate, and motion sickness may occur. Thus, although microgravity may be unique for the lack of any gravitational reference for vertical, it has in common with other gravity levels that sensory-motor functions become temporarily disrupted due to the transition to a new gravity level. This might also account for the problems during return to Earth gravity. There is some indication that, due to the complete loss of the all-permeating gravity vector, microgravity represents a qualitatively different state for the sensory motor, and in fact for all physiological systems.

The issue of gravity-level transitions should be considered an important factor in developing intermittent artificial gravity programs, where astronauts will repeatedly experience gravity-level transitions. An optimal artificial gravity stimulus should therefore retain a memory of gravity, without inducing sickness every time they enter or leave the artificial gravity device. Research should determine the acceptable gravity-level "dose", which is defined by the combination of gravity level and duration of the artificial gravity stimulus. With the centrifuge paradigm being the only known ground-based test that seems to predict the astronauts' susceptibility to space motion sickness, it offers a tool to investigate such gravity dose value. In a recent ground-based study, a first attempt was made to this effect (Nooij and Bos 2006). This showed that 90 min of centrifugation at 2 g hardly caused any problems afterwards, whereas 45 min at 3 g did provoke space motion sickness symptoms afterwards. Clearly, in-flight artificial gravity levels will be lower than 3 g, but there the transitions are from a baseline level of 0 g. This reduces the signal-to-noise ratio, so that problems may already occur at smaller transitions. This also opens the possibility to study the effect of specific medication against space motion sickness.

3.3 Coriolis Induced Sickness

The most disturbing aspect of centrifugation is probably the cross-coupled angular acceleration detected by the semicircular canals of the vestibular system. As stated above, the function of the canals is to detect angular velocity of the head relative to inertial space for most normal head movements. However, because of their mechanical structure, they fail to register long-lasting constant velocity motion and, instead, indicate that one is stationary in a turn that lasts more than 10-20 s.

When centrifuged subjects move their heads about an axis that is not parallel to the spin axis, two unexpected angular accelerations occur. First, during the head movement a *Coriolis force* occurs, equal to the product of the spin rate and the head velocity that produces transient acceleration about a third orthogonal axis. Second, when the head is turned, the spin angular velocity is moved from one head plane to another, producing a sensation of deceleration about the first axis and acceleration about the second one, the so-called *cross-coupled angular acceleration*. Following this complex stimulation, a sensation of rotation with components around both axes usually occurs for up to 10 s, as the cupulae in the semicircular canals return to their neutral position. This unexpected and confusing sensation is generally accompanied by motion sickness symptoms, a condition often referred to as *Coriolis induced sickness*. However, it is mostly the cross-coupled angular acceleration that is responsible for the confusing sensation and motion sickness. The directions of both the Coriolis force and the cross-coupled angular acceleration depend on the direction the subject is facing in the rotating device, as well as the direction of head movement (see Chapter 2, Section 2.3), thereby complicating the process of general adaptation to the unusual environment.

Notably, the provocative nature of gravity-level transitions, as observed with the SIC paradigm, is essentially different from Coriolis stimulation that happens when making voluntary head movements out of the plane of rotation. Coriolis stimulation causes immediate problems *during* centrifugation, whereas the associated change in gravity level causes problems *after* centrifugation. Remarkably, most research related to artificial gravity has centered on the Coriolis-type of motion sickness, especially in relation to short-radius centrifuges that require high rotation speeds to produce a substantial gravity level (Brown *et al.* 2003, Mast *et al.* 2003, Young *et al.* 2003). Theoretically, Coriolis sickness should not be a problem if the astronauts keep their head still during centrifugation, such as in an artificial gravity sleeper (Lackner and Dizio 2000). However, it is foreseen that the crew activity schedule requires the astronauts to combine their artificial gravity training with other forms of fitness. In addition, it is questionable whether an artificial gravity sleeper would be effective in retaining sensory-motor functions with the astronaut being asleep.

So, most likely, astronauts will have to perform activities during in-flight artificial gravity training. If this is done in short-radius centrifuges, they will have to adapt to high-speed rotations. It has been shown that exposure to a slowly rotating environment, produced by a ground-based rotating room, causes motion sickness for some period of time before adaptation occurs

(Guedry *et al.* 1964, Graybiel and Knepton 1972). At rotation rates above 3 rpm, head rotations made out of the axis of rotation were provocative. However, when the rotation rate was increased gradually with small increments, and subjects made head movements during every plateau, they were able to adapt to rotation rates of 10 rpm without ever experiencing symptoms of motion sickness (Reason and Graybiel 1970). Adaptation to higher rotation rates on a rotating chair can also be achieved by exposure to gradually progressing stimuli: a principle generally applied in the desensitization of airsick aviators (Cheung and Hofer 2005).

As mentioned earlier, many adaptation studies have addressed the acute type of motion sickness induced by Coriolis stimulation (Guedry *et al.* 1964, Reason and Graybiel 1970, Clément *et al.* 2001, Brown *et al.* 2003, Dai *et al.* 2003). However, the extent to which a person can adapt to Coriolis stimuli remains undefined. Obviously, desensitization for rotation stimuli will allow the astronaut to freely move his head on the centrifuge. However, it is unlikely that this desensitization transfers to the astronaut's sensitivity to space motion sickness. An important question that remains to be answered is whether it is possible to desensitize astronauts to intermittent gravity level transitions that are inherent to artificial gravity procedures. The ground-based centrifuge paradigm can be suitable to answer this question.

Figure 4-06. The Bombardier Transportation Super Voyager tilting train for Virgin Trains, United Kingdom. Tilting trains are trains on which the upper part, where the passengers are seated, can be tilted sideways. In a curve to the right, it tilts to the right to compensate for the centrifugal force to the left, and conversely. The angle of tilt is determined by the speed of the vehicles, a faster speed requires more banking. Tilting trains can still cause nausea to passengers, as they do not reduce the Coriolis effect. The effect is usually felt under maximum speed and tilt, when the combination of the tilting outside view and lack of corresponding sideways forces can be very disconcerting to the passengers. Optimal tilt is about 50% of the tilt required for full compensation.

The ability to control susceptibility to motion sickness by adapting the vestibular system is a major advance and has broad application on Earth. Indeed, head movements in a moving or rotating environment such as boats, airplanes, tilting trains (Figure 4-06), and automobiles often provoke symptoms of motion sickness or other discomfort. Understanding motor adaptation to Coriolis forces in a rotating environment is relevant for understanding clinical deficits of complex whole body movement on Earth. Finally, the basic understanding of the roles played by vestibular and other sensors in adaptation to unusual environments and the associated disorientation and motion sickness will contribute to astronaut comfort and safety in flight and after landing.

4 EYE MOVEMENTS

Eye and head movement are crucial aspects of human visual perception. A reflex called the *vestibulo-ocular reflex* (VOR) coordinates body movements with head and eye movements to provide a stable platform that basically minimize motion blur during self-motion. Other eye movements include gaze shifts (saccades), and visual tracking of a single target (smooth pursuit) or a large visual scene (optokinetic nystagmus). These reflexive eye movements allow stabilization of the retinal image, which is fundamental for object recognition and spatial orientation by enhancing visual acuity. We are unaware of these eye movements, and the visual world appears stable.

Eye movements reflect vestibular functioning in a number of ways. For that reason, eye movement measurement belongs to the standard instrumentation for research and clinical diagnosis of the vestibular patients. This applies equally to the examination of the sensory-motor system under weightless conditions. Otolith-mediated information plays a role in the temporal (time) and spatial (three-dimensional) organization of the VOR and the other eye movement responses. However, as will be discussed below, most of the otolith effects are indirect, and require sophisticated recording techniques. Current state-of-the-art video eye tracking equipment facilitates the necessary accuracy and subject-friendly recording of three-dimensional eye movements (Clarke *et al.* 2002), and this technology is available as a standard facility on board the ISS (Figure 4-07).

Eye movement control is affected by changes in gravity level, indicating that these effects are centrally mediated. There is evidence that the VOR during head motion in pitch or roll and the vertical optokinetic nystagmus, which are under the influence of the otolith organs, are disturbed in weightlessness (see Clément 1998 for review). A systematic study of the horizontal, vertical, and torsional VOR during active head movements was performed over the duration of a six-month spaceflight mission. The findings demonstrate that the torsional VOR is radically reduced during prolonged microgravity, with an adaptive recovery during the first weeks postflight (Clarke *et al.* 2000). This can be understood as the effect of removing the otolith-mediated component of the dynamic VOR.

The latency of saccadic eye movements increased, whereas the peak velocities decreased in orbital flight, and the vertical pursuit movements are disrupted. As a result of these changes, astronauts commonly experience *oscillopsia*, i.e., an apparent motion of the visual surroundings, which implies that the VOR is no longer tuned to the head movement. This visual motion illusion might contribute to the genesis of space motion sickness.

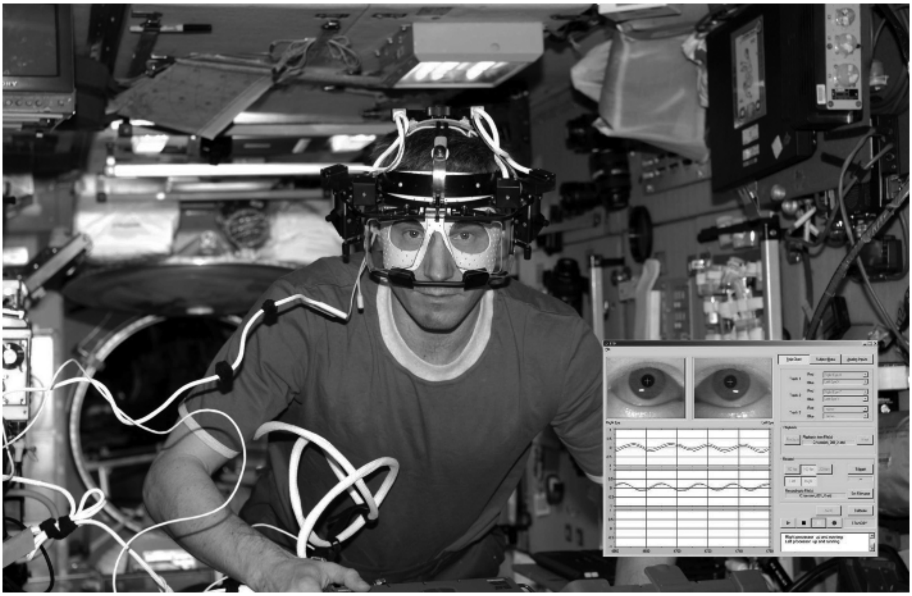

Figure 4-07. State-of-the-art DLR Eye Tracking Device currently installed on the ISS as a standard facility for vestibular, visuo-motor, and sensory-motor experimentation. The inlay shows the computer display for the online acquisition mode. Based on the CMOS imaging technology, the device permits recording of three-dimensional binocular eye movement, plus head rotation and translation. Sampling rates of up to 200/s are user-selectable. Photo courtesy of Chronos Vision, Berlin. See also color plate.

4.1 Eye Movements during Centrifugation

Changes in eye movements have also been observed under conditions of hypergravity (see Lackner and DiZio 2000 for review). In particular, when an increase in gravity level along the Gz axis elicits a VOR of otolith origin that drives the eyes downward. Attempting to stabilize visually the objects in a fixed position relative to the observer, such as displays in the cockpit, causes those objects to appear to shift upward when the gravity level is increased. Furthermore, tilting the head in pitch or in roll while exposed to an increased gravity level generates a sensation of excess tilt (Figure 4-08). If subjects are attempting to look at a visual target during this motion, vertical VOR will tend to compensate for this illusory excess tilt, and fail to stabilize the gaze on the target.

A false sensation of pitch or roll is also observed during centrifugation when the head is moved out of the plane or rotation. Horizontal, vertical, and torsional eye movements that tend to "compensate" for the perceived direction of the stimulus accompany this Coriolis illusion. The *nystagmus*, the succession of slow and fast eye movements, produced by these head movements is gradually reduced with the repetitions of the head movements (Brown *et al.* 2003, Dai *et al.* 2003). This reduction is retained even after long periods following the centrifugation. However, if centrifugation is always applied in the same direction of rotation, clockwise or counterclockwise, the subjects experience after effects in the opposite direction immediately after the rotation stops (Guedry *et al.* 1964).

Nystagmus is also induced by the angular accelerations used in starting and stopping the centrifuge. The repetitive exposure to this type of stimulation is accompanied by a progressive decline in the intensity of the pre- and postrotatory nystagmus, as well as retention of this decline from one session to another, a phenomenon known as *vestibular habituation* (Collins 1973). Subsequent static tests indicated changes in subjective vertical and sensation of vection (Clément *et al.* 2006). These changes suggest that the habituation of nystagmus and sensation of rotation to this paradigm generalizes to higher, more cognitive spatial orientation reactions.

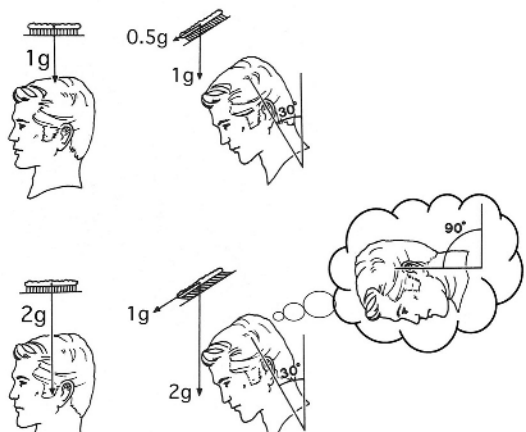

Figure 4-08. These drawings illustrate the shearing force in the plane of the utricular otolith membranes when a subject's head is upright or tilted 30 deg off the vertical in a 1-g (upper figures) and 2-g (lower figure) environment (Gz). In the 2-g environment, a 30-deg head tilt elicits a force equivalent to 1 g in the plane of the utricular macula, and the subject may perceive an illusory head tilt of 90 deg. The amplitude of the compensatory vertical eye movements under this circumstance is larger than in 1 g. Adapted from Gillingham and Wolfe (1985).

4.2 Ocular Counter-Rolling

Ocular counter-rolling (OCR) is an otolith-driven orienting eye movement that is generated when tilting (rolling) the head to the side. Typically, the magnitude of OCR is about 5 deg for a 45 deg static head roll tilt. Comparison of the response to static head tilt under 1-g and in-flight 0-g conditions demonstrates that this response vanishes in microgravity (Clarke

1998), although it does re-appear under in-flight, artificial gravity conditions using a centrifuge (Moore *et al.* 2001). Accordingly, this reflex has been used in many postflight studies to gauge the effect of microgravity exposure on otolith function, i.e., after transition from 0 g to 1 g. While the findings of earlier studies are inconsistent (see Moore *et al.* 2001 for review), a more recent study with 14 crewmembers indicated that postflight OCR magnitude is equivalent to preflight values (Clément *et al.* in press). However, it was found that OCR was systematically reduced in subjects who had been adapted to hypergravity, i.e., after 90 min of 3 g centrifugation in the +Gx direction and transition from 3 g to 1 g (Groen *et al.* 1996). Systematic modulation of OCR has also been measured during the modulation of the gravity level during parabolic flight (Clarke *et al.* 1992) and using a linear acceleration sled on the ground (Merfeld *et al.* 1996).

It has been hypothesized that, under 1-g terrestrial conditions, the natural imbalance or asymmetry in otoconial mass between the left-ear and right-ear utricles and saccules leads to differences in the primary otolith signals from the left and right labyrinths. Accordingly, the CNS compensates for this imbalance. Upon entry into weightlessness, the otoconial mass no longer deflects the sensory hairs and the neural impulse rate from the left and right otolith organs reduces to a resting rate. However, CNS adaptation to 0-g conditions proceeds with a slower time constant, and during this interval the system will be temporarily uncompensated. This raises the question as to whether (intermittent) artificial gravity exposure would interfere with this adaptive compensation process.

Interestingly, in some spaceflight and parabolic flight studies, the torsional eye position was found to be offset from its preflight position, resulting in binocular disconjugacy (Diamond and Markham 1992, 1998) The authors interpreted this as supporting the *otolith mass asymmetry* hypothesis and its role in eliciting space motion sickness.

In the context of artificial gravity measures it is also relevant to discuss those eye movements elicited by dynamic stimulation of the otolith organs. A comparative study of eye movement responses to active head-to-trunk tilt was performed between 1-g and 0-g conditions during long-duration flights on the Mir space station (Clarke *et al.* 2000). Under 1-g conditions an active head tilt elicits a combined canal- and otolith-mediated oculomotor response. This manifests as a volley of torsional nystagmus beats combined with a tonic OCR. In microgravity, only the transitory canal-mediated torsional nystagmus response remains.

However eye-to-head position and velocity gain, measured after fast-phase elimination and slow-phase reconstruction, was found to be enhanced in 0-g conditions, and to return to baseline after return to normal gravity (Clarke, in press). This is strong evidence that under normal 1-g conditions, otolith and canal contributions are not simply added linearly, but rather that the afferent otolith signal also plays an inhibitory, or stabilizing role in the otolith-canal interaction. The findings obtained from a single-case, longitudinal study over the course of a 400-day space mission indicate that the initially enhanced response is again reduced, over the course of several months, to preflight baseline level. It is hypothesized that in addition to a re-weighting of otolithic afferent information during prolonged microgravity, a corollary inverse re-weighting of neck-proprioceptive afferences provides an effective substitute (Clarke, in press). These findings have some bearing on the velocity storage mechanism discussed in the next section.

4.3 Velocity Storage

Because of the relatively short time constant of the semicircular canals relative to acceleration in the physiologic frequency range of head movement, which is roughly 0.05-1.0 Hz, the CNS has developed a brainstem mechanism that prolongs the afferent activity, and consequently the VOR, so that it better matches head velocity for a longer period of time. This mechanism is called *velocity storage* because it essentially stores the initial head velocity as transduced by the canals, and maintains it despite the decay in the firing rate of the canal afferent (Raphan *et al.* 1979). It has been clearly demonstrated that the time constant of this velocity storage is influenced by gravity inputs from the otolith organs (Bos *et al.* 2003, Dai *et al.* 2001). Further, the velocity storage time constant has been found to be reduced in microgravity (Oman and Kulbaski 1988, Oman and Balkwill 1993) and after adaptation to hypergravity in a centrifuge (Groen 1997). These findings suggest that the gravito-inertial force level does not alter peripheral vestibular responses to acceleration but does affect central vestibular processing.

Interestingly, the velocity storage mechanism also plays a role in the spatial organization of the VOR and optokinetic nystagmus. In general, the response tends to align to the gravitational vertical on Earth (Gizzi *et al.* 1994). In weightlessness, it was found that this property was still maintained when a steady-state gravito-inertial force was present, such as during centrifugation (Moore *et al.* 2005). Another interesting finding is that there seems to be a close relationship between velocity storage and motion sickness. Using Coriolis stimulation, Dai *et al.* (2003) showed that nausea was greatest in subjects whose eye velocity vector deviated most from gravity. If we assume that the tendency of the velocity storage to align with the spatial vertical relies on, or represents, the internal representation of the vertical, this finding is concordant with the subjective vertical theory on motion sickness. Further evidence of a link between velocity storage and motion sickness lies in the recent finding that Baclofen, a GABA(B) agonist, shortens the time constant of velocity storage and prevents motion sickness symptoms in specific forms of vertigo (Dai *et al.* 2006). All these findings indicate that the velocity storage mechanism is of central importance in the study of the influence of gravity-level transitions.

Quite apart from changes in eye movement responses to vestibular or optokinetic stimulation, recent findings from experiments during six-month missions on the ISS demonstrate that the oculomotor system, in itself, is modified by the loss of the gravity vector (Clarke *et al.* 2005). This is presumably due to a gravity-biased component in the oculomotor control system. This may be related to findings reported by Frens *et al.* (2004) and Reschke *et al.* (2004), which also indicate that the visuo-motor control of eye position is modified by a gravity bias.

5 HEAD AND ARM MOVEMENTS, AND OBJECT MANIPULATION

5.1 Microgravity Environment

Astronauts' anecdotal observations, surveys of video footage, and recent quantitative studies suggest that coordinated movements such as grasping, pointing, and tracking targets (hand-eye coordination) may be degraded during spaceflight. Alterations in arm pointing motions have been reported both during and after spaceflight (Watt 1997, Bock *et al.* 1992). The trajectory of hand-drawn ellipses in the frontal plane in the air with eyes closed revealed a decrease in the vertical length of the ellipses, whereas the horizontal length of the figures was basically unchanged (Gurfinkel *et al.* 1993, Bock *et al.* 2001). Similarly, the vertical size (height) of cubes drawn by hand with eyes closed by astronauts in space was decreased in weightlessness as compared to similar figures drawn on the ground (Lathan *et al.* 2000). Handwriting with eyes closed also showed a decrease in the spacing between characters in the vertical plane in weightlessness (Clément *et al.* 1987).

Rather than an alteration in motor function, due to changes in muscle strength fiber types or innervation, these rapid changes in movement control may be related to alterations in cortical maps of somatosensation. For example, there is a performance decrement in the ability to evaluate the "heaviness" of objects lifted in weightlessness (Ross *et al.* 1986). The perceived position sense of the limbs is also affected, presumably because of a mismatch between muscle length and tension in weightlessness. One Apollo astronaut recalled: "The first night in space when I was drifting off to sleep, I suddenly realized that I had lost track of ... my arms and legs. For all my mind could tell, my limbs were not there. However, with a conscious command for an arm or leg to move, it instantly reappeared – only to disappear again when I relaxed". A Gemini astronaut reported that he awoke to see a disembodied phosphorescent watch glowing and floating in the air in front of his eyes and not even realizing for a time that the watch was his very own, strapped to his wrist at the end of his floating arm (Godwin 1999). All of these examples of alterations in the sensation of body limbs and their motion control as well as the inability to accurately judge object "heaviness" in weightlessness point to a significant alteration in limb proprioception in microgravity (Lackner and DiZio 2000).

Besides sensory and motor dysfunctions, an alternative explanation for the observed changes in weightlessness is that these automated movements were acquired on Earth in the presence of gravity and, when played back in space, still include a "built-in" compensation for a gravitational force that is no longer adequate (Pozzo *et al.* 1998). In support of this hypothesis, astronauts were able to catch balls released from a spring-loaded canon in microgravity, despite the fact that they moved with a constant speed as opposed to a constant acceleration as they would on Earth. However, their timing was a bit off. They reacted as if they expected the ball to move faster than it did, i.e., as if gravity was still present. Yet for nearly fifteen days, the astronauts' brains continued to predict that the balls would be accelerated as if on Earth, even in the face of contrary evidence. Such rigid, inflexible behavior supports the notion that the brain contains a built-in model of gravity (McIntyre *et al.* 2001).

Other experiments performed in parabolic flight, and currently planned for the ISS, have also shown that each new gravitational field is rapidly incorporated into an internal model within the CNS. These internal models are presumably used to predict load forces and generate appropriate grip forces during object manipulation with the hand (Augurelle *et al.* 2003). Indeed, gravity normally provides constant force acting on the object, depending on its weight, which is adequately taken into account by an appropriate level of grip force. Microgravity, or hypergravity for that matter, presents a significant challenge to dexterous object manipulation because the CNS might involve a greater reliance on visual, tactile or memory cues to the mass of an object. In addition, there might be over-gripping to reduce the consequence of an erroneous estimate of mass. Alternatively, the hand might initially be moved more slowly than normal to allow more time for feedback-based adjustments to grip force (White *et al.* 2005).

5.2 Rotating Environment

The changes in coordinated movements discussed above, which occur during short-duration spaceflight, are relatively minor but highly systematic and consistent. After a six-month exposure to weightlessness en route to Mars, there is a strong possibility that astronauts may be unable to deal with an emergency situation upon return to a significant (0.38 g) gravitational field if they are unable to control their movements. The astronauts are also unlikely to possess the ability to execute an emergency egress upon landing on the

Martian surface. The use of artificial gravity may provide an effective way to avoid these changes in sensory-motor control mechanisms. However, the effects will be quite different using a short-radius centrifuge, where body movements are limited, as compared to the rotation of an entire spacecraft or a large centrifuge inside it, wherein subjects can move around freely.

As discussed in Chapter 2 (Section 2.3), Coriolis forces act on moving objects in rotating environment (Figure 4-09). Consequently, they will perturb head, limb, and body movement. The Coriolis force is proportional to the linear velocity of the imparted motion, the mass of the moving limb, and the angular velocity of rotation. The Coriolis force is transient, i.e., it is absent at the beginning and at the end of a reaching movement, because at those times the linear velocity of the arm is zero. Its magnitude does not depend on the radius of the rotating environment. Therefore it is equally present in both short- and long-radius centrifuges.

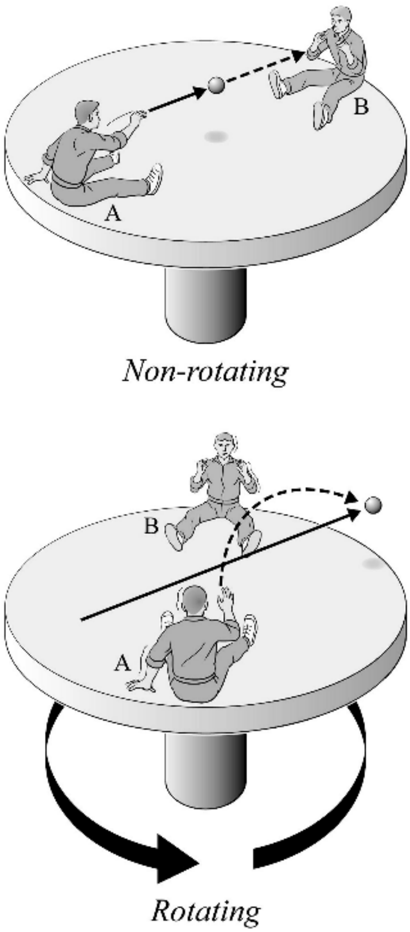

Figure 4-09. The Coriolis effect is the apparent deflection of a moving object in a rotating frame of reference. When a subject A throws a ball to another subject B, it travels in a straight line (solid line). However, when on a rotating platform, before the ball reaches B, the platform has rotated and the ball passes to the right of B (as seen from A). To the observer A on the rotating platform, the trajectory of the ball appears to have been deflected to the right (dashed line) by an imaginary force, the Coriolis force. Drawing Philippe Tauzin (SCOM, Toulouse).

The direct consequence of the stimulation of the vestibular system by Coriolis forces and cross-coupled stimulation of the semicircular canals and otolith organs during head movements out of the plane of rotation is motion sickness. In a short-radius centrifuge (see Figure 3-01), head restraint systems can be used to minimize head movements during rotation, which will prevent motion sickness during centrifugation. It has been suggested that, because of the limitation in the ability to perform head, arm or body movements, a short-radius centrifuge would contribute little to the maintenance of sensory-motor calibration of the movement control mechanisms. Consequently, such a device would be unlikely to attenuate the severe disturbance of movements and postural control that present a hazard when landing on Mars (Lackner and Dizio 2000). Because changes in proprioceptive inputs may be important to postflight balance disturbances (Kozlovskaya *et al.* 1982), loading the lower extremities using a short-radius centrifuge and simultaneously forcing a subject to maintain balance (via a freely moving backplate for example) could aid crewmembers in retaining terrestrial internal models of sensory-motor integration. If the crewmember could be placed far enough off-axis to sufficiently load the otoliths, then this component of the internal model might also be retained.

In a rotating spacecraft or in a large module rotating within it, the crew will be able to move freely. In this environment, however, the Coriolis accelerations will cause deviations in voluntary movements, potentially disrupting performance. If an object is raised from the floor toward the center of rotation, it will become lighter, and then heavier again as it is lowered back toward the floor (Stone 1973). Similarly, an astronaut walking rapidly in the direction of rotation along the wall (floor!) at the radius of a rotating vehicle would experience an effective increase in body weight due to the Coriolis accelerations and the increase in relative angular velocity. Walking in a direction opposite of the direction of rotation produces the opposite effect, i.e., the astronaut experiences an effective decrease in body weight (see Chapter 2 for the physics explaining these effects). The only direction the astronaut can move and not experience the Coriolis effect is one parallel to the axis of rotation of the vehicle or centrifuge.

As discussed in Chapter 3 (Section 3.1), the pioneering studies on human performance in slow rotating rooms executed in the 1960s showed that for rotation rates above 3 rpm, head movements induced motion sickness symptoms that never fully abated (Guedry *et al.* 1964). The subjects again experienced motion sickness symptoms after the room stopped rotating when they moved their heads. These early experiments involved single exposures to rooms rotating at constant velocities. However, it has since been shown that if the rooms are gradually spun up to their eventual terminal velocity, adaptation to rotation rate of up to 10 rpm with no motion sickness is possible, both during and after rotation (Graybiel and Knepton 1978).

Hand-eye coordination was also affected during these rotating room studies. These adapted gradually with time after continuous exposure. Upon cessation of the rotation of the room, motor performance was again disrupted. In more recent studies it has been shown that if the same reaching movement toward a single target is executed using the same movement pattern over and over again for a number of repetitions, then full adaptation can be achieved in 15-20 reaches (Figure 4-10). It is notable that during the first few reaches in the rotating environment, the subjects felt the Coriolis forces deviating their arm. Interestingly, after multiple reaches, test subjects no longer perceived the Coriolis force, and the movements seemed completely normal. After adaptation to the rotating environment, limb movement feels completely natural and indistinguishable from the normal non-rotating environment (DiZio and Lackner 1995).

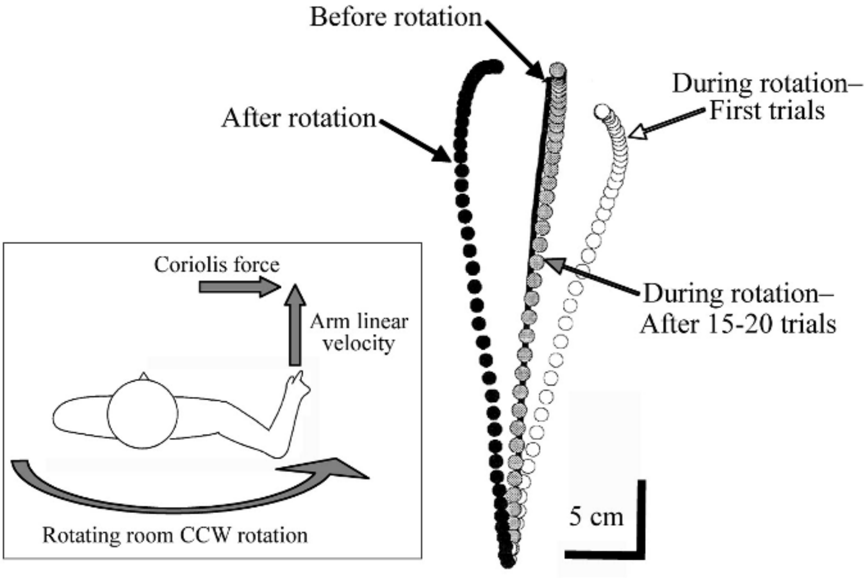

Figure 4-10. Trajectory of arm movement reaching towards a previously seen luminous targets at rest before rotation, during rotation at 10 rpm (first trials and after 15-20 trials), and immediately after rotation. Forward arm movements generated rightward Coriolis force during counterclockwise rotation (insert). The curve trajectory reflects the action of the Coriolis forces during rotation. After 15-20 movements, subjects are back to straight and accurate reaching movements despite the absence of visual feedback. Immediately after rotation, the reaches are mirror images of the first trials during rotation. This pattern of adaptation and aftereffects means that the nervous system is precisely anticipating the Coriolis forces and programming motor compensation from them. When subjects are allowed full sight of their limbs during pointing movements, they adapt within 8-10 movements. Adapted from Lackner and DiZio (1997).

Similarly, with repeated head movements, deviations of the trajectory of the head caused by the Coriolis forces and cross-coupled angular accelerations can be restored to normal within 30-40 movements (Lackner and DiZio 1998). Aftereffects in the opposite direction occur post-rotation. However, regular on-board experimenters acquire a dual-adaptation to both the rotating room and the normal 1-g environment in the course of carrying out their everyday activities in the slow rotating room. They feel and act completely normal in the rotating room and don't have aftereffects when the room stops rotating. Recent studies also suggest only minor problems in manipulating and controlling relatively low-mass objects during rotation at rate up to 10 rpm (Lackner and DiZio 2000).

Another aspect related to adaptation to rotating environment is that human intuitions about physics problems are often erroneous. For example, many people erroneously believe that an object that is carried by another moving object, like a bomb carried by an airplane, will fall to the ground in a straight vertical line when dropped. In fact, such an object will fall forward in a parabolic arc (McCloskey *et al.* 1980, 1983). It is argued that people acquire a primitive, non-Newtonian view of the world from their experiences in the world. This view is then revised by using a combination of contextual cues (i.e., more experiences) and relevant knowledge (i.e., more education) (Clement 1982). We have no experience of moving objects in a rotating environment and most subjects are likely to have serious difficulties acquiring intuitions about Coriolis forces and their interaction with centrifugal force and gravity gradient (Figure 4-11). The orientation and motion of the centrifuged subject and the objects with respect to rotation plane and direction will become a new cognitive and perceptual dimension. As pointed out by Hecht (2001), "we have not even started to think about the added perceptual and cognitive load that is required to function in artificial gravity".

Figure 4-11. While inside a slow rotating room, a subject is tossing an object in a trashcan. The trajectory of the object deviates from the straight path due to Coriolis force. This deviation will depend on the direction in which the subject is facing on the centrifuge. Hence, in order to predict object (and its own) motion an accurate spatial orientation is needed. Photo courtesy of NASA.

In conclusion, ground-based studies indicate that head and arm movements and object manipulation can be adapted to continuous rotation in both short- and long-radius centrifuges. Results obtained recently from experiments in slowly rotating rooms indicate that the 3-rpm limit for adaptation of voluntary movements might be too low. If an incremental exposure schedule is used, then 10 rpm can be achieved. Dual-adaptation of complex movements to both rotating and non-rotating (1 g) environments may be accelerated with controlled exposure to Coriolis forces and vestibular cross-coupled stimulation. The appropriate adaptation schedule and whether a dual-adaptation can also be maintained when astronauts will go back and forth between artificial gravity and microgravity need to be validated during actual space conditions. The cognitive and perceptual implications of artificial gravity also need to be investigated.

6 POSTURE AND GAIT

Following from the preceding Sections of this Chapter, it should not be a surprise that balance control and locomotor disturbances have been observed consistently following spaceflight since the earliest missions. The prolonged exposure to microgravity on board a spacecraft has numerous effects on an astronaut's physiology, clearly affecting postural behavior. The anti-gravity function of the core and lower limb musculature is no longer required in 0 g, resulting in adoption of a quasi-embryonic (flexor posture) attitude. Early in-flight many try to minimize head movements to reduce visual and orientation illusions as well as provocation of space motion sickness (see this Chapter, Section 3). Initially many are more comfortable and efficient when orienting themselves to the visual vertical contours of the modules, corresponding to their orientation during training, but over time and presumably after adaptation to the new environment, they more freely assume whichever orientation is most convenient. These behavioral changes reflect adaptive responses necessary to optimize sensory-motor performance in the new environment, and, as with other sensory-motor and behavioral learning, practice tends to improve the performance and make the behaviors permanent. Unfortunately, upon return to Earth the sensory-motor programs developed to optimize performance in space are no longer optimal. Thus, terrestrial sensory-motor control programs must be reacquired through processes requiring hours to weeks to be completed.

Postflight balance control deficits resulting from in-flight sensory-motor adaptation to 0 g were predicted early on as a potential operationally-important side effect of spaceflight. In 1965, Graybiel and Fregly (1965) introduced a "rails test", which was subsequently used to demonstrate balance control deficits in U.S. crewmembers returning from orbital missions. Also during the 1960's, Roberts (1968) introduced the concept of a labyrinthine-generated "behavioral vertical" to explain a critical role the vestibular apparatus plays in providing a dynamic internal reference frame for neuromotor control of upright stance (see Section 1 of this Chapter for more information), and in a series of symposia on "The Role of the Vestibular Organs in the Exploration of Space" (Graybiel 1965, 1966, 1968, 1970, 1973), a number of investigators presented data demonstrating the confluence of multi-sensory information in the vestibular nuclei and the cerebellum (see Section 2.2 for more detail).

Since those days our understanding of terrestrial balance control has progressed rapidly. In parallel, numerous spaceflight investigations have contributed to our understanding of the characteristics, demographics, and mechanisms underlying the transient disruption of balance control following spaceflight. Human studies of integrated balance control performance, neuromotor reflex function, proprioceptive function, and visuo-perceptive function have been performed. Animal studies of remodeling in the cerebellum and vestibular end organs have also been performed.

Today postflight decrements in posture and gait control have been well characterized from both basic science and occupational health perspectives. Early after flight postural stability and locomotor control are disrupted in all crewmembers. The degree of disruption decreases with increasing spaceflight experience (the number of previous flights), but increases with mission duration. As mission duration increases there is also an increased incidence of postflight autonomic nervous system problems. For example, orthostatic hypotension, which can exacerbate the balance control deficits, may result in part from vestibular autonomic system alterations.

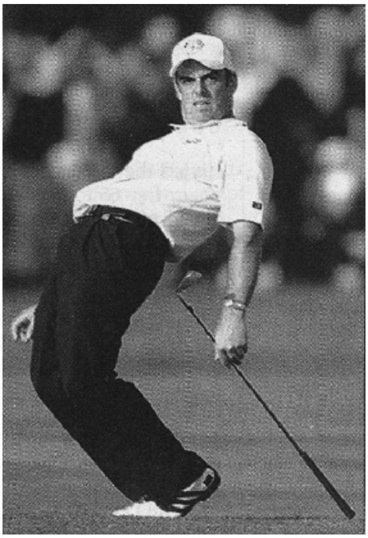

Figure 4-12. Illustration of the reliance of the central nervous system on using gravity as a fundamental spatial orientation reference indicating Earth-vertical. Notice how despite the highly unusual (and unstable) posture being assumed by this golfer, he manages to maintain his head orientation along the gravity vector. This photograph appeared in the Portland Oregonian *newspaper on October 2nd, 2002 (source unknown).*

6.1 Role of Gravity

That the central nervous system uses gravity-related sensory inputs as a fundamental reference for spatial orientation and balance control is not immediately obvious from observing posture and gait behaviors in everyday life. However, by observing the debilitating effects of vestibular disorders on posture and gait or by closely observing the behavioral patterns of normal individuals performing at or near their limits of stability (Figure 4-12) it becomes more obvious. So, by learning during spaceflight new sensory-motor programs that allow one to orient, navigate, and move about effectively without gravity, the CNS learns to overcome (eliminate?) its dependence on a fundamental physical orientation reference.

It is of interest, therefore, to examine in detail the postural behavior of astronauts immediately after spaceflight, during the time that they must recalibrate their equilibrium systems to the 1-g environment. While the severity and duration of the postflight behavioral responses varies widely from person-to-person, ranging from complete ataxia to only subtle effects, all returning crewmembers have observable behavioral changes. Most adopt a wide stance and gait with their feet farther apart than normal. Initiating and, more noticeably, terminating gait appear to take more effort and generally result in body oscillations that give the impression of compromised stability. Many minimize head movements and some move their head-trunk segments *en bloc*, presumably to avoid disorientation, instability, and motion sickness. Most have difficulty controlling the trajectories of their centers-of-mass, particularly when negotiating corners: often they make very wide-radius turns but sometimes they clip turns short. Many report unusual perceptions while climbing stairs, often that they feel more like they are pushing the stairs down than like the stairs are propelling them up. When standing still, many long-duration crewmembers exhibit co-contractions and occasionally tremor in their lower limbs, but when sitting down, their leg muscles appear to be without tone, literally hanging off their bones.

Quantitative assessment of postflight posture and gait disturbances began with the first human spaceflights. As noted above, in the U.S. Apollo and Skylab programs, investigators used a sharpened Romberg test, performed while standing on rails of various widths, to quantify deficits and track recovery (Homick and Reschke 1977). Later investigators introduced various postural perturbation tests (Kozlovskaya *et al.* 1983, Clément *et al.* 1985, Kenyon and Young 1986), postural reflex tests (Kozlovskaya *et al.* 1982, Reschke *et al.* 1986), gait coordination and locomotor performance tests (Bloomberg *et al.* 1999), and more sophisticated tests designed to elucidate the roles of specific sensory systems in the observed postural deficits (Bles and de Graaf 1993, Paloski *et al.* 1999). The results all point to underlying causes expected from the arguments presented throughout this chapter: CNS reinterpretation of vestibular information seems to be the primary driver of postflight posture and gait disturbances following short-duration missions, but as mission duration increases somatosensory and motor control system adaptation seems to play an increasingly important role. The exact mechanisms of this slower phase of in-flight adaptation are not yet well understood.

An on-going, long-term quantitative study of postflight balance control performance uses a clinical computerized dynamic posturography system (Figure 4-13). This system cleverly employs "sway-referencing" to reduce or disassociate visual and ankle proprioceptive information from Earth-vertical, making it possible to isolate the role of vestibular information in the highly integrated sensory-motor balance control task. Results from this study have been useful in characterizing the amplitudes and recovery time courses of the postflight balance control deficits (Figure 4-14). They have also demonstrated that the postflight deficits of experienced astronauts are less severe than those of novice astronauts, primarily because experienced astronauts seem to have learned how to better use vestibular information early after landing, and that the initial deficits in balance control become far more profound and persist much longer as mission durations increase from two weeks to six months.

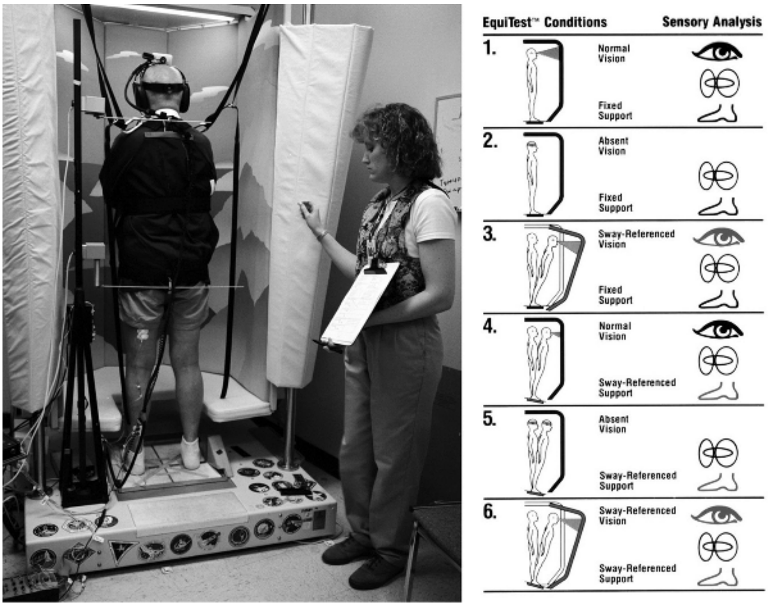

Figure 4-13. Computerized dynamic posturography system (EquiTest, NeuroCom International, Clackamas, Oregon, USA) and schematic representation of the six sensory organization test conditions used. Note that tests 5 and 6 artificially disrupt visual and proprioceptive information, forcing the system to rely on vestibular information as the sole veridical source of vertical reference information.

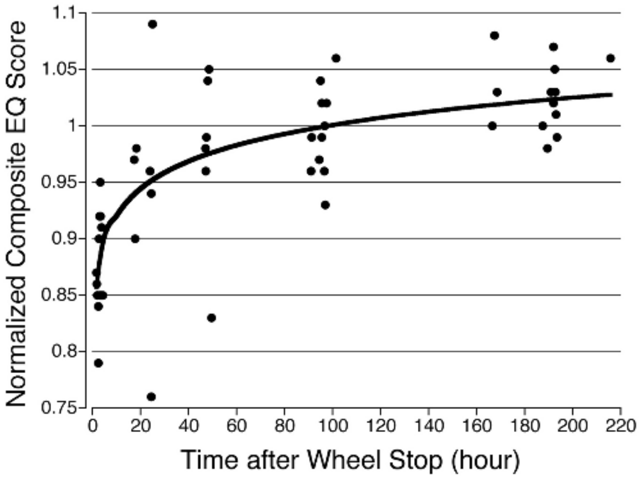

Figure 4-14. Balance control loss and recovery from 13 crewmembers following short-duration (4-17 days) Space Shuttle missions. The Composite Equilibrium (EQ) Score *is a weighted average of the computerized dynamic posturography performances measured using the six sensory organization tests shown in Figure 4-13. Adapted from Paloski* et al. *(1999).*

6.2 Effects of Artificial Gravity

Artificial gravity may have a salutary effect on postflight posture and gait disturbances. Standing, as such, is of course not possible without mechanical aids, such as bungee cords, on board present spacecrafts. While bungees can putatively provide sufficient loading to reduce anti-gravity muscle atrophy and bone demineralization during extended exposure to 0 g, they can result in unnatural loading of the body and new sensory-motor coordination programs for maintaining posture and gait. While they can maintain loading of lower limb proprioceptors and exteroceptors, and require integration of those receptors into sensory-motor control schemes, they do not load the otolith organs, nor do they provide hydrostatic loading of the cardiovascular system. Artificial gravity, on the other hand, being an inertial load could stimulate bone, muscle, sensory, and cardiovascular systems in much the same way that gravity does. Depending on the artificial gravity configuration, however, additional (non-gravitational) loading associated with Coriolis forces and semicircular canal stimuli associated with cross coupling could offset these salutary effects.

In Section 5 the theoretical considerations for moving about in a rotating spacecraft are described. How this may affect gait and posture remains unknown, because astronauts have not yet experienced it. An indication of the effects can be experienced on Earth by walking radially outwards on a spinning carousel. The inertial acceleration generates a sideward force, the Coriolis force, according to Newton's second law, and the subject must counter that unexpected force to avoid losing balance or taking a path that is curved relative to the carousel (see Figure 4-11). As noted in Section 3.3, however, subjects exposed to similar Coriolis forces on board a slow rotating room were able to learn how to effectively move about in that environment after a few days of exposure. Additionally, anyone trying to walk along the rim of a spinning vehicle in the direction of the spin is subject to a radial inertial acceleration inward, which generates a downward Coriolis force, making the space walker feel heavier. If the astronaut were to turn around and walk along the rim in the direction opposite to the spin, the Coriolis force would be directed upwards and the weight of the astronaut would be reduced (see Chapter 2, Section 2.3). This is not a condition that can be reproduced on Earth.

The only human studies of gait and balance changes associated with prolonged continuous rotation come from the multi-day rotating room experiments performed in the 1960's (see Chapter 3, Section 3.1). These demonstrated that posture and gait were disrupted to about the same extent at the beginning of the exposure to the rotating environment and after returning to the terrestrial environment (Graybiel *et al.* 1965). The magnitudes and time constants of the observed disruptions were similar to those observed in crewmembers returning from short-duration spaceflight missions.

The first comparison between the effects of spaceflight and intermittent centrifugation on posture and locomotion was carried out on three European science astronauts. These astronauts were tested immediately after their return to Earth from a Spacelab mission (Bles and Van Raaij 1988) and, a few years later, after a 3-g (+Gx) exposure in a centrifuge for 1.5 hours (Bles and de Graaf 1993). After the spaceflight, the astronauts were tested in a room that could tilt sinusoidally in roll with a peak amplitude of 5 deg at frequencies of 0.025, 0.05, 0.1, and 0.2 Hz. The subjects stood on a fixed-base stabilometer platform beneath the floor, i.e., only the visual surround was tilted. On the first day, one of the astronauts was completely visually dependent, swaying together with the room. However, he was back to normal on the second day. Interestingly, he experienced the room and the platform as stationary, his weight shifting from one foot to the other. Subjects who do not perceive the room as moving normally perceive the platform as tilting. The other astronauts could remain upright, but only with considerable effort. The general impression here is that postural movements were limited to an inverted cone after the spaceflight, the aperture of the cone growing wider every day. Getting out of that cone was considered to be provocative to motion sickness and had therefore to be avoided. The study also revealed that the subjects tried to minimize head movements as much as possible, by turning head and trunk together.

Some years later the same astronauts participated in an experiment at TNO and at the Aeromedical Institute in Soesterberg where they were exposed to 3 g on a centrifuge (Gx) for 1.5 hours (see also this Chapter, Section 3.2). After the centrifuge runs, their postural behavior in the tilting room was similar to that observed after spaceflight (Bles and de Graaf 1993).

Associated signs were the destabilizing effects of head movements on posture and gait. Accordingly the subjects walked very carefully, trying to minimize head movements as much as possible. Illusory motion perception was reported ("floor motion"), for instance when they climbed the staircase out of the centrifuge pit. Results of studies on many subjects indicate that some of the subjects recovered quickly within 2 hours, but the majority suffer from this sickness-induced centrifugation paradigm for many hours. However, adaptation is faster if they move around, and make head movements instead of remaining motionless. Convincing the subjects to move around, and being nauseated but adapting faster, is not easy.

Other studies of physiological responses to intermittent gravity have been performed in ground-based laboratories, but most have targeted cardiovascular responses (Iwasaki *et al.* 2001, Iwase *et al.* 2002, Evans *et al.* 2004) or motion sickness responses (Young *et al.* 2001, Hecht *et al.* 2002). Intermittent rotating room studies discussed in Section 5.2 provide some insight into per- and post-rotatory adaptation of body segment movements related to posture and gait. Very recent evidence is being generated by a study being performed with subjects deconditioned by 21 days of head-down-tilt bed rest to simulate spaceflight. Subjects in the treatment group are exposed to daily 1-hour artificial gravity therapy on a short radius centrifuge having a radius of less than 3 m such that the Gz stimulation was 2.5 g at the feet-support interface and 1 g at the heart level. For the first seven subjects, the incidence of motion sickness symptoms has been very low, and the post-bed rest effects on posture and gait have been unremarkable, in part, because bed rest has little effect on the vestibular system. These preliminary results are promising, but, clearly, there is a need for more integrated physiology (sensory-motor, cardiovascular, muscle, at least) studies of intermittent artificial gravity before we can fully understand its effects on posture and gait.

7 CONCLUSION

The present review of current data indicates that the vestibular system is intimately linked to the question of the efficacy of using artificial gravity as a countermeasure during spaceflight. A number of observations demonstrate that we still have much to learn about vestibular and CNS reactions to the application of an artificially generated linear acceleration. These include oscillopsia, an erroneous sensation of translation when tilting the head, motion sickness symptoms, inappropriate eye movements for any given head motion, and uncoordinated limb movements.

Few studies have been performed on the effects of long-term exposure to microgravity on the vestibular system. Only recently have the necessary facilities been made available on board the ISS, and the first systematic studies commenced. Consequently, there is currently insufficient experimental data available to identify a beneficial prescription for artificial gravity for the sensory-motor system, or for the other physiological systems, (see the following chapters) for long-duration space missions. Priorities must be given to research establishing the parameters, such as centrifuge radius, rotation rate, duration, and repetition rate of artificial gravity sessions, which prove effective for maintenance of musculo-skeletal and cardiovascular condition while remaining compatible with the neurovestibular system. Knowledge gathered from medication studies as well as from adaptation mechanisms in patients suffering acute vestibular lesions may provide additional information that might help to set up the appropriate stimulus paradigms.

Considered as a neurovestibular countermeasure, artificial gravity is a double-edged sword. While it might be employed usefully for pre-adapting crewmembers to planetary gravity, it may well introduce problems with spatial orientation, vestibular conflict, and motor and postural disturbances (cf. Lichtenberg 1988). In a typical scenario, with a 2-m-radius human centrifuge rotation rate at above 60 rpm is necessary to produce an artificial gravity level of 1 g or greater. In such a device, when the astronaut attempts to move the head or limbs out of the plane of rotation, the Coriolis forces on the inner ear organs and on moving limbs would induce spatial disorientation, non-stabilizing compensatory eye movements, loss of coordination, and motion sickness.

It is possible that the sensory-motor system would adapt to repeated artificial gravity exposure, as has been observed in comparable conflicting conditions on Earth. However, assuming that the centrifuged astronauts adapt to motion sickness, motor recalibration, and neurovestibular side effects, cognitive adaptation to this complex environment will remain a challenge. Perhaps this is the price to pay for a countermeasure that could result in long-term stabilization of bone demineralization, muscular atrophy, and cardiovascular deconditioning. Clearly, an interdisciplinary approach is necessary to research this complex area. It would appear that the current ground-based bed rest studies are not fully adequate for this purpose. Although useful for the examination of cardiovascular, muscle, and bone deconditioning, the bed rest paradigm is unsuitable for the study of sensory-motor problems because the predominant 1-g vector remains as a central reference of the orientation senses. Because the sensory-motor issues seem to be more related primarily to transitions between gravity levels, testing under ground-based hypergravity in a centrifuge and hypogravity in parabolic flight conditions is likely to provide more relevant information for their solution.

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Chapter 5

PHYSIOLOGICAL TARGETS OF ARTIFICIAL GRAVITY: THE CARDIOVASCULAR SYSTEM

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The evolution of man took place in a constant gravitational environment on Earth. As a consequence, some systems of the human body function because of gravity, whereas others function in spite of gravity. The cardiovascular system fulfills the latter description, delivering blood in just the right amounts at appropriate pressures. Spaceflight challenges the cardiovascular function. Artificial gravity might prove to be an effective countermeasure during long-term space missions. Herein we propose a road map aimed at investigating the effects of acceleration, which is viewed as an independent variable, on the cardiovascular system and evaluating various devices that could be used on board a space vehicle.

Figure 5-01. Mercury Astronaut Grissom is receiving assistance in adjusting the breathing apparatus in preparation for centrifuge training. Photo courtesy of NASA.

1 CARDIOVASCULAR PHYSIOLOGY

Humans on Earth are exposed to a gravity acceleration of 9.81 m/s^2, or 1 g, generating a hydrostatic factor that affects blood pressure and volume distribution in standing individuals. On Earth, the hydrostatic component of the arterial pressure (ΔP) is given by

$$\Delta P = \rho \, g \, h \qquad [1]$$

where ρ is the blood density, g the acceleration of gravity and h the vertical distance between the left ventricle and the point in question. Therefore, at any level in the circulatory system, the prevailing pressure is given by the sum of the pressure generated by the heart plus or minus the hydrostatic component ΔP. The blood pressure in the lower limbs is much higher than at head level. The veins in the head do not collapse because of the rigid structure of the skull. The heart pumps blood at a pressure that is normally sufficient to carry blood to the brain. Yet, because of the hydrostatic factor, evolution acted in such a way as to develop sensitive mechanisms of blood flow and oxygen flow regulation that include the action of baroreflexes and chemoreflexes. Curiously enough, the sensors of these reflexes are essentially located at the bifurcation of the common carotid artery along the way taken by arterial blood to the brain. Specific adaptations to permanent life on Earth follow.

2 EFFECTS OF SPACEFLIGHT

2.1 During the Flight

As a consequence, when humans started to explore the outer space, some 45 years ago, they also started to be exposed to a new gravitational environment, called microgravity (0 m/s^2 or 0 g), for which they were not suited, although some of the effects of microgravity exposure are mimicked by water immersion or by supine posture. Notably, as far as the cardiovascular system is concerned, astronauts were affected by blood volume displacement from the lower limbs toward the thorax and the head, and this for the entire duration of a space mission. Related to this was the extracellular fluid shift along the same direction. Blood and fluid shifts have significant impacts on the regulation of the cardiovascular system, as they entail a sudden increase in central blood volume and in central venous pressure, with consequent chronic stimulation of baroreceptors. Such a condition cannot be stood with in absence of adaptive changes in the settings of the overall regulatory system, of both mechanical and neural origin.

The main chronic response to body fluid displacement is an increased fluid loss, leading to decreased central blood volume and decreased plasma volume (Nicogossian *et al.* 1993). Moreover, an increase in venous compliance occurs (Convertino *et al.* 1988, Herault *et al.* 2000), facilitating blood pooling in the extremities. In these conditions, alterations of the neural control of the cardiovascular system have been demonstrated. A progressive impairment of arterial baroreflex control of heart rate at rest (Fritsch-Yelle *et al.* 1992, 1994) and an enhancement of muscle metaboreflexes during dynamic exercise (Iellamo *et al.* 2006) were reported to occur during spaceflights. Long-term bed rest studies showed a lack of lower limb vasoconstriction during exposure to *Lower Body Negative Pressure* (LBNP) and during stand tests (Arbeille *et al.* 1995, 1998, Herault *et al.* 2000). In addition, decreased myocardial performance was observed (Perhonen *et al.* 2001), which may lead to reduced stroke volume of the heart at exercise (Shykoff *et al.* 1997).

Although the pathways of these adaptations remain largely unknown, the final outcome is a wide functional reorganization of cardiovascular regulation in microgravity, such that, and in spite of the changes outlined above:

a. Cardiovascular and sympathetic neural responses to handgrip and cold presser stimuli are maintained during spaceflight (Fu *et al.* 2002).
b. The relationship between cardiac output and oxygen consumption during steady-state exercise is essentially unchanged in microgravity (Shykoff *et al.* 1997).
c. The maximal oxygen uptake and supposedly the maximal cardiac output are not decreased in microgravity (Levine *et al.* 1996).

Thus, thanks to the new equilibrium attained in cardiovascular regulation after adaptation to microgravity, astronauts can perform and work reasonably well during spaceflight, even missions of long duration, despite the progressive loss of muscle mass.

2.2 After the Flight

However, when these astronauts return to Earth, they are not adapted to the 1-g gravitational environment anymore. The new functional organization of cardiovascular regulation is optimized for a condition of upward fluid displacement, reduced plasma volume and highly compliant veins, whereas the returning astronauts are suddenly and acutely exposed to the gravitational force, which pushes blood downward to the limbs into very compliant veins. This occurs in an organism with blunted cardiovascular responses, that is, reduced baroreflex sensitivity. Central blood volume drops dramatically in upright posture, venous return as well, and the stroke volume of the heart is greatly reduced. This reduction is not compensated for by a subsequent increase in heart rate, so that the relationship between cardiac output and oxygen consumption during steady-state exercise is suddenly displaced downward. Consequently, maximal cardiac output is drastically decreased, as is the maximal oxygen consumption (Saltin *et al.* 1968, Ferretti *et al.* 1997, 1998, Convertino 1997, Capelli *et al.* 2006). The ensemble of these phenomena is often referred to as *cardiovascular deconditioning*. Under these conditions, orthostatic intolerance frequently appears, which is perhaps the most important and potentially harmful event occurring upon return from prolonged spaceflights.

3 EFFECTS OF HYPERGRAVITY

It is not surprising then that the physicians responsible for astronaut health after prolonged spaceflight seek countermeasures that are apt to prevent or reduce cardiovascular deconditioning. Artificial gravity, by generating hydrostatic gradients in the circulatory system and reproducing gravity proprioception during exercise, is the only way to simultaneously prevent both the decay of the cardiovascular function and the musculo-skeletal system.

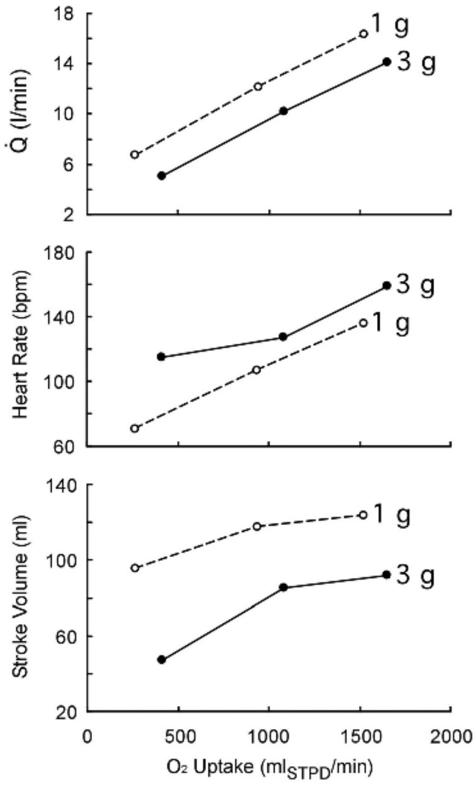

Figure 5-02. Cardiac output (Q), heart rate, and stroke volume as functions of oxygen uptake during rest and dynamic leg exercise at normal (1 g) and three times increased gravity (3 g) in the head-to-foot direction. N=8. Adapted from Rosenhamer (1967, 1968).

On Earth, an increase in gravity is typically obtained by means of centrifuges. In the past, the principal use of exposure to hypergravity in human centrifuges was to study the various aspects of pilot performance in high-performance aircrafts (see Glaister Prior 1999 and Green 1999 for review). Such studies have focused on hypergravity exposures in the 4-9 g range. Only a limited number of studies have addressed the range of gravity levels of 3 g and below (Rosenhamer 1967, 1968, Bjurstedt *et al.* 1968, Linnarsson and Rosenhamer 1968, Nunneley *et al.* 1975), which is the range that future systems for artificial gravity are likely to operate (Lackner and DiZio 2000, Clément and Pavy-Le Traon 2004). In the section below, we analyze the acute pulmonary and cardiovascular effects of gravity acceleration in the 1-3 g range, and review the use of artificial gravity as a countermeasure against cardiovascular deconditioning during spaceflight.

3.1 Acute Effects of Hypergravity on the Lungs

3.1.1 Gas Transport in the Lungs

Rosenhamer (1967, 1968) and Bjurstedt *et al.* (1968) presented the most comprehensive analysis of gas transport in human lungs during exercise in hypergravity. They studied subjects during sitting dynamic leg exercise in a human centrifuge with up to 3 g acting in the head-to-foot direction, or the +Gz direction. Arterial blood gases were determined continuously by arterial sampling and in-line analysis of PO_2, PCO_2, pH, and O_2 saturation. Cardiac output was determined by remote-controlled venous injection and arterial analysis of indocyanine green. Standard ventilatory and gas exchange determinations were performed with a remote-controlled Douglas technique. Both at rest and during exercise at about 50 and 100 W intensities (corresponding to 300 and 600 kpm/min[15], respectively), pulmonary blood flow for a given level of oxygen uptake was found to be reduced by 2.5 to 3 L/min at 3 g compared to 1 g (Figure 5-02).

At the same time, pulmonary ventilation was markedly increased (Figure 5-03). In terms of overall ventilation-perfusion ratio, the efficiency of the lungs as gas exchangers was reduced to about 50% of normal at 3 g during rest and to about 60% during exercise.

At least three mechanisms act in concert to increase the ventilation-perfusion ratio during high-g exposure: (a) an increased respiratory drive;

[15] In exercise physiology, *work* is usually measured in kilopond-meters (kpm); one kpm is the work required to move a one-kilogram mass a vertical distance of one meter against gravity. Work per unit time is *power* or kpm/min, which is often converted into watts (600 kpm/min is roughly equal to 100 watts). For example, a 70-kg person walking on a treadmill at 3 mph, 5% grade, generates approximately 300 kpm/min or 50 watts of power.

(b) a decreased alveolar ventilation-perfusion homogeneity; and (c) an overall reduction of pulmonary blood flow. These mechanisms are described thereafter.

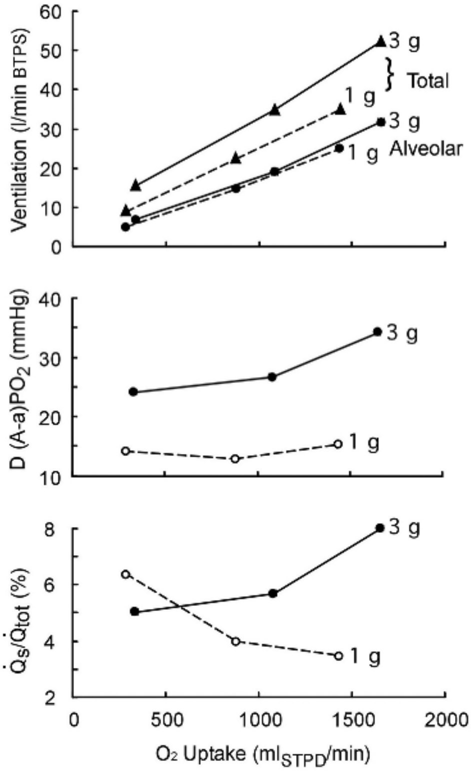

Figure 5-03. Total ventilation, alveolar ventilation, alveolar-arterial PO_2 difference [Δ(A-a) PO_2], and pulmonary shunt fraction (Q_s / Q_{tot}) as functions of oxygen uptake at normal (1 g) and three times increased gravity (3 g) in the head-to-foot direction. N=8. Adapted from Rosenhamer (1967, 1968).

3.1.2 Respiratory Drive

Figure 5-04 shows the pulmonary ventilation as a function of $PaCO_2$ and exercise intensity. This parameter is markedly increased at 3 g compared to 1 g. This demonstrates the existence of other powerful additional respiratory stimuli, beyond $PaCO_2$. Rosenhamer (1967) showed also that arterial pH levels did not differ between gravity levels. Thus the arterial pH per se could not be the additional stimulus. Rosenhamer (1967) proposed that it rather was the presence of a relative arterial hypotension at the level of the carotid sinus (Linnarsson and Rosenhamer 1968, Bjurstedt *et al.* 1968) that induced the additional ventilatory stimulus. However, with increasing work intensity, lactacidosis (Bjursted *et al.* 1968) may contribute as a ventilatory stimulus in high-g exercise by displacing CO_2 from tissue and blood stores, thereby increasing the pulmonary CO_2 load (Wasserman et al 1967) more than in proportion to the increased metabolic cost of exercise (see this Chapter, Section 3.3).

In summary, the markedly increased pulmonary ventilation at 3 g for a given $PaCO_2$ and metabolic rate both at rest and during exercise appear to be caused by a combination of mechano- and chemoreceptor inputs, and result in a modest respiratory alkalosis at rest, and an essentially compensated metabolic acidosis during exercise.

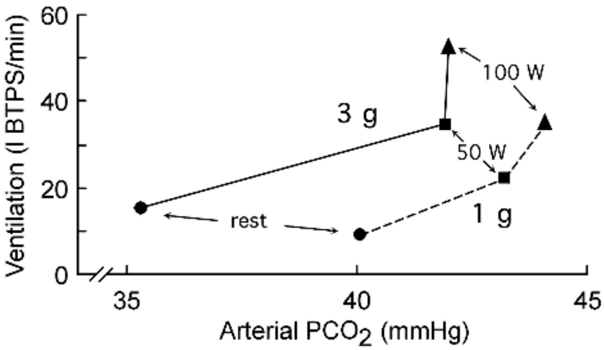

Figure 5-04. Graph of the total ventilation as a function of arterial PCO_2 at rest, and for 50 W and 100 W of mechanical power. For a given $PaCO_2$, ventilation is markedly elevated at 3 g. Adapted from Rosenhamer (1967, 1968).

3.1.3 Ventilation-Perfusion Relationship within the Lungs

Figure 5-03 shows effective alveolar ventilation (computed from the ratio of CO_2 output to $PaCO_2$) as a function of oxygen uptake in resting and exercising men (Rosenhamer 1967). The additional ventilatory effort at 3 g compared to 1 g does not represent an increase in alveolar ventilation. Rather levels of alveolar ventilation for a given oxygen uptake appear identical at 1 and 3 g. During both rest and exercise alveolar-to-arterial PO_2 differences [Δ(A-a) PO_2] are about twice as large at 3 g than at 1 g. In further support of the notion of a gravity-induced impairment of lung function, data obtained by Rohdin *et al.* (2002) show reduced lung diffusing capacity and signs of lung blood sequestration in sitting resting humans at 3 g.

From the data of arterial O_2 saturation obtained at the same time, the shunt fraction could be computed for a theoretical lung model with two compartments, one compartment shunting mixed venous blood through the lungs without any additional oxygenation, and the other providing fully oxygenated pulmonary end-capillary blood. Figure 5-03 illustrates that the normal pattern of decreasing shunt fraction with transition from rest to exercise is reversed at 3 g. The shunt fraction increases with transition to exercise and increased exercise intensity. In Rosenhamer's data (1967), during exercising at 100 W, the mixed venous O_2 deficit, relative to 100% O_2 saturation, averaged 99 and 127 mL/L at 1 g and 3 g, respectively. Out of this reduction of mixed venous O_2 content relative to full saturation, about one-third could be ascribed to the arterial O_2 deficit and about two-thirds to a widening of the artero-venous O_2 difference. Thus it appears from a quantitative standpoint that both the distribution and the overall rate of pulmonary perfusion are of importance, but the latter factor is the most critical.

Further studies from the same laboratory supported the notion of a gravity-induced limitation of exercise capacity. For example, Bjurstedt *et al.* (1968) showed that out of eight healthy male subjects, one could not complete 6 min of 150 W exercise at 3 g, and in two others the increase in O_2 uptake with increasing external work load tended to level off at the transition from 100 to 150 W. This study, however, was not designed to allow conclusions about the site (pulmonary or circulatory) of the O_2 transport limitation. Nunneley and Shindell (1975) performed similar studies on exercising, sitting men including continuous mass-spectrometric determinations of intra-breath gas composition. Although they provide no quantitative data, they present a qualitative analysis of cardiogenic oscillations of expired PCO_2. Heart-synchronous oscillations of expired CO_2 can only occur if there is a combination of PCO_2 differences between lung regions and time-varying contributions of the expired flow contribution from these regions to the total expired flow (Fowler and Reed 1961, Prisk *et al.* 1994). Nunneley and Shindell (1975) reported that at both normal and high gravity levels the amplitude of cardiogenic PCO_2 oscillations were reduced with the transition from rest to exercise but were always larger at 3 g than at normal gravity. These observations suggest that abnormally large intraregional PCO_2 differences remain in the lungs during exercise in hypergravity, despite the exercise-induced increase of pulmonary blood flow. This lends further support to the findings by Rosenhamer (1967) of impaired gas exchange between the lung gas and the pulmonary-capillary blood in sitting exercising men at 3 g.

3.2 Acute Effects of Hypergravity on the Systemic Circulation

Hydrostatic pressure gradients within the systemic circulation increase as a function of gravity level. In the sitting or standing human at rest, these gradients tend to curtail systemic blood circulation by two mechanisms (Blomqvist *et al.* 1983, Rowell 1993). First, diastolic cardiac filling is reduced because of peripheral pooling of blood. Already at 1 g, the central blood volume in a standing, resting human is reduced by approximately 0.7 L compared to supine position (Sjöstrand 1962). Rosenhamer (1967) estimated central blood volume from curve parameters of dye dilution recordings and demonstrated a further decrease of 0.7 L at 3 g compared to 1 g in sitting resting men.

Second, arterial pressures above a hydrostatic indifference point are reduced with associated reductions of the effective tissue perfusion pressure. A *hydrostatic indifference point* is defined as a point along the long axis of the body where the intravascular pressure is the same regardless of posture (Gauer and Thron 1965). In the upright human, any gravity-induced reduction of perfusion pressure in man will be most marked in the head. To a limited extent, the brain will be protected by a counteracting hydrostatic pressure drop in veins surrounded by bone (Henry *et al.* 1951). The perfusion in the eye is especially sensitive to reductions of arterial pressure because its tissue pressure is elevated by up to 20 mmHg.

Dynamic leg exercise results in a dramatically different situation because of the pumping action of the rhythmically contracting muscles on the deep veins of the legs. It has been proposed that up to 30% of the overall pump work required to drive blood through the vascular system during exercise is performed by the muscle pump (Stegall 1996). The efficiency of the muscle pump in the lower limbs is greatly enhanced by a hydrostatic pressure gradient in the head-to-foot (Gz) direction (Folkow *et al.* 1971). This is so because venous valves prevent back-flow of blood into the muscles resulting in very low, if not sub-atmospheric, venous pressures between rhythmic contractions. Thus the effective perfusion pressure in the lower limb of an upright human performing dynamic leg exercise is the sum of the dynamic pressure generated by the cardiac pump and the hydrostatic pressure gradient between the heart and the muscle (Rowell 1993).

The antigravity effects of exercise have been demonstrated by Rosenhamer (1968) who compared responses to a 13-min exposure to 3 g during sitting at rest and sitting exercise. Out of eight healthy men only three could tolerate the full exposure time at rest, and in other three subjects the exposure to 3 g had to be terminated as early as after five to six minutes. Six of the subjects experienced dimming of the peripheral vision in the first four to five minutes. In the five cases where 3 g exposure was terminated prematurely, rapidly increased dimming of the vision and impending loss of consciousness necessitated this. By contrast, when leg exercise at 100 W was performed for the last 12 of the 13 min, the 3-g exposure was experienced as less exhausting than at rest and there were no symptoms to suggest impaired blood perfusion in the eyes or the brain.

Figure 5-05 illustrates the time course of arterial blood pressure at the level of the heart from an experiment performed by Linnarsson and Rosenhamer (1968) in which subjects first sat at rest at 1 and 3 g and then started to exercise after six minutes. There was a clear trend for both mean arterial pressure and pulse pressure to fall towards the end of the resting period, followed by a marked and rapid recovery at the onset of leg exercise.

Gravity-induced alterations of central blood volume differ between rest and exercise. Thus, central blood volume, as estimated from parameters of dye dilution curves, does not differ between 1 g and 3 g in sitting exercising men (Rosenhamer 1967). Despite this index of normal intrathoracic blood volume at 3 g, exercise stroke volumes are reduced by

25-30% (see Figure 5-02). This may in part be due to an increased cardiac after-load at 3 g, because mean arterial blood pressure at heart level is increased (Linnarsson and Rosenhamer 1968). It may also be speculated that, despite an apparently normal central blood volume, some of that is functionally sequestered in a congested dependent part of the pulmonary circulation, so that the normal central blood volume during 3-g exercise not necessarily reflects a normal preload. No data appear to be available on end-diastolic ventricular dimensions and filling pressures in exercising men during hypergravity conditions.

The dramatic increase of stroke volume in the transition from rest to exercise, however, may to some extent be an exaggerated representation of the exercise-induced increase of venous return. Part of the cause of the very low resting stroke volume at 3-g rest, which is less than 50% that of 1-g rest, may be a result of the very marked tachycardia, which does not appear to be effective in maintaining cardiac output in the face of reduced venous return (Rowell 1993). The relative tachycardia at 3 g is less pronounced during exercise. Most likely, the tachycardia is caused by a hypotensive stimulus perceived at the carotid sinus, where arterial pressures are reduced, due to the increased hydrostatic pressure difference between the heart and the carotid sinus, despite an elevated arterial pressure at the level of the heart (Linnarsson and Rosenhamer 1968, Linnarsson *et al.* 1996).

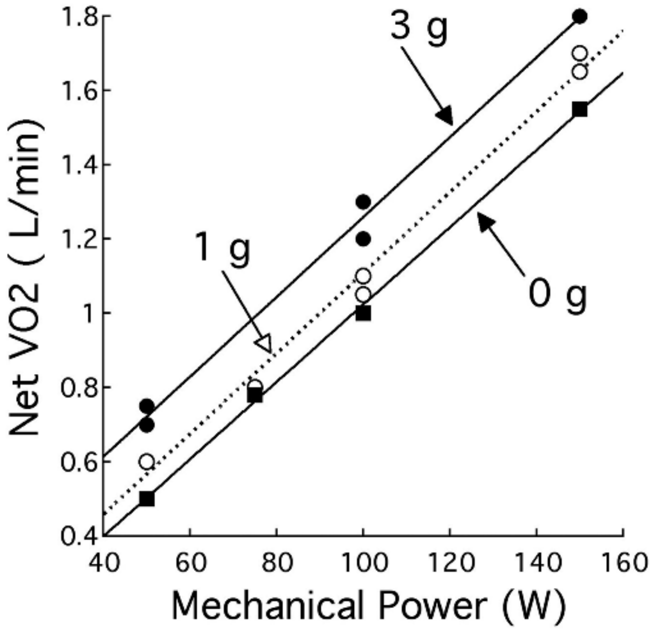

Figure 5-05. Net VO_2 (resting–exercise) is plotted as a function of external power output in 0 g, 1 g, and 3 g. Adapted from Girardis et al. *(1999).*

It should be noted that exposure to gravity perpendicular to the long axis of the body (Gx or Gy) is not likely to alleviate the negative influence of hypergravity on gas transport to the exercising muscles. Apart from not recreating the normal direction of gravity, there is also a marked impairment of alveolar-to-blood transfer of O_2 in the lung with hypergravity in the antero-posterior direction (Rohdin *et al.* 2003a, 2003b, 2004).

3.3 Acute Effects of Hypergravity on the Oxygen Requirements of Exercising Muscles

The oxygen cost of a given external work intensity during sitting dynamic leg exercise increases with gravity in the head-to-foot, or +Gz direction (Linnarsson 1980). Whereas the relationships between oxygen uptake and power at various gravity levels stay parallel, the y-intercept of the same relationships is displaced upward as gravity is increased (Girardis *et al.* 1999) (see Figure 5-02). The changes in oxygen uptake as a function of gravity correspond well to predictions that can be made from models of internal work during cycling, that are also known to increase with gravity level. By contrast, the fact that the lines in Figure 5-05 are parallel implies that the oxygen cost of delivering a given mechanical power, or its reciprocal, the mechanical efficiency of cycling exercise, is unaffected by gravity.

Assuming that the maximal heart rate is unchanged, the higher heart rate at any given power at elevated gravity levels would imply a reduction of the individual maximal oxygen uptake. The fact that the oxygen cost of cycling at any given power is increased as a function of gravity implies that the fall of the maximal aerobic mechanical power is even larger than that of maximal oxygen uptake. Thus, the maximal working capacity should be decreased on planets with a mass greater than that of the Earth, and increased on the Moon, Mars, and in microgravity. The apparently unchanged maximal oxygen consumption found during spaceflight may follow from the concomitant reduction of muscle mass.

4 LONG- VERSUS SHORT-RADIUS CENTRIFUGE

The reviewed studies performed in hypergravity reveal that alterations in the direction and magnitude of gravity force have multiple influences on the gas transport between the environment and the working muscles in humans. The need for oxygen flux through respiration and circulation for a given external power output increases with gravity level in the head-to-foot (+Gz) direction. At the same time systemic circulatory transport is curtailed in increased gravity by reduced venous return and increased hydrostatic pressure differences to cranial tissues. The efficiency of the lungs as a gas exchanger is markedly reduced at high gravity, and the shunt fraction increases with transition from rest to exercise and further with increasing exercise intensity.

In summary, increased gravity acting in the +Gz direction has a profound negative impact on gas exchange in exercising humans.

The results summarized in the previous paragraphs were all obtained using long-radius centrifuges with radii greater than 6 meters. This is an optimal condition for artificial gravity, because the gravity gradient is reduced in these conditions. However, long-radius centrifuges are difficult to implement in a space station. Instead, several authors have proposed to use short-radius centrifuges on board space vehicle (Burton 1994, Burton and Meeker 1997, Cardùs 1994, Greenleaf *et al.* 1996, Vil-Viliams *et al.* 1997). Short-radius centrifuges have their drawbacks too. As described in Chapter 2, they need an external power supply and their mechanics are not easily compatible with an exercising subject. Moreover, in a short-radius centrifuge, the subject's head is placed relatively close to the center of rotation. Therefore, the centripetal acceleration varies between the head and the feet, thus generating a gravity gradient. Hence, (a) the data obtained on long-radius centrifuges cannot as such be transferred to represent the situation that may occur on a short-radius centrifuge; and (b) specific studies aimed at analyzing the cardiovascular effects of spinning a human on a short-radius centrifuge must be performed.

Amongst the required studies, the level at which a given acceleration is applied ought to be investigated. Short-radius centrifuges have mainly been used in a patho-physiological context to evaluate motion sickness issues (see Chapter 4, Section 3). However, little is known on the cardiovascular effects of spinning a human exposed to a gravity gradient along his body, and no systematic study of the cardiovascular system under these conditions has been carried out so far, to our knowledge.

5 SHORT-RADIUS CENTRIFUGATION AS A COUNTERMEASURE

With the exception of the Neurolab Spacelab mission (Moore *et al.* 2001), no actual data on the effects of artificial gravity induced by short-radius centrifugation during spaceflight exists. However, several studies using intermittent short-radius centrifugation been performed on Earth during head-down bed rest and dry immersion. In these studies, centrifugation has been used either as a <u>countermeasure</u> primarily for cardiovascular deconditioning, or as a means to evaluate the <u>severity</u> of cardiovascular deconditioning resulting following bed rest or dry immersion (Clément and Pavy-Le Traon 2004). The severity of cardiovascular deconditioning is assessed by comparing the tolerance to accelerations that are generally greater than 3 g along the Gz direction before and after the experiment.

5.1 Bed Rest Studies

White *et al.* (1965, 1966) performed the first experiments with short-radius centrifugation during bed rest by using a 1.25-m centrifuge providing 1 to 4 g at the subject's feet in the +Gz direction. Centrifugation was applied four times per day during the bed rest study for either 7.5 or 11.2 min per exposure. Syncope did not occur in the centrifuged subjects after bed rest during the head-up tilt. Compared to the control subjects, the centrifuged subjects also had a lower decrease in arterial pressure and a higher heart rate. They also experienced less weight loss and reduced loss in plasma volume. The same authors performed a 10-day bed rest study in which the subjects were scheduled for exposure to 2.5 g at the heart level four times daily for 20 min per exposure. However, the prescribed regimen exceeded the acceleration tolerance level, so the modal regimen was finally reduced to 1.75 g (White *et al.* 1966). The post bed rest orthostatic intolerance was alleviated with this regimen.

Japanese investigators also performed several –6° *head-down bed rest* (HDBR) studies using centrifugation. Ten healthy males participated in a four-day HDBR study wherein they were exposed to 2-g centrifugation for 60 min daily in a 1.8-m short-radius centrifuge. In contrast to previous HDBR experiments, no significant change in plasma volume, which was indirectly assessed by hematocrit measurements, was observed at the end of the study (Yajima *et al.* 1994, 2000). To further evaluate the effects of centrifugation on cardiovascular function, twelve male volunteers participated in a four-day HDBR study. Eight were exposed to 2 g for 30 min twice daily. The other four subjects were controls. The cardiovascular regulation by the autonomic nervous system was assessed before and after the HDBR study. The time duration between two consecutive R waves of the ECG, the R-R interval, parasympathetic nervous activity, which was evaluated by heart rate variability, and baroreflex sensitivity decreased significantly in the control group. However, these parameters did not vary significantly in the centrifuged group (Sasaki *et al.* 1999). In another four-day HDBR study, 20 healthy male subjects were tested. Ten subjects were controls while ten were exposed to 2 g for 30 min twice daily. A significant decrease in parasympathetic activity and baroreflex gain was observed in the control group, but no significant change was observed in the centrifuged group. A significant decrease in maximal oxygen consumption was also observed in both groups (Iwasaki et al 1998, 2001). The authors concluded that the daily 60-min exposure to 2 g counteracted the changes in autonomic cardiovascular control, partly by reversing hypovolemia induced by HDBR, but could not prevent the decrease in exercise capacity (Iwasaki *et al.* 2001).

Centrifugation in HDBR was also evaluated in monkeys (Korolkov *et al.* 2001). Twelve animals (M*acaca mulatta*) were restrained and tilted at –5°

for 28 days. Six of the twelve animals were exposed to 1.2 to 1.6 g along the +Gz direction for 30 to 40 min daily four to five times per week for the duration of the study. A lower decrease in total body fluid and plasma volume and an increased tolerance to a 3-g acceleration at the end of the experiment were observed in centrifuged animals. The same trend was observed for daily exposure to 1.2 g for 30 min twice weekly.

5.2 Dry Immersion

The effects of short-radius centrifugation have been assessed during dry immersion, which is another method used to mimic the effect of microgravity on the cardiovascular system (see Figure 1-13). Shulzhenko *et al.* (1992) performed several series of three-day immersion experiments with different centrifugation levels (0.8, 1.2, and 1.6 g) alone or combined with a water and salt supplement. The time of centrifugation exposure was 40 to 60 min at a frequency of two to three times per day. The tolerance to 3-g acceleration in the +Gz direction was decreased by 7% after intermittent exposure to 1.2 g. The decrease was only 4% if centrifugation was combined with a water and salt supplement.

The short-radius centrifugation exposure was also exclusively applied during a 28-day immersion experiment from days 9 to 19, as well as in combination with 10 min of physical exercise on a bicycle ergometer from days 23 to 27 done three times during the 60-minute daily rotation period. Exercise was performed exclusively from days 16 to 21. In this experiment, the authors reported that with the combined use of centrifugation, centrifugation plus exercise, and exercise alone, the 3-g acceleration tolerance had a tendency to recover to the initial level (Vil-Viliams *et al.* 1980).

In a more recent review based on the results from three-day and 28-day immersion experiments with a 2-m radius centrifuge performed in Russia during the past 20 years, Vil-Viliams *et al.* (2001) concluded that the 0.8, 1.2, and 1.6-g exposures contribute to preserving tolerance to a 3-g acceleration with a significant positive effect of combining centrifugation with exercise on bicycle ergometer or a water and salt supplement.

The authors proposed three recommendations for the application of short-radius centrifugation:

a. Artificial gravity levels should be close to terrestrial gravity, ranging from 0.8 to 1.6 g.
b. Centrifuge runs should be planned in cycles and alternate with the other countermeasures.
c. Centrifuge runs should be combined with exercise and a water and salt supplement.

6 OTHER "GRAVITY-LIKE" COUNTERMEASURES DURING SPACEFLIGHT AND BED REST

6.1 Lower Body Negative Pressure

A *lower body negative pressure* (LBNP) device induces a fluid shift from the upper to the lower part of the body. The subject's legs are enclosed below the iliac crests in a chamber or trousers and exposed to negative pressure (see Figure 1-06). Levels of about –40 to –50 mmHg are considered to produce, in supine subjects, blood shifts very similar to those induced by the upright posture. LBNP has been developed to assess cardiovascular responses to orthostatic stress and is commonly used in flight and during HDBR experiments. LBNP is also used as a countermeasure to prevent the orthostatic arterial hypotension experienced during re-entry and after landing (Charles *et al.* 1994, Kozlovskaya *et al.* 1995).

Russians have a significant experience in applying LBNP during space missions using special trousers called "Chibis". During long-duration missions, the effects of countermeasures and orthostatic intolerance are evaluated using LBNP about every other month. LBNP has been also used as a countermeasure during the last month of the missions in association with other countermeasures, like fluid loading, which is the intake of water and salt tablets during the last days of the flight, and regular muscular exercise that is performed throughout the flight. The pre-landing training sessions with LBNP began 16 to 20 days before landing and consisted of a 20-min session every four days and of two sessions lasting nearly one hour each the last two days before landing (Gazenko *et al.* 1991). These LBNP sessions in association with the other countermeasures have beneficial effects on orthostatic tolerance (Kozlovskaya *et al.* 1995). LBNP in combination with fluid loading is believed to act by promoting a transient positive fluid balance resulting in an increase in vascular, as well as extra-vascular fluid. LBNP also may provide beneficial orthostatic effects by restoring baroreceptor reflex functions and/or lower body venous compliance (Fortney *et al.* 1991).

On Earth, LBNP alone or in combination with other countermeasures has been used during HDBR. Guell *et al.* (1991) showed that daily regular LBNP sessions at –30 mmHg applied in three to four sessions per day, and up to six sessions during the last three days, had beneficial effects on orthostatic intolerance after a 30-day –6° HDBR, mainly by maintaining plasma and extra cellular fluid volume (Gharib *et al.* 1992) with some beneficial effects on vasomotor tone (Arbeille *et al.* 1992). However, LBNP sessions had no preventive effects on lower limb venous distensibility and loss in lower limb muscles (Berry *et al.* 1993). In another 28-day HDBR experiment, daily LBNP sessions of 15 min duration at –30 mmHg were performed during the third and fourth week in combination with muscular exercise. The exercise consisted of combined graded dynamic and isotonic leg exercises performed daily in two sessions of 15-20 min each, six days per week. These countermeasures also improved orthostatic tolerance (Pavy-Le Traon *et al.* 1995), but the effects of LBNP and muscular exercise could not be easily dissociated. There was probably a combined action on plasma volume (Maillet *et al.* 1996).

LBNP sessions require a compromise between duration and pressure level. A pressure of –30 mmHg is well tolerated, but pressures of –40 to –50 mmHg better simulate the upright position. However, the possibility of the subject fainting due to reduced blood pressure at the head level prohibits prolonged static LBNP exposure above –50 mmHg.

Both bed rest and spaceflight reduce exercise fitness because of cardiovascular deconditioning and muscular atrophy. The bed rest experiments have confirmed the advantage of combining LBNP with other countermeasures, in particular muscular exercise. As a result, during the last few years, U.S. scientists, including investigators from NASA Ames Research Center, have been testing the effects of muscular exercise in conjunction with LBNP sessions during bed rest experiments. LBNP combined with treadmill exercise in supine subjects provides both cardiovascular and musculo-skeletal stimulation. First, Murthy *et al.* (1994a, 1994b) compared exercise of 5 min duration in a supine position within an LBNP chamber with pressure -100 mmHg to 5 min of exercise in the upright position. The authors concluded that this combination of exercise and LBNP produces the same musculo-skeletal stress in the legs and greater cardiovascular stress than exercise in the upright position. Lee *et al.* (1997) showed that 30-min bouts of intense upright interval exercise training or supine exercise on a treadmill against a LBNP of –52 mmHg followed by five min of static LBNP was sufficient to maintain upright exercise training after five days of bed rest. Watenpaugh *et al.* (2001) also reported beneficial effects on exercise performance resulting from 40 min of supine exercise per day in a LBNP chamber at –52 mmHg during a 15-day HDBR study. However, the same team recently reported that moderate exercise performed against a –52 mmHg LBNP without post-exercise static LBNP failed to protect orthostatic tolerance after 15 days of bed rest (Schneider *et al.* 2002). This combined LBNP and exercise followed by a post-exercise static LBNP has been recently evaluated in a 60-day HDBR in women (Hargens et al 2006).

6.2 Effect of Standing or Walking during Bed Rest

The simplest way to study the role of +Gz exposure as a countermeasure during simulated weightlessness is to have the subjects stand upright during brief periods throughout the bed rest period. Vernikos *et al.* (1996) executed a series of five four-day experiments conducted using the same nine male volunteers to assess the effectiveness of intermittent exposure to passive (standing) and active (walking) 1 g along the body +Gz direction. The subjects were instructed to walk or stand for a total of two or four hours per day in 15-min increments hourly. During a following HDBR, the subjects remained in bed as control. Maximal oxygen uptake and orthostatic tolerance were assessed during a 30-min 60° head-up tilt test both before and after the HDBR study. The main conclusions were:

a. Standing completely (4 h) or partially (2 h) prevented the post HDBR orthostatic intolerance.
b. Walking (2 h and 4 h) and standing (4 h) attenuated the decrease in peak oxygen uptake.
c. Standing (4 h) and walking (4 h) attenuated plasma volume loss.
d. Walking (2 h and 4 h) attenuated the increase in urinary calcium excretion.

The authors of these studies attributed different benefits derived from passive or active 1-g exposure according to the physiological system. They also point out that, in addition to their duration, the number of exposures to postural stimuli may be an important factor (Vernikos *et al.* 1996, 1997).

Also worth mentioning here is the study by Hastreiter and Young (1997) who have investigated the effects of a gravity gradient on human cardiovascular responses. Eight subjects were supine on a 2-m radius centrifuge with the top of their heads at the center of rotation. Acceleration levels at the feet ranged from 0.5 to 1.5 g for one hour. Measurements of heart rate, calf impedance, calf volume, and blood pressure indicated that 1.5 g at the feet was similar to standing, but that 0.5 g at the feet failed to produce significant effects.

7 THE TWIN BIKE SYSTEM

To overcome some of the drawbacks of a short-radius centrifuge, in particular the needs for external power and the considerable mass of the motor and its associated electronics, a human powered device called the *Twin Bike System* (TBS) has been proposed (Figure 5-06). The TBS is a short radius human-powered centrifuge consisting of two coupled bicycles, ridden by two astronauts counter-rotating along the inner wall of a cylindrical space module (Antonutto *et al.* 1991, Di Prampero and Antonutto 1996, 1997, Di Prampero 2000). The objectives of the TBS are essentially for the astronauts to perform physical exercise and to re-create artificial gravity along the +Gz direction while performing this exercise. Because the two subjects move along a circular path, they generate a centripetal acceleration (A_c) oriented along their body axis, the module of which is equal to

$$A_c = v^2 / r, \qquad [2]$$

where v is the peripheral tangential velocity and r is the inner radius of the space module.

Thus, for a given r value, A_c can be modulated by changing v. For instance if r = 2 m, as in a conventional space module, the v yielding 1 g at the foot level is equal to 4.5 m/s (Antonutto *et al.* 1991). Assuming that the forces opposing motion, the air and rolling the resistances, are the same as observed on Earth at P = 760 mmHg, T = 293°K, and for a knobby tired bicycle moving on a concrete surface (Di Prampero 2000, Capelli *et al.* 1993). The corresponding mechanical and metabolic powers can be calculated for these conditions. These amount to 75 W and to 1.2 LO_2/min. It goes without saying that if r is increased from 2 m to 6 m, the velocity yielding A_c = 1 g at the feet will increase to 7.7 m/s in this specific instance, and the corresponding mechanical and metabolic power will rise to 240 W and to 3.05 LO_2/min.

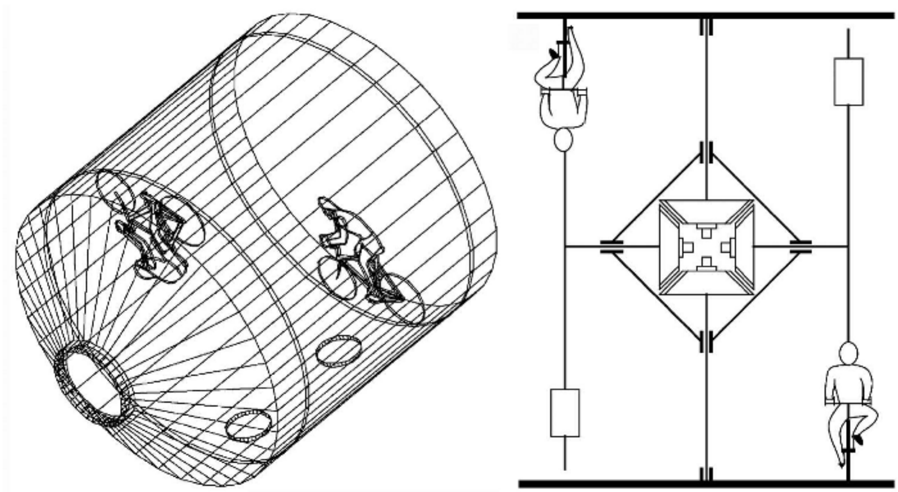

Figure 5-06. In the Twin Bike System*, two mechanically coupled counter-rotating bicycles move along the cylindrical walls of a space module. The angular velocity of cycling then determines the level of artificial gravity along the rider's longitudinal body (Gz) axis. To avoid counter-rotation of the space module, the two cyclists move at the same speed, but in opposite directions. They are coupled by a differential gear (drawn on a larger scale). Two adjustable masses prevent the repetitive yaws that would otherwise occur when the two bicycles cross on the same side of the space module. The wheels run on parallel rails providing the initial friction. Thick lines indicate the space module walls. (Antonutto* et al. *1991, Di Prampero 2000).*

The mechanical and metabolic powers depend on the air density prevailing inside the space module and on the wheels to rail friction, itself a function of A_c. As a first approximation, the latter accounts for a minor fraction of the mechanical and metabolic power, which is mainly set by the air resistance and the peripheral speed. It is likely that the rotation of the two exercising subjects will move also the inner atmosphere of the space module, thus reducing the aerodynamic drag. This effect could be compensated by increasing the rolling resistance by means of a mechanism of feedback friction acting on the central coupling gear or on the wheels of the bicycles.

Moreover, because the inner radius of the space module is of the same order of magnitude as the stature of the pedaling subjects, a head-to-foot acceleration gradient will be established along their body axis because, when riding the TBS, their heads will be closer to the rotation center, as compared to their feet. The ratio of A_c at the feet to A_c at the head, will be equal to five for $r = 2$ m and to 1.5 for $r = 6$ m.

The TBS ought to be effective in protecting against cardiovascular deconditioning because the weight of the blood column induced by A_c will act, as is the case on Earth, throughout the circulatory system. On board the space module, when riding the TBS, the hydrostatic component ΔP will be equal to

$$\Delta P = \rho\, A_c\, h. \qquad [3]$$

Therefore, because for a given v, A_c increases from head to foot, ΔP depends on the level within the circulatory system, the distance from heart because of (a) the geometrical term h, and (b) the local value of A_c, itself depending on r and hence, once again, on the distance from the heart. This can be expressed formally as follows. For a given constant v, the angular velocity ω (rad/s) is also constant. Because $v = \omega$ r, it follows from Equation [2] that $A_c = \omega^2$ r. The average A_c between any two points at distances r_1 and r_2 from the center of gyration is given by

$$A_c = (\omega^2\, r_1 + \omega^2\, r_2) / 2 = [\omega^2\, (r_1 + r_2)] / 2. \qquad [4]$$

The hydrostatic pressure gradient between the two points can be therefore calculated substituting h with (r_2-r_1) and rearranging to obtain equations [5] and [6].

$$\Delta P = \rho\, [\, \omega^2\, (r_1 + r_2)] / 2 \bullet (r_2 - r_1) \qquad [5]$$

$$\Delta P = \rho\, \omega^2\, (r_1^2 - r_2^2) / 2 \qquad [6]$$

Taking r_2 to be at heart level, Equation [6] permits us to calculate the arterial pressure at any given point in the circulatory system, provided that the pressure at heart level is known. For A_c = 1 g at the subject's feet and an average pressure of 100 mmHg at the aortic arch, the average arterial pressures at the head and foot levels will be 95 and 150 mmHg, if r = 2 m and 80 and 170 mmHg, if r = 6 m, respectively.

Because of the ergonomic design of the TBS, the centrifugal force due to the mass of the upper part of the subjects' bodies is supported by the frames of the bicycles. On the contrary, the lower limbs will sustain only a force equal to their own mass times A_c. Therefore, whereas the spine supports the upper part of the body, as is the case on Earth, femurs and tibiae are mechanically stimulated only by their own weight and by the forces generated by the muscle action during pedaling, a fact which somewhat reduces the effectiveness of the TBS in counteracting bone demineralization.

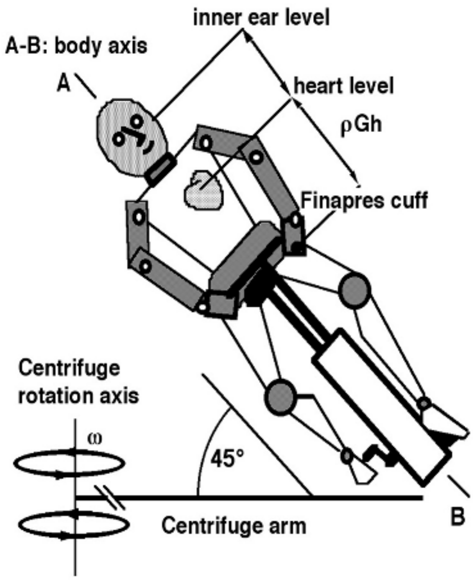

Figure 5-07. On-Earth simulation of the TBS. Schematic view of the subject exercising on the cycle ergometer fixed on the arm of the human centrifuge of the Karolinska Institute of Stockholm. The cyclo-ergometer was inclined by 45 deg and the angular velocity (ω in rad/s) of the centrifuge was equal to that required in the TBS to attain 1 g at the subject's feet level. This resulted in a horizontal vector G whose module was equal to 1.41 g ($G = (Ac^2 + g^2)^{1/2}$), applied at the subject's inner ear and aligned along his body axis. For further details see Antonutto et al. *(1993, 1994).*

Slight head movements during cycling on the TBS may lead to vestibular disturbances due to the Coriolis and cross-coupled angular acceleration generated by the head movements out of the plane of rotation. According to Benson (1988), the resulting sensory conflict is the major cause of acute motion sickness. To test the capability of TBS to induce motion sickness, a model of the TBS has been realized on Earth using the human centrifuge located in the Karolinska Institute at Stockholm (Antonutto *et al.* 1993), as shown in Figure 5-07. Six healthy males pedaled on a cycle ergometer inclined 45° and fixed to the arm of the centrifuge at 2.2 m from the center of rotation, essentially equal to the radius of a conventional space station module. Because $A_c = \omega^2 r$, the centrifuge rotation rate to yield A_c = 1 g at the inner ear level of the pedaling subject was 21 rpm. The vectorial sum of A_c plus the Earth gravity resulted in 1.41 g applied at the subject's inner ear and aligned along his body axis.

All subjects pedaled for at least 20 min at 50 W during centrifuge rotation, i.e., at a mechanical power slightly less than that required on the TBS to yield 1 g at the feet level (r = 2 m, see above). To assess their motion sickness susceptibility, the subjects were asked to move their heads according to a protocol involving various degrees of rolling, pitching, and yawing. Movements were repeated with eyes open and eyes closed. Only one subject out of six suffered of mild motion sickness symptoms, scoring 3 out of a maximum of 16 according to the scale proposed by Lackner and Graybiel 1986. The symptoms worsened with eyes opened but, in any case, they disappeared rapidly after the end of the runs.

This confirms that the discomfort deriving from the rotating environment necessary to generate artificial gravity is reasonably low and well tolerated. Considering that the TBS does not need any external power, being operated by the space crews themselves, and that a gravity threshold lower that 1 g is likely to be sufficient to reduce the deconditioning due to microgravity, we strongly endorse further studies on the possibility of practically realizing the TBS system.

8 CONCLUSION

The above review of the physiological aspects and the use of artificial gravity as a countermeasure for the cardiovascular system raises several questions. The first is the definition of the objectives of a countermeasure prescription, whether it is artificial gravity, exercise, or something else. For the cardiovascular system, should the objective of the countermeasure prescription be to maintain the cardiovascular function as it was before flight or simulated weightlessness, or to maintain the physiological function required for a minimum safety level without compromising the long-term health of the astronaut?

Another question is how should the efficiency of the centrifugation on the cardiovascular function be assessed? As shown in the literature review, different tests have been used to assess cardiovascular function after simulated weightlessness experiments. Standardization of these tests and the main evaluation criteria would facilitate the comparison of the experimental data and are required for the realization of multi-centric studies. In addition, cognitive and psychological aspects must also be considered.

Then, there is the fundamental question: how much artificial gravity, i.e., what level, duration, and frequency, are needed to prevent cardiovascular deconditioning? We believe that, for practical reasons, the duration of intermittent artificial gravity exposure should be less than the current duration of exercise imposed on a long-duration crew, i.e., less than two hours per day. There is no data on human physiological responses to gravito-inertial forces comprised between 1 g and 0 g. However, the studies described above using short-radius centrifugation indicate that intermittent centrifugation at levels of

0.8 g to 4 g prevents cardiovascular deconditioning after bed rest. In most experiments, the gravity level ranges from 1.2 g to 2 g with a time exposure from 30-120 min.

In these studies, the number of exposures to centrifugation ranged from one to four per day, depending on the artificial gravity level and the duration of each exposure. Two exposures per day were more frequently used. Centrifugation exposures executed in several shorter time periods instead of one longer one are likely to improve both the efficiency and the tolerance of the centrifugation by the astronaut. This aspect must be defined taking into account operational constraints. During one single session, an intermittent exposure to centrifugation may improve its efficiency. Some particular physiological effects of short-radius centrifugation, such those due to the gravity gradients however, must be clarified.

One thing is certain. There is a limitation in the cardiovascular tolerance to centrifugation. This limit depends on the g-level and the duration of exposure. An artificial gravity level at or exceeding 2 g may raise some tolerance issues. Wearing an anti-gravity suit or other countermeasure would be required if higher gravity levels or longer duration of centrifugation were to be applied. Combining exercise with centrifugation may affect this tolerance level, but this is unknown. Most studies on the effects of centrifugation and its tolerance were performed on healthy male subjects. Gender may influence tolerance and centrifugation efficiency, as might physical fitness.

This consideration brings us to another, more operational, issue: How should the artificial gravity prescription be applied in accordance with the flight schedule and return to Earth? No data addressing this aspect have been collected yet. Concerning the cardiovascular system, the exposures could be more frequent at the end of the mission to prepare the return to Earth, in the same way it has been applied for LBNP during spaceflights and bed rest studies. However, this aspect will be probably less relevant if centrifugation is also used to prevent other long-term physiological changes like bone changes.

There is evidence that a combination of centrifugation and other countermeasures is likely to yield more protective effects. The studies performed with short-radius centrifuges during bed rest and dry immersion have indicated potential value-added by combining centrifugation with exercise, or with water and salt supplement. Combining centrifugation with exercise will also undoubtedly contribute to reducing muscle atrophy and bone changes. The potential benefits of human powered centrifuges, such as the *Twin Bike System,* or similar systems developed at NASA-Ames (Greenleaf *et al.* 1997) and at the University of California-Irvine (Caiozzo *et al.* 2004) (see Chapter 3, Section 3.3), definitely need to be further investigated.

The downsides of the subjects doing head and body movements while exercising on the centrifuge device are the motion sickness and altered coordination resulting from the Coriolis and cross-coupled angular accelerations. Motion sickness, however, could be reduced if subjects are restricted from moving their heads, or if they are pre-adapted to this type of conflicting stimuli (Young *et al.* 2001).

Whereas the validation of artificial gravity prescription for long-term space missions will eventually need to be performed during spaceflight, the effects of most criteria could be investigated during ground-based studies on Earth. The effects of centrifugation combined with exercise and other means on cardiovascular deconditioning could be assessed in simulations lasting from a few days. A step approach for these studies is proposed in Chapter 7. However, the assessment of other physiological systems, in particular muscle atrophy and bone integrity, would presumably require longer duration experiments.

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Chapter 6

PHYSIOLOGICAL TARGETS OF ARTIFICIAL GRAVITY: THE NEUROMUSCULAR SYSTEM

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Skeletal muscle is highly adaptable, responding to the stresses placed upon it. These demands vary from growth, the maintenance of posture, extreme athletic performance to the repair of injury. In addition to these positive physiological responses, skeletal muscle declines in mass and function with age, disuse, starvation, and disease. This chapter focuses specifically on the effects of microgravity on muscle structure, function, and neuromuscular control. The role and effectiveness of the most commonly used countermeasures during bed rest and spaceflight, including aerobic training, resistive training, electrical muscle stimulation, low body negative pressure training, and various means of achieving artificial gravity are discussed.

Figure 6-01. The human centrifuge situated in the Karolinska Institute in Stockholm is used for studying the tolerance to angular and linear accelerations, the muscular and cardiovascular responses to artificial gravity, and the susceptibility to motion sickness. Photo courtesy of Dag Linnarsson.

1 EFFECTS OF DETRAINING AND INACTIVITY ON MUSCLE SINGLE FIBER

1.1 Structure

Disuse in microgravity and on Earth leads to a rapid decrease in muscle mass. This information has been obtained using variable disuse paradigms, spaceflight, limb suspension, immobilization, and bed rest. In animals, the magnitude of atrophy is generally fiber-type specific. Postural muscles normally containing a higher proportion of type I slow fibers, such as the *soleus*, *vastus intermedius* and *adductor longus* are more prone to atrophy than non postural muscles with a higher proportion of type II fast fibers, such as the *tibialis anterior* and extensor *digitorum longus* (Roy *et al.* 1987, Ohira *et al.* 1992, Tischler *et al.* 1993). In rats a decrease in muscle mass up to 37% has been found after just one week of spaceflight (Russian Cosmos and US Shuttle missions).

In humans, based on observations made during short-term spaceflight, it has been suggested that type II fibers are at least as, if not more so, susceptible to atrophy than type I fibers (Fitts *et al.* 2001). For instance, type II fibers of the *vastus lateralis* (VL) muscle were found to display greater atrophy that the type I fibers after an 11-day spaceflight (Edgerton *et al.* 1995). Similarly, after a 17-day Space Shuttle flight (STS-78), *soleus* (SOL) muscle type II fiber *cross-sectional area* (CSA) was reduced by 26% but only by 15% for the type I fibers (Widrick *et al.* 1999).

However, quite a different picture emerges when recent data from prolonged bed rest are analyzed. After 12 weeks of bed rest, type I and type II fiber CSA respectively decreased by 35% and 20% in the VL muscle, and by 42% and 25% in the SOL muscle (Rudnick *et al.* 2004). Similarly, after 84 days of bed rest, VL-type I fibers diameter decreased by 15% while that of type II fibers decreased by 8% (Trappe *et al.* 2004). Therefore it seems that, like in rats, human type I fibers are more susceptible to disuse-atrophy than type II fibers.

1.2 Myosin Heavy Chain

In response to spaceflight and hind limb suspension in rats, a shift from slow to fast *myosin heavy chain* (MHC) isoforms occurs (Baldwin and Haddad 2001). These adaptations involve a down-regulation of the slow type I MHC, together with a *de novo* expression of the fast type IIx MHC. Recent data obtained during a 84-day bed rest study show that this shift towards the faster fiber phenotype also occurs in humans, resulting in a 2.8-fold increase in the typeI/IIa MHC ratio (Trappe *et al.* 2004). Furthermore, as found in rats, the proportion of hybrid fibers co-expressing more that one isoform considerably increases. Before bed rest, the total proportion of hybrid fibers was 13-14%, whereas after bed rest, the number of hybrid fibers increased to 49% (Trappe *et al.* 2004).

These transformations of MHC from slow to fast isoforms that are observed with bed rest and hind limb suspension are qualitatively similar to those observed in animals and humans following spinal chord injury (Andersen *et al.* 1996) or spinal transection (Talmadge *et al.* 1999). These observations also show that the fast MHC is the default phenotype towards which fibers, in the absence of innervation or following prolonged inactivity, tend to. However, in humans, the time course of these MHC transformations is about three times as long as in animals (10 months versus 3 months) (Baldwin and Haddad 2002).

1.3 Contractile Properties

Both animal and human data show significant alterations in single fiber contractile properties as a result of exposure to actual or simulated microgravity. These changes concern the following contractile parameters: (a) peak force (Po), (b) peak force/CSA (Po/CSA), (c) maximal unloaded contractile velocity (Vo), and (d) force-power characteristics.

1.3.1 Maximum Isometric Force (Po) and Specific Tension (Po/CSA)

Peak force of rat *soleus* single fibers has been found to decrease by 25% and 45% after 14 (Cosmos 2044) and 18.5 days of spaceflight (Cosmos 936 and 1129), respectively (Fitts *et al.* 2000). Scant data exists on the effects of spaceflight on rat single fiber Po/CSA. However, hind limb suspension experiments show a significant decrease in Po/CSA with unloading. After just seven days of a 3-week hind limb suspension study in rats, Po/CSA was found to decrease by 17% (McDonald and Fitts 1995). Similarly, in humans, Po/CSA of *soleus* fibers decreased by 4% after a 17-day spaceflight that included in-flight countermeasures (Widrick *et al.* 1999). These findings are also confirmed by the results of prolonged unloading in humans showing a 40% and ~25% reduction in MHC I fiber Po/CSA after 42 and 84 days of bed rest, respectively (Larsson *et al.* 1996, Trappe *et al.* 2004).

The reasons for this decline in single fiber specific tension (Po/CSA) have been attributed to a reduction in myofibrillar protein density, suggesting a reduction in the number of cross-bridges rather than in the force exerted by each cross-bridge (D'Antona *et al.* 2003). It seems unlikely that the decreases in specific tension were due to a selective loss of actin, which was observed in spaceflight and suspected to cause an increase in lattice spacing, because Po/CSA has been found to be maintained even in the presence of selective actin loss (Widrick *et al.* 1999). However other mechanisms, such as calcium kinetics or fiber damage, cannot be excluded.

1.3.2 Maximum Unloaded Velocity (Vo)

Judging from the shifts in MHC composition, changes in Vo are to be expected. As a matter of fact, both rat and human experiments have shown an increase in Vo of the calf muscle following spaceflight (Caiozzo *et al.* 1996, Widrick *et al.* 1999). This effect on Vo is very pronounced. After just 6 and 14 days of spaceflight, rat *soleus* Vo increased by 14% and 20%, respectively. These effects were associated with an increased expression of type IIx MHC isoforms and with a decreased expression of type I MHC isoform.

In humans, Widrick *et al.* (1999) reported an increase in *soleus* fiber Vo and Vmax of 30% and 44%, respectively, after 17 days of spaceflight (Space Shuttle mission STS-78). This increase in both Vo and Vmax indicates that the increase in shortening velocity of the plantar flexors is not simply due to an increased expression of IIx fibers but also to a change in shortening velocity of the individual fibers (Fitts *et al.* 2001).

The actual cause of the increased in Vo and Vmax is still unclear, but it may be related to a disproportionate loss of actin found to occur in rats with microgravity exposure (Riley *et al.* 2000). It has been suggested that the selective loss of actin would lead to an increase lattice in spacing. As a result, the cycling cross-bridges would be expected to detach sooner, and because of a reduction in internal drag, the Vo would increase (Riley *et al.* 2000).

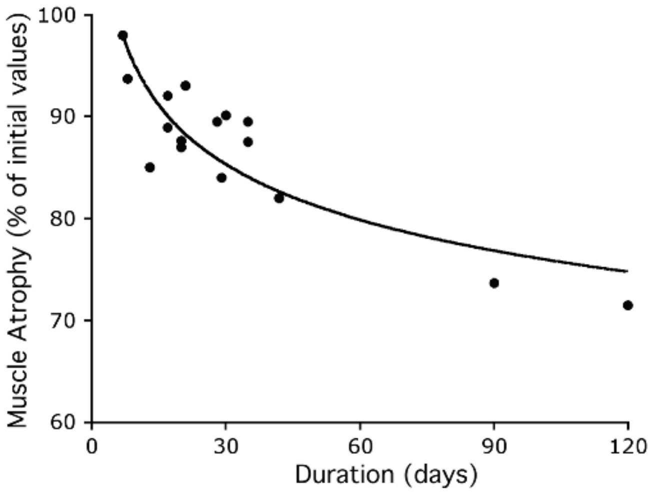
However, conflicting findings are noted in prolonged bed rest. Trappe *et al.* (2004) reported a 21% and 6% decrease in MHC I and IIa fibers of the human *vastus lateralis* after 84 days of bed rest. Despite being in contrast with the observations of Widrick *et al.* (1999) and of Yamashita-Goto *et al.* (2001), these results are in agreement with those of Larsson *et al.* (1996) and of Widrick *et al.* (2002). Upon scrutiny of these studies, it appears that increases in Vo were present mainly when the subjects performed physical countermeasures, whereas a decrease in Vo seems to be found when no countermeasures were used (Trappe *et al.* 2004). These authors therefore concluded that muscle activity plays an important part in modulating shortening velocity.

1.3.3 Peak Power

In both rat and human, single fiber peak power has been found to decrease after actual and simulated microgravity. In rats, *soleus* muscle peak power decreased by 16-20% after 6-14 days of spaceflight (Caiozzo *et al.* 1996). This decline occurred despite a 14-20% increase in Vmax, indicating that the loss of muscle power was consequential to the loss in force. Scant evidence is available on the effect of spaceflight on human single fibers. Nevertheless the results obtained by Widrick *et al.* (1999) during a 17-day Space Shuttle mission show that peak power of *soleus* type I fibers declined by about 20% in two crewmembers. In two others, the increase in Vmax was high enough to compensate for the loss of force, and as a result peak power was not different from preflight values.

A clearer picture emerges from the Toulouse bed rest study (ESA LTBR 2000-1). In six subjects undergoing bed rest with no countermeasures, the composite single muscle fiber power of the *soleus* muscle decreased by 23%, whereas in six subjects performing regular flywheel resistive countermeasures, peak power was maintained. This finding suggests that resistive exercise plays an important role in maintaining muscle power by increasing Vo.

Figure 6-02. Calf muscle atrophy due to unloading in actual microgravity during spaceflight or simulated micro-gravity during unilateral lower limb suspension or during bed rest.



2 EFFECTS OF DETRAINING AND INACTIVITY ON THE WHOLE MUSCLE

2.1 Structure

The results of studies performed in simulated or actual microgravity consistently show that human and animal muscles undergo substantial atrophy, due to a decrease in fiber size, with no change in fiber number (Roy *et al.* 1987, Templeton *et al.* 1984, Thomason and Booth 1990). These studies also show that in humans, atrophy is considerably greater for postural muscles, i.e., for those muscles that on ground support the weight of the body, as compared to non-postural muscles, which do undergo only marginal changes. In addition, substantial differences also exist among the postural muscles themselves. In general the plantarflexors of the ankle, the *gastrocnemius medialis*, *lateralis*, and *soleus*, undergo the largest decrease in volume, followed in decreasing order by the dorsiflexors, the (*tibialis* *anterior*), the knee extensors, the knee flexors and the intrinsic lower back muscles (LeBlanc *et al.* 1988, LeBlanc *et al.* 1997).

Whereas common agreement exists regarding this general picture, the time course of atrophy is less well documented. On the whole, the picture resulting from the results of bed rest studies, combined with those obtained by other unloading models, such as lower limb suspension (Convertino *et al.* 1989, Berg *et al.* 1991, Hather *et al.* 1992, Adams *et al.* 1994) suggests that atrophy is described by an exponential function of time (Figure 6-02), such that after about 120 days of simulated microgravity the muscle mass attains at a constant value of about 70% of the initial one. As a matter of fact, the findings from the 90-day bed rest study performed in Toulouse (ESA-LTBR 2001-1) show a 30% loss of calf muscle mass after bed rest (Figure 6-03). Thus, this process may be even faster than predicted from the analysis of the above cross-sectional data.

This observation generates considerable concern, because from a clinical point of view a loss of lean body mass greater than 40% is associated with an increased risk of death (Roubenoff 2001). These considerations are derived from data obtained on the postural muscles of the calf in humans during bed rest studies of a maximal duration of 120 days without countermeasures. As such, their application to actual flight with countermeasures, or with high-intensity physical activity, is unwarranted.

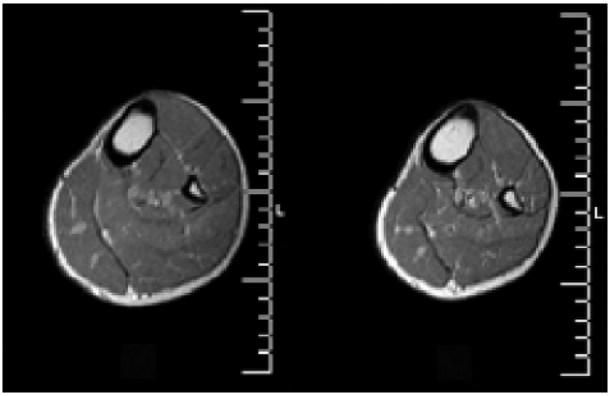


Figure 6-03. MRI images of the calf muscles taken before (left) and after 90 days of bed rest (right). Atrophy of the extensor muscles is most evident when comparing the two images.

For simulated or actual microgravity, animal and human muscle atrophy is due to an imbalance between the rate of protein synthesis and the rate of degradation (Gamrin *et al.* 1998). Indeed, during the first two weeks of hind limb suspension in rats, protein synthesis decreases and protein degradation increases. In the following two weeks, the equilibrium between synthesis and degradation is achieved again, thus stabilizing muscle protein content, albeit at a lower level than before hind limb suspension (Loughna *et al.* 1987, Thomason *et al.* 1989).

In humans, data obtained both during spaceflight and bed rest suggest that the loss of muscle mass is due to a depression in protein synthesis rather than an increase in breakdown. Indeed, after three months on board the Mir space station, whole-body protein synthesis decreased by 45% as compared to preflight values (Stein *et al.* 1999). At the same time, protein breakdown, which is indirectly assessed from the rate of appearance in the blood of 3-methylhistidine, was actually found to decrease in flight. Hence, it seems that the loss of muscle mass during spaceflight is due to a decrease in protein synthesis rather than to an increase in protein breakdown (Ferrando *et al.* 2002). Even if the effects of a decreases dietary intake may not be ruled out, there is evidence of a direct effect of microgravity *per se* on protein synthesis. Indeed, experiments performed on cultured avian muscles cells during spaceflight showed that microgravity directly depressed protein synthesis (Vandenburgh *et al.* 1999).

These observations of changes in protein turnover with spaceflight are similar with those made during short-term bed rest. After 14 days of strict bed rest in young healthy volunteers, whole body protein synthesis was found to decrease by 14% and skeletal muscle protein synthesis by ~50% (Ferrando *et al.* 1996). This depression in protein synthesis by inactivity was also demonstrated by investigating the stimulation in protein synthesis in response to amino acid infusion during 14 days of strict bed rest (Biolo *et al.* 2004). During bed rest, the net leucine deposition (synthesis minus breakdown) into body protein was 8% lower than that observed in ambulatory subjects, highlighting the reduction in protein anabolism caused by bed rest.

2.2 Muscle Architecture

Similar to what is observed in senile sarcopenia (Narici and Maganaris 2006), disuse atrophy in humans also entails a decrease in fascicle length and in pennation angle (Kawakami *et al.* 2000, Bleakney and Maffulli 2002, Narici and Cerretelli 1998, Reeves *et al.* 2002). After 90 days of strict bed rest in healthy young males, which is the longest bed rest study of those listed, pennation angle and fascicle length of the GAS muscle were found to decrease by 10% and 13%, respectively, in those participants not performing exercise countermeasures (Reeves *et al.* 2002).

In the same study, it was always the case that those participants performing countermeasures, which comprised high-intensity resistive exercise performed every three days, showed only a partial mitigation of muscle atrophy and changes in muscle architecture were only marginally smaller than those of the no-exercise group that experienced a 7% decrease in fascicle length and 13% decrease in pennation angle, indicating that a greater volume of exercise would be required to prevent GAS atrophy.

These findings suggest that changes in muscle architecture associated with disuse involve a loss of sarcomeres both in parallel (reduction in muscle

CSA) and in series (reduction in fascicle length) and as such would be expected to play a significant role in the loss of muscle force and power observed after prolonged disuse.

2.3 Force and Power

Several studies have reported substantial decreases in muscle strength after bed rest or after other simulation models in humans (LeBlanc *et al.* 1988, Berg *et al.* 1991, Berg *et al.* 1993, Berg and Tesch 1996, Berg *et al.* 1997). After 42 days of bed rest, the maximal strength of the lower limbs muscles was decreased by about 30%, independent of the angular velocity (Berg and Tesch 1996). No changes in time to peak tension or in half-relaxation time were found after 17 days of bed rest (Narici *et al.* 1997), whereas in the same conditions the ratio of tetanic force to CSA significantly decreased (8 and 13%, respectively). The decrease of the ratio between tetanic force and CSA was previously observed (LeBlanc *et al.* 1988, Dudley *et al.* 1989, Berg and Tesch 1996) and may due to: (a) a reduction in fiber specific tension due to a decrease in myofibrillar density (Larsson *et al.* 1996); (b) a reduction in motor drive to the muscle (Duchateau 1995, Berg and Tesch 1996, Koryak 1998); (c) a reduction of the "efficiency" of the electromechanical coupling (Milesi *et al.* 2000); and (d) an increase in the amount of non-contractile tissue (Riley *et al.* 1992).

After the Skylab missions the maximal force of several muscle groups (*quadriceps*, trunk flexors and extensors) showed a decrease from 6.5% to 25% as compared to preflight depending on the muscle group and on the duration of the flight. Because during these missions the crews performed physical exercise to prevent muscular deconditioning, these results are difficult to interpret in terms of underlying muscle fiber function.

This substantial decline of muscle force after spaceflight is accompanied by an even greater fall of maximal muscle power. Indeed, data obtained before and after the Euromir-94 and -95 missions on five astronauts indicated that the maximal explosive power of the lower limbs, as determined during maximal "all-out" pushes on a force platform was reduced to about 67% after 31 days and to about 45% of preflight values after 180 days (Antonutto *et al.* 1991, Antonutto *et al.* 1998, Antonutto *et al.* 1999).

At variance with these data, the maximal power developed during 6-7 seconds all-out bouts on a cycle ergometer was reduced to a lesser extent, attaining about 75% of preflight values, regardless of the flight duration. Because of the fact that in the same subjects, the muscle mass of the lower limbs decreased only 9-13%, irrespective of the flight duration, these data suggest that a large fraction of the decline of the maximal power, at least during the very short "explosive" efforts, may be due to the effects of weightlessness on motor unit recruitment pattern, electromechanical efficiency and predisposition to muscle damage (Antonutto *et al.* 1998, Antonutto *et al.* 1999, Di Prampero and Narici 2003).

This hypothesis is similar to that put forward by other authors and defined as *hypogravitational ataxia* (Grigoriev and Egorov 1991). This large fall of maximal explosive power seems to be a characteristic of spaceflight that may not be easily reproduced by bed rest. Indeed, after 42 days of strict bed rest, the maximal explosive power was reduced to 76% of preflight in and average of six subjects (Ferretti *et al.* 2001) compared with 67% after 31 days of spaceflight featuring two hours of exercise per day (see above).

These observations support the hypothesis that the absence of gravity, favoring smooth and delicately balanced muscle actions, brings about a substantial rearrangement of the motor control system that is responsible, at least to a large extent, for the observed decline in the maximal explosive power during all-out short lasting muscle actions. This rearrangement does not seem to manifest itself or, if it does, to be markedly less effective after bed rest wherein the pull of gravity is not abolished, but simply shifted by 90 degrees (Di Prampero and Narici 2003).

2.4 Muscle Energy Metabolism

Skeletal muscle fiber types can be differentiated into three main classes: type I or slow-twitch-oxidative, type IIA or fast-twitch-oxidative-glycolytic, and type IIX (previously called IIB) or fast-twitch-glycolytic. Various intermediate forms can be found, probably showing transition forms occurring in the adaptation to altered mechanical loading (Bottinelli and Reggiani 2000, Bottinelli 2001). Muscle biopsy samples analyzed for activities of enzymes typical for different metabolic pathways can be used to study the specific adaptations of different muscle fiber types to training or unloading. Alternatively muscle energy metabolism can be examined as a whole by non-invasive methods like *31P-magnetic resonance spectroscopy* (31P-MRS).

In human leg muscle bed rest and limb suspension studies, both performed without exercise countermeasures, a decreased specific capacity of mitochondrial enzymes and no or only small and varying changes on glycolytic enzymes was observed (Hikida *et al.* 1989, Dudley *et al.* 1992, Hather *et al.* 1992, Berg *et al.* 1993, Ferretti *et al.* 1997). Muscles of different fiber type composition react quantitatively different, but show the same qualitative pattern.

Only one study has investigated 31P-MRS data from leg muscle before and after prolonged bed rest (Berry *et al.* 1987). After one month bed rest, PCr consumption for a given workload seem to be increased as shown by a pronounced increase in the phosphate/phosphocreatine ratio during exercise. This effect of bed rest could be avoided by countermeasure exercise on an isokinetic dynamometer (LIDO) device.

Biochemical and histological studies on the energy metabolism of human muscle in spaceflight are few. This is because of the invasive nature of biopsy analysis. It was shown that short-term spaceflight of 5 and partly 11 days duration (Edgerton *et al.* 1995) performed without exercise countermeasures does not result in a change in mitochondrial enzyme activity; however, an increase in glycolytic enzymes in slow fibers, but not in fast fibers, is induced.

Long-term spaceflight performed on board Mir and ISS includes an obligatory exercise countermeasure program of about two hours treadmill running or velo-ergometer cycling per day (see Chapter 1, Section 5.1). In non-invasive 31P-MRS examinations on the calf muscle of astronauts before and after a 3.5-week (N=1) or 6-month (N=3) spaceflight, no indications of changes in the glycolytic or the aerobic work capacities were found (Zange *et al.* 1996, Zange *et al.* 1997). Parallel examinations of biopsy samples from *vastus lateralis* in the same subjects also did not show any significant changes in the percentage of fiber types. However, the consumption of phosphocreatine at a given workload determined by 31P-MRS was significantly increased in the initial phase of contraction. This indicates a reduced metabolic efficiency of muscle contraction after spaceflight. Final explanations of these phenomena will require knowledge of other processes as well, such as changes of fiber type recruitment pattern.

Nevertheless, changes in energy metabolism do not contribute to muscle weakness caused by spaceflight. Moreover, exercise intolerance after six months onboard Mir was characterized by a reduced ability to deplete the phosphocreatine pool by voluntary contraction (Zange *et al.* 1996, Zange *et al.* 1997). More work is needed in this area, in particular concerning the evaluation of ATP turnover at different exercise levels in relation to actual work output. Apart from muscle fiber type content, the effect of fiber type recruitment in such studies needs further evaluation.

In rat muscle, the effects of unloading on energy metabolism have been studied in the scope of simulation studies and in actual spaceflight. The effects observed in different types of leg or tail muscles were varying in quantitative terms. However, in tail suspension, a common unloading simulation model, it was generally observed that atrophy occurs in all types of muscle fibers. A decrease in the mitochondrial density or in the activity of mitochondrial enzymes and an increase in the capacities of glycolytic enzymes was a frequent, but not general observation that predominantly occurred in slow fibers (Chi *et al.* 1992, Musacchia *et al.* 1992, Ohira *et al.* 1992). These modifications in oxidative and glycolytic capacities support the hypothesis that tail suspension may induce a transition towards less oxidative fiber types in rat leg muscle. This has recently been confirmed by examinations on gene regulation in rat *soleus* muscle after tail suspension (Stein *et al.* 2002). The expression of carnitine palmitoyltransferase I and II, as a marker of oxidative metabolism of fatty acids, was reduced; whereas, the expression of three glycolytic enzymes was increased.

In spaceflight, rat muscles show no or smaller reductions in the capacity of oxidative enzymes in comparison with the immobilization model. The increase in glycolytic capacities was less pronounced after spaceflight as compared to the simulation model (Desplanches *et al.* 1991, Chi *et al.* 1992, Musacchia *et al.* 1992, Ohira *et al.* 1992, Baldwin *et al.* 1993, Jiang *et al.* 1993). A probable explanation for the smaller effect of spaceflight was a lower degree of immobilization in space compared with tail suspension. So, it would appear that immobilization is perhaps more important than microgravity.

2.5 Muscle Fatigability

In rats, weightlessness and hind limb suspension have been shown to increase the fatigability of the soleus muscle (McDonald *et al.* 1992). Scant data exist on human muscle fatigability in both actual and simulated microgravity. In one of these few studies, Narici *et al.* (2003) assessed the fatigue properties of the human plantarflexors using electrically evoked contractions during a 17-day spaceflight. Fatigability was considerably increased (~16%) after the flight and persisted during recovery. Several factors were proposed to contribute to this phenomenon: (a) an increased proportion of fast-twitch fibers as suggested by a greater expression of fast MHCs (Widrick *et al.* 1999); (b) energy substrate changes, as shown by a reduced ability to oxidize fatty acids and increased utilization of carbohydrates (Baldwin *et al.* 1993), also reflected by an increased utilization of glycogen and lactate production (Grichko *et al.* 2000); and (c) a reduced blood flow during exercise (Jasperse *et al.* 1999).

2.6 Tendon Mechanical Properties

Despite the importance of human tendons for the transmission of force to the bones enabling movement, and for their influence on the behavior of the contractile element in static and dynamic contractions, tendon adaptations to prolonged disuse have received little attention. Recently however, changes in tendon mechanical properties in response to two disuse paradigms, simulated microgravity (*long-term bed rest*, LTBR) and *spinal cord injury* (SCI), have been described (Reeves *et al.* 2005, Maganaris *et al.* 2006).

During a 90-day bed rest study organized by ESA (ESA LTBR 2001-2 study), tendon stiffness, length, and CSA were measured in 18 young healthy males before and after this chronic period of inactivity. Nine subjects performed resistive exercise (BREx group), and nine underwent bed rest only (BR group). Calf raise and leg-press exercises were performed every third day using a gravity-independent flywheel device. Isometric plantar flexions and ultrasound imaging were used to determine the tensile deformation of the gastrocnemius tendon during contraction. At the end of the bed rest period, in the BR group, tendon stiffness and Young's modulus[16] decreased by 58%, and 57%, respectively (Figures 6-04 and 6-05). Despite the intensive resistive exercise of the BREx group, tendon stiffness and Young's modulus decreased by 37%, and 38%, respectively (Reeves *et al.* 2005). These findings showed that unloading causes a decrease in tendon stiffness due to a change in tendon material properties, but not in tendon dimensions and that a very large volume of resistive exercises is needed to protect the tendon from disuse.

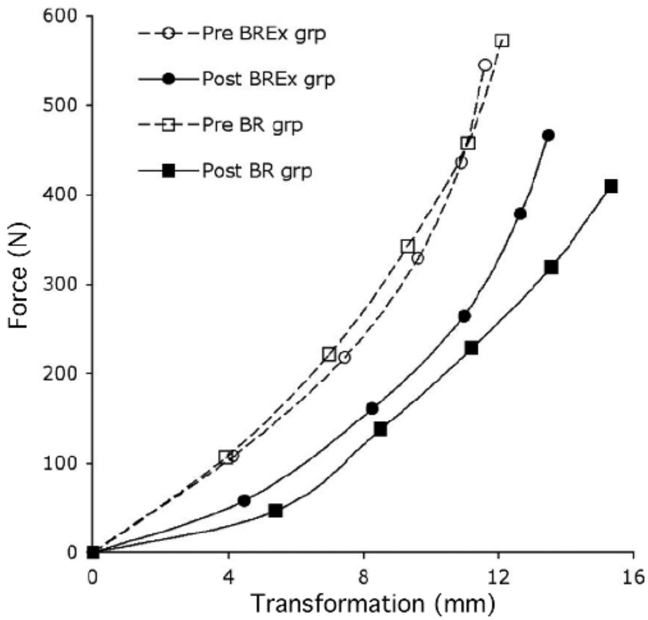


Figure 6-04. Tendon elongation pre and post 90 days bed rest in the bed rest only (BR) and bed rest plus exercise (BRex) groups. Reproduced with permission from Reeves et al. *(2005).*

In the second paradigm of prolonged disuse, the mechanical properties of the patellar tendon were compared in six men affected by SCI and in eight able-bodied men. Tendon stiffness and Young's modulus were lower by 77% and 59% in the SCI than in the able-bodied subjects. The CSA of the tendon was 17% smaller in the SCI subjects, but there was no difference in tendon length between the two groups (Maganaris *et al.* 2006). Hence the results of these two studies provide evidence of marked alterations in tendon mechanical properties in response to prolonged disuse.

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[16] Young's modulus is the property of an object (here a tendon) characterized by a constant ratio of stress to strain.

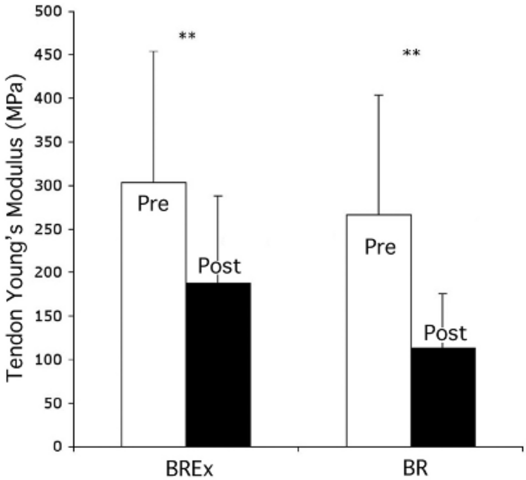


Figure 6-05. Gastrocnemius tendon Young's modulus in the BR and BRex groups. Reproduced with permission from Reeves et al. *(2005).*

2.7 Muscle Damage

Evidence exists that simulated and actual microgravity results in a greater susceptibility to damage upon reloading of animal and human muscles (Hikida *et al.* 1989, Hodgson *et al.* 1991, D'Amelio and Daunton 1992, Kasper 1995, Riley *et al.* 1995, Bigard *et al.* 1997, Vijayan *et al.* 1998, Vijayan *et al.* 2001). Eccentric contraction-like lesions manifesting smeared, less dense Z-bands and lesioned endomisium characterize this damage. In addition, the presence of helical polyribosomes indicating active protein synthesis suggests a brisk repair processes. Muscle damage is accompanied by microcirculatory changes and interstitial edema, responsible for the swelling of the whole muscle. However, at present, evidence of greater susceptibility to damage of human muscle after spaceflight is sparse because few studies have addressed this problem. Although the exact causes of this postflight fiber damage are unknown, it is plausible that the atrophic state of muscle fibers and the selective loss of contractile proteins or of structural proteins such as titin, desmin and dystrophin (Fitts *et al.* 2001) makes them susceptible to muscle damage because they would experience a greater relative load when weight-bearing is resumed in 1 g. This hypothesis seems in line with the observations of a continuous fall in human plantarflexor tetanic torque, despite a progressive reversal of muscle atrophy, during the recovery phase following spaceflight (Narici *et al.* 2003).

2.8 Neural Drive and Muscle Activation Capacity

Chronic EMG recordings obtained with intramuscular electrodes on animals during prolonged periods of hind limb suspension of one to four weeks duration show a rapid decrease occurring within the first week in antigravity muscle activity (plantarflexors) and a slight increase in non-antigravity muscle activity (*tibialis anterior*) due to stretching of the latter muscles (Edgerton and Roy 1994). In humans, the little available data on chronic EMG activity during prolonged bed rest or spaceflight show a marked increase in the total EMG activity of the *tibialis anterior* and the *soleus* but no change in the *gastrocnemius medialis* during a 17-day spaceflight (Edgerton *et al.* 2001). As far as maximum EMG activity is concerned, a 44% decrease in knee extensors' maximum EMG activity has been found after 42 days of bed rest in humans, suggesting a decrease in voluntary drive to the muscle with prolonged disuse (Berg *et al.* 1997). Similarly, a decrease in knee extensor EMG activity has been observed by Akima *et al.* (2005) after 20 days of bed rest. These observations are also in line with that of Duchateau and Hainaut (1987, 1995) who reported a significant decrease in thumb muscle EMG activity after 6-week immobilization of the human forearm following fracture. It seems therefore quite clear that prolonged disuse leads to a decrease in maximum neural drive to the muscle. In the initial phases of unloading, this effect seems to be related to a decrease in afferent activity (De-Doncker *et al.* 2005). However, other mechanisms such as a decrease in activation capacity likely explain the long-term decrease in EMG activity during prolonged disuse. As a matter of fact, a 33% deficit in central activation was found by Duchateau (1995) after five-weeks of bed rest.

In most actual and simulated microgravity studies, muscle function has been measured during unilateral muscle actions and only in a few has bilateral muscle function been assessed. However, when comparing the deficit in muscle power generated during bilateral muscle contractions, i.e., maximal extension with both lower limbs, to that produced during unilateral contractions as in cycling, the deficit in power was far greater for the bilateral movement. This finding was attributed to the effects of weightlessness on motor unit recruitment pattern, electromechanical efficiency, and predisposition to muscle damage (Antonutto *et al.* 1991, Antonutto *et al.* 1998, Antonutto *et al.* 1999, Di Prampero and Narici 2003). The observation of a greater decrease in power in the bilateral than in the unilateral movement indeed suggests a larger reduction in motor unit recruitment in the bilateral motor task. It has been known for some time that the force exerted by a single limb during a maximal bilateral contraction is less than the force associated with a maximal unilateral contraction (Howard and Enoka 1991). It seems therefore possible that this phenomenon, known as *bilateral deficit*, may be accentuated by disuse.

3 EFFECTS OF COUNTERMEASURES

Several approaches have been proposed to combat the atrophy and deteriorated of skeletal muscle that occurs in space owing to the lack of weight-bearing action. It is fair to say that none of these methods has been thoroughly evaluated with regard to their efficacy to prevent or ameliorate muscle wasting and function impairment in humans exposed to chronic microgravity. However, and regardless of the mechanism(s) responsible for the negative impact of spaceflight on skeletal muscle, countermeasures to this effect are imperative for maintaining crew-health and mobility during long-duration space missions.

A large number of astronauts and cosmonauts have carried out in-flight exercise using different paradigms (Convertino *et al.* 1989, Greenleaf *et al.* 1989, Convertino 1991, Tesch and Berg 1997, Convertino 2002, Di Prampero and Narici 2003), yet they suffered from loss of strength upon return to Earth. Because these activities were not logged, rather little has been learned about the efficacy of exercise countermeasures from past spaceflights. However, from the existing studies published in the literature, the following may be concluded.

3.1 Aerobic Exercise

In-flight cycle ergometer exercise (see Figure 1-04) has been used mainly to maintain cardiovascular function (Chase *et al.* 1966). However, such exercises have been shown to be ineffective for maintaining musculo-skeletal function during spaceflight simply because the mechanical load provided by aerobic exercise programs is too low to prevent muscle atrophy or to induce muscle hypertrophy in 0 g or in 1 g. For instance, results from a 30-day bed rest study show that 30 min of cycle ergometer exercise performed five days per week failed to prevent muscle wasting and weakness when compared to non-exercising controls (Greenleaf *et al.* 1989). Similarly, daily supine cycle ergometry exercise for 60 min at 40% of maximal aerobic power did not protect against muscle or strength loss in individuals subjected to 20-day bed rest (Suzuki et al 1994).

3.2 Resistive Exercise

Part of the decrease in muscle mass observed with spaceflight and inactivity is due to a depression in protein synthesis (Ferrando *et al.* 2002). Healthy subjects who were confined to bed rest for two weeks and performed knee extensor and ankle extensor resistance exercise every other day using a 5-set, 6 to 10 repetition regimen at about 80% of maximum were able to maintain muscle protein synthesis rate. Subjects who performed no training showed decreased muscle strength, muscle mass, and protein synthesis rate. The protocol was also sufficient to maintain dynamic strength, yet isometric strength and neural activation were reduced (Bamman *et al.* 1997, Ferrando *et al.* 1997, Bamman *et al.* 1998).

A protective effect of resistive training on protein synthesis has also been shown in rats in which four weeks of flywheel training significantly attenuated the reduction in *soleus* muscle mass and protein synthesis when compared to non-exercising rats (Fluckey *et al.* 2002). This mode of training based on concentric and contractions against a flywheel, introduced by Prof. Per Tesch of the Karolinska Institute of Stockholm (Berg and Tesch 1998), has been used for the prevention of muscle atrophy and weakness in two models of simulated microgravity, unilateral lower limb suspension, and bed rest. For instance, *quadriceps* muscle atrophy, induced by five weeks of lower limb suspension, was prevented by four sets of seven maximal concentric and eccentric knee extensions, performed twice or thrice weekly and using flywheel training (Tesch *et al.* 2004).

However, in humans, the *soleus* muscle shows limited susceptibility to work-induced hypertrophy, especially when compared to the *quadriceps*. Whereas high-intensity flywheel exercised performed twice per week during 90-day bed rest study fully prevented *quadriceps* atrophy, it only partially mitigated atrophy of the *soleus* muscle (Alkner and Tesch 2004b). This limited predisposition to hypertrophy of the human *soleus* is also confirmed by findings of a poor increase in protein synthesis of this muscle in response to an acute resistive exercise bout (Trappe *et al.* 2004).

Taken together, these results suggest that resistive exercise is presently the method of choice for mitigating or even preventing the negative effects of unloading on skeletal muscle. However, significant differences in the response to training exist among muscles and the causes thereof warrant further investigation.

3.3 "Penguin" Suit

This type of passive exercise, introduced by Russian space scientists, consists of an all-body suit with sewn-in elastic bands for maintaining a stretching load on antigravity muscles (see Figure 1-09). It is difficult to judge whether this type of exercise is really effective in combating muscle atrophy and weakness during disuse in space or on Earth. However, in a small group of subjects (N=4), who were bedridden for about 120 days, fiber size of the *soleus* muscle appeared maintained after performance of a single daily 10-hour bout of modest loading, i.e., about 10 kg, using the "Penguin" suit. Instead, three subjects, who did not load the ankle extensor muscles, showed *soleus* atrophy (Ohira *et al.* 1999). Despite these results may sound promising, no hard conclusions may be drawn from observations made on such small sample and it seems unlikely that such low loads may prove effective in preventing muscle wasting and weakness of large antigravity muscles.

3.4 Lower Body Negative Pressure

Lower Body Negative Pressure (LBNP) is a commonly used tool in space medicine (see Figure 1-06). In microgravity or in a supine position at 1 g, the LBNP conditions approximately simulate the fluid shifts that naturally occur during orthostasis, i.e., upright standing at 1 g. LBNP applied at physical rest is frequently used by astronauts as a countermeasure against the loss in orthostatic tolerance occurring after the return to Earth.

Physical training under LNBP conditions is still in the state of evaluation. Most work in this field has been done by Hargens and co-workers (Hargens *et al.* 1991). They added LBNP to a kind of treadmill running in horizontal supine position that mimics microgravity by a weight compensation of the legs. In studies with 5, 15, and 30 days of bed rest, respectively, treadmill running under LBNP conditions conserved the loss of leg muscle performance that was found in the control groups treated with bed rest without countermeasures (Lee *et al.* 1997, Schneider *et al.* 2002, Macias *et al.* 2005). However, orthostatic tolerance was only preserved when LBNP exercise was followed by a period of 5 min LBNP at rest (Schneider *et al.* 2002, Macias *et al.* 2005). The duration of LBNP exercise on the treadmill typically was 40 min per day. This is a considerable progress compared with the usual training time of 120 min per day that astronauts currently spend for training in-flight. However, recent bed rest studies testing different types of resistive strength training (flywheel training, vibration training plus resistive isometric exercise) as countermeasure against the loss of muscle performance during bed rest have shown an even better efficiency (Alkner and Tesch 2004a, Tesch *et al.* 2004, Rittweger *et al.* 2005, Blottner *et al.* 2006). The combination of these training measures with LBNP is surely worth to be tested in future as well.

LBNP may improve the aerobic character of a training measure including intervals or short peaks of loading and ischemia followed by phases of unloading allowing blood perfusion. In experiments applying LBNP in the magnet of a 31P-MRS instrument it was found that the consumption of phosphocreatine in the *anterior tibialis* muscle during contraction in supine horizontal body position was increased during LBNP compared with ambient pressure conditions. However, the subsequent recovery of phosphocreatine was significantly enhanced by LBNP, indicating improvements of the mitochondrial function (Baerwalde *et al.* 1999).

Leg muscle exercise under LBNP conditions has a big advantage in comparison to training under artificial gravity on a centrifuge. Indeed, the Coriolis effect should not disturbed exercise with LBNP.

3.5 Electrical Stimulation

The use of transcutaneous *electrical muscle stimulation* (EMS) has been tested as a countermeasure against muscle atrophy and weakness during a 30-day bed rest study (Duvoisin *et al.* 1989). In this investigation, three healthy subjects were treated unilaterally with EMS (frequency: 60 Hz, pulse width: 0.30 ms, train duration: 4 s) twice daily every third day. The treatment resulted in less decrease in strength and muscle mass in the limb treated with

EMS than in the non-stimulated limb. Although these results show a mitigation of muscle atrophy and weakness by EMS, they do not show a prevention of these conditions and do not provide a comparison between the effects of EMG and those of voluntary contractions. In a recent hind limb suspension study in rats, daily transcutaneous EMS plus hind limb suspension did not provide protection against muscle atrophy when compared to rats exposed to hind limb suspension only (Yoshida *et al.* 2003). Although EMS has the advantage of standardizing muscle activation, contraction level and duration, to compare in terms of efficacy to voluntary contractions, it requires high stimulation currents, and these are quite uncomfortable.

3.6 Artificial Gravity

This countermeasure concept is probably the most innovative but also the most challenging. Given the fact that mechanical loading of muscle seems necessary to maintain muscle mass and strength, several authors have suggested that passive centrifugation on a short-radius centrifuge will not be effective in maintaining skeletal muscle mass during long exposures to microgravity. Hence, as a complement for passive centrifugation, they have pursued the development of active centrifugation, where the subjects exercise while being centrifuged, as potential multipurpose countermeasures to microgravity. Currently two methods have been proposed for exercising with Earth-like gravity: conditioning with short-radius centrifuges and human powered centrifuges (see Chapter 3, Section 3).

3.6.1 Short-Radius Centrifugation

On Earth, several experiments aimed at determining the different levels and durations of artificial gravity needed to prevent cardiovascular and muscular deconditioning have been performed using short-radius centrifuges. In hind limb suspended rats, the application of 1 g for four hours per day was found to be sufficient for preventing *soleus* muscle atrophy while increasing the gravity level to 2.6 g had no additional benefit (Zhang *et al.* 2003). In humans, the application of artificial gravity combined with intensive aerobic training has been found to maintain muscle size during 20 days of bed rest (Akima *et al.* 2005). In this study, five healthy men were assigned to a countermeasure group and five to a non-exercising control group. The countermeasure group undertook intensive cycle training at up to 90% of maximum heart rate with short-radius centrifuge-induced artificial gravity on alternate days. The results showed that the volume of the total thigh muscles was maintained in the countermeasure group, whereas it decreased by 9% in the non-exercising controls. Knee extensors maximum voluntary contraction decreased by 7% in the countermeasure group, and by as much as 23% in the non-exercising controls. These results seem very promising. However the minimum intensity and duration of the gravity level necessary to prevent muscle atrophy and torque loss during spaceflight still must be established.

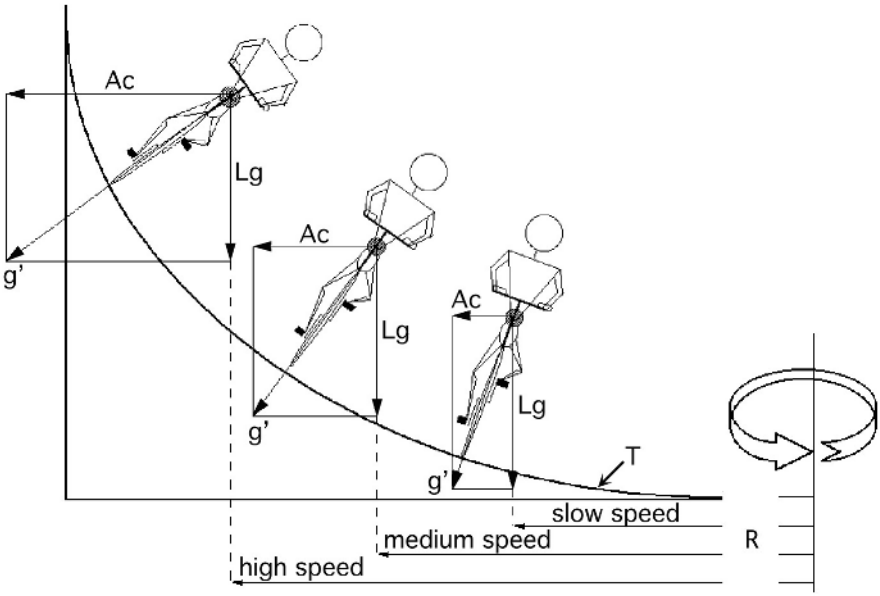


Figure 6-06. Scheme of the frontal view of a cyclist pedaling on the curved path of a "lunar track" (T). To compensate for the centrifugal acceleration (Ac), which varies with radius of gyration (R) and the ground speed, the cyclist leans inwards so that the vectorial sum (g') of Ac and the lunar gravity (Lg) lies in the plane that includes the center of mass (grey circles) and the points of contact between the wheels and terrain. The three drawings indicate the progressively larger Ac (and hence g') values. In addition, the angle between g' and the local vertical increases with Ac, so that the track must be appropriately constructed to avoid skidding.

3.6.2 Human Powered Centrifuges

In human powered centrifuges, the effects of artificial gravity and exercise are combined while the subjects exercise, usually by pedaling, on a centrifuge device. The NASA *Human Powered Centrifuge*, the *Space Cycle*, the *Twin Bikes System* (see Chapter 3, Section 3.3) are all based on the same principle. These systems require no external power, being operated by the subjects themselves, and they combine exercise and simulated gravity to simultaneously prevent muscle atrophy, bone demineralization, and cardiovascular deconditioning.

The *Twin Bike System*, described in detail in Chapter 5, Section 7, consists of two bicycles that move at the same speed, but in the opposite directions, along the inner wall of a cylindrically shaped space module (Antonutto *et al.* 1991, Di Prampero, 2000). The circular trajectories induce artificial gravity oriented along the subject's +Gz direction, the level of which varies according to the rider's muscle activity. For a radius of rotation of 2 m, as is generally the case for a conventional space module, the tangential velocity yielding 1 g at the feet level would amount to 4.5 m/s (Figure 6-06). Ground-based experiments have demonstrated that the discomfort deriving from pedaling in such a rotating environment necessary to generate artificial gravity is reasonably low and well tolerated. Thus, these devices may indeed prove to be useful tools for maintaining both the astronauts' physical fitness and cardiovascular conditioning.

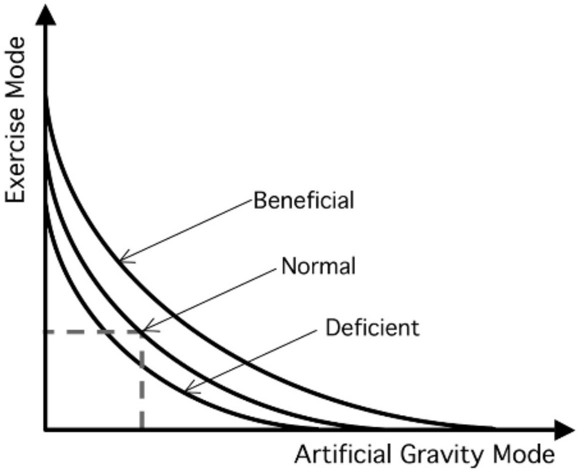
4 CONCLUSION

In response to actual and simulated microgravity both animal and human muscle undergo significant wasting and weakness. Muscle atrophy affects mainly the antigravity muscles. The loss in muscle strength and power tends to exceed that of muscle size and volume, both at whole muscle and at single fiber level. Both cellular and neural mechanisms seem to contribute to this phenomenon. The presence of muscle damage caused by reloading of muscles in 1 g cannot be excluded. Several countermeasures against muscle wasting and weakness have been proposed, based on pharmacological interventions, aerobic exercises, resistive exercises, or artificial gravity. Separately, most of these methods have yielded positive results in terms of combating either muscular or cardiovascular deconditioning. However one of the main challenges for the future will be that of identifying a countermeasure that may simultaneously ameliorate muscular, cardiovascular and vestibular deconditioning. In this respect, exercising in artificial gravity seems promising.

As with the other physiological systems, the main question to be addressed by research on artificial gravity effects on muscle function is what is the relationship between the exercise modality (intensity, duration, etc) and the parameters of artificial gravity (level, duration, frequency) for maintaining optimal performance? This investigation requires testing different combinations of artificial gravity loading and exercise programs to find the combination that ensure muscle mass, force, power and endurance, and maintain tendon functional integrity.

The expected results of this investigation may be summarized by the hypothetical curves illustrated in Figure 6-07. The middle curve, indicated by the broken lines, represents the situation in normal gravity. The lower curve refers to all exercise and artificial gravity combination mode, a roll-up of intensity, duration, and frequency, leading to an insufficient stimulus for maintaining muscle integrity. The higher curve refers to all exercise and artificial gravity combination modes leading to a beneficial effect. Similar curves may likely apply to other physiological systems than the muscular system. At this time these curves have not been quantified.

Figure 6-07. Hypothetical curves of the relationship between exercise mode and artificial gravity mode for preventing muscle deconditioning. Adapted from Burton and Russel (1994).



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Chapter 7

PHYSIOLOGICAL TARGETS OF ARTIFICIAL GRAVITY: ADAPTIVE PROCESSES IN BONE

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In this chapter, the importance of maintaining bone integrity is first discussed. Then a brief overview is given on what is known and what is hypothesized about the fundamental physiological processes underlying the adaptive responses of the bone to altering environments. After that, the most relevant literature regarding the known effects of exercise on bone, and how this interferes with other factors such as nutrition is reviewed. From there, a rationale for how exercise paradigms may take advantage of artificial gravity in order to prevent bone loss is discussed. Next, a review of what is already known about the effects of artificial gravity upon bone is presented. Finally, pertinent questions for research in the very near future are developed. Little is known regarding the effects of disuse and microgravity upon tendon or even other connective tissues. However, because a good number of physiological processes are similar in bone and other connective tissues, there is a brief discussion of this analogy in the end of this chapter.

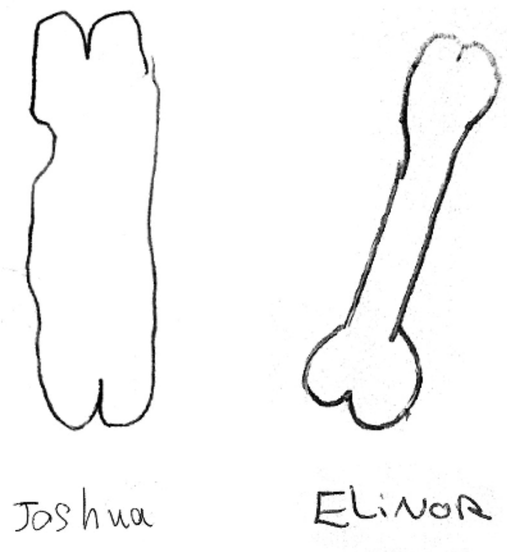

Figure 7-01. Drawing of bones by Joshua (age 7) and Elinor (age 9).

1 INTRODUCTION

Bones, despite being our ever-lasting remnants after death, are adaptive, living organs. Like the other constituents of the organismic network, they respond to environmental challenges and thus contribute to phenotypic adaptation. In many ways, our recognition of bone biology seemingly lags behind our understanding of other fields. This is for two reasons. Firstly, bone is a rigid material and its cells are therefore inaccessible to direct manipulations by researchers. Secondly, and even more importantly, the study of bone requires a thoroughly inter-disciplinary approach. Poor communication across disciplines has given rise to semantic and conceptual flaws, confusion and misunderstanding. Therefore, before addressing this relation's topic, I will review the basic concepts of bone biology.

Why the Study of Bone is Relevant to Microgravity Research?

Bone fractures are a major concern for societies in which people become ever older (Baron *et al.* 1996, Gullberg *et al.* 1997). There is ample evidence that, at least in part, the risk of fracture increases in older people <u>as a consequence</u> of a reduced amount of bone material (Kanis *et al.* 2001), which negatively affects bone strength (Ebbesen *et al.* 1997, Ebbesen *et al.* 1999). There is also evidence accumulating that factors other than bone mass, or bone mineral density, contribute to the problem (Cummings 2002). Additional factors comprise whole-bone geometry, the architecture of trabecular networks, the molecular build of both the organic and the mineral phase, and the accumulation of microdamage and thus material fatigue (Frost 1960, 2004, Diab *et al.* 2006). The latter very likely plays a crucial role for bone fragility at old age. However, even if such other factors are important, there is no doubt that loss of bone mass constitutes a powerful risk of fracture.

Bone loss during spaceflight was recognized as early as in 1965 during the Gemini 4, 5, and 7 missions (Mack *et al.* 1967). As an artifact of the technology applied, bone loss was over-estimated in that study. However, radiographic measurements subsequently obtained on the crews of Apollo 7 and 8, and absorbtiometric measurements on the crews of Apollo 14, 15, and 16 qualitatively confirmed the earlier findings (Rambaut *et al.* 1975). Thereafter, bone loss has been documented in the crews of the Salyut missions (Stupakov *et al.* 1984), of the Skylab program (Smith *et al.* 1978, Tilton *et al.* 1980), and from crew members who stayed on board the Mir space station (Oganov *et al.* 1992). Very importantly, bone material obtained from biopsies in cosmonauts indicates that the composition and material properties of bone are unaltered by spaceflight (Gazenko *et al.* 1977, Prokhonchukov *et al.* 1978, Prokhonchukov *et al.* 1980).

In qualitative terms, therefore, we know that the exposure to microgravity leads to bone loss[17] rather than an alteration of the existing bone material. However, our knowledge is quite limited when it comes to quantitative terms. This is due to the small samples sizes and different durations of space missions, the large inter-individual variability of responses to microgravity exposure (Tilton *et al.* 1980, Vico *et al.* 2000), and to the different methodological approaches chosen to assess microgravity related bone losses.

It is currently unknown how long bone loss would continue during spaceflight and how much bone material would be lost in the end. Indirect evidence to address this important question is from ground based research, such as bed rest studies (Vico *et al.* 1987, LeBlanc *et al.* 1990, Watanabe *et al.* 2004) or clinical cases of immobilization-related bone loss, such as spinal cord injury (Biering-Sorensen *et al.* 1990, Eser *et al.* 2005). During bed rest studies, bone seems to be lost at a rate of about 2% per month in the distal tibia (Rittweger *et al.* 2005). Single individuals however, can lose as much as 6% per month. Assuming that the pace of bone loss continues over longer periods, it follows that some astronauts are at risk of losing more than 50% of their trabecular bone mass within one year (and accordingly 75% or more of their bone strength, explanation see below). By comparison, it is well documented that approximately two thirds of the trabecular bone mass are lost from the paralyzed limbs after spinal cord injury. In these patients, bone is being lost during a period of two years or more. A standstill seems to occur thereafter, probably because the bones have then adapted to their new environment (Rittweger *et al.* 2006a). Importantly, patients with spinal cord injury have a two-fold increase in the risk of fracturing their leg bones (Vestergaard *et al.* 1998). These fractures typically occur in the absence of severe trauma or falls. Their main cause is the loss of bone strength.

Therefore, assuming that bone loss is comparable between astronauts and patients with spinal cord injury, deterioration of bone strength is to be anticipated for long-term space missions that pose a considerable risk of fracture. It is self-explanatory that such fractures, be they on Mars or on board a spacecraft, must be avoided at all cost. Therefore, bone loss currently constitutes a strong limitation to human spaceflight. It is in this context that the search for effective countermeasures to maintain skeletal integrity has been recognized as a corner stone to the progress of astronautics.

2 BASIC BONE BIOLOGY

Much of our current understanding in bone biology arises from insights by Harold M. Frost (Frost 1960, Takahashi *et al.* 1964, Epker and Frost 1966a, Jett *et al.* 1966, Frost 1987a, 1990b, 1990a, Schiessl *et al.* 1998).

[17] Necessarily ensuing a change in bone geometry and / or architectural structure.

In reviewing the basic principles of bone biology, let's begin with the big picture before detailing the cellular and molecular mechanisms and finally discussing bone adaptation to mechanical usage and disuse.

The term *bone* can be used in three different senses, relating either to bone as an organ, as a type of tissue, or as a material. Distinguishing these levels is fundamentally important as should be self-evident, e.g., for the concept of bone "density".

Figure 7-02. Peripheral Quantitative Computed Tomography scan of a human metatarsal 1. Proximal joint surfaces at the bottom, distal joint surface at the top. Note that the compact cortical bone structure disperses into a fine spongy network towards the ends. Interestingly, the bone mineral content is more or less the same in each horizontal layer.

2.1 Bone as an Organ

Bones as organs provide rigidity and serve as resistors to muscle pull or help to protect soft tissue organs like the brain and the heart from external forces. During development, bones can generate from either mesenchyme or cartilage (intramembranous and endochondral ossification, respectively). Later on in life, transformation of other tissues into bone does not occur[18]. As a rare exception to that rule, progressive ossifying fibrodysplasia is linked to a genetic linked in BMP-4 signaling and causes ossification of connective tissues such as tendons and ligaments (Kaplan *et al.* 2006).

Anatomically, bones are clad by the periosteum, i.e., an epithelium rich in blood vessels and nerve fibers. The latter is the anatomical substrate for pain sensed with fractures or contusion. Underneath the periosteum lies the cortex or outer shell of the bone. In all bones, except some specialized air-filled bones in birds, the space within the bone is filled up with either fatty or

[18] Caveat: Calcified connective tissue is different from bone tissue.

haematopoietic (red) bone marrow, the mechanical role of which is not understood (Currey 2003).

Bones can be classed as long bones (e.g., tibia, radius), short bones (e.g., os naviculare), flat bones (e.g., os frontale), irregular bones (e.g., in the pelvis), or sesamoid bones (e.g., patella). In the long bones, we distinguish between three different zones that are defined by the physes (growth plates). The zone beyond a physis (i.e., next to the joints) is the epiphysis, the zones that adjoin the physes towards the centre of the bones are the metaphyses, and the central region itself is the diaphysis. The principle idea behind the design of a long bone can be understood when considering the forces it conveys (Figure 7-02). Obviously, when longitudinally compressed, a bone is subjected to the identical magnitude of force at each cross section throughout its length, including the joint surfaces. The latter, however, are covered by cartilage, the material properties of which are inferior to those of bone. Consequently, the joint force needs to be dispersed over a larger area. In order to achieve this, bone struts have to branch off the thick cortical shells found in the diaphysis, and support the joint surface as a trabecular network. As we see, there needs to be different kinds of bone tissue.

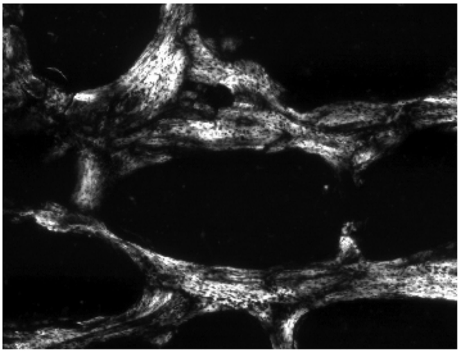

Figure 7-03. Section of human undecalcified cancellous bone from the femoral neck, seen with polarized light microscopy. Polarization affects the transmission of light according to the grain orientation of the bone matrix. As a result, arrest lines are seen as dark to black lines in this image, while other bone tissue appears white to grey, depending on the orientation of the bone lamellae. Note the pronounced anisotropy, and the many arrest lines that clearly indicate that the visible structure is a result of the complicated history of formation.

2.2 Bone as a Tissue

Regarding bone as a tissue, we discern between compartments of compact and trabecular (spongy) bone. **Trabecular bone** (Figure 7-03) is also called cancellous bone and consists of interconnected rods or plates. It is found in the epiphyses and metaphyses of the long bones, as the “sandwich filler” of flat bones, and in the core of most irregular bones. The rod- or plate-like trabecular structure seems to be anatomically specific. In rat vertebrae, for example, rods are found close to the endplates whereas rods predominate in the centre of the vertebral body (Figure 7-04). The relative fraction of bone (*bone volume per tissue volume*, or BV/TV) in cancellous bone is typically around 25%, although it varies widely and can reach values above 50% in horse’s leg bones.

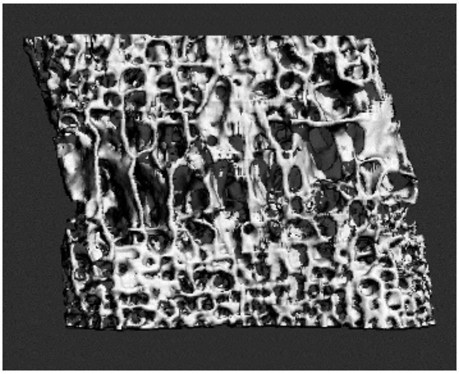

Figure 7-04. MicroCT scan of the trabecular network in a rat vertebral body. Note the rods at the upper and lower end and the plates in the centre. Image courtesy of Juerg Gasser.

In the diaphyses, virtually all of the bone is **compact bone.** Many authors use the terms *compact* and *cortical* interchangeably. This is not entirely correct. By definition, the cortex is just the outer shell of the bone. Compact bone is found in the diaphysis where the cortex is thickest (more than 30 cm in the shafts of some sauropods' bones). Getting gradually thinner towards the ends of the bone, the cortex is not thicker than other trabecular plates at the epiphyses, close to the joint.

Compact bone can be either lamellar, fibro-lamellar (plexiform), Haversian, or woven bone. Fibro-lamellar bone is normally not seen in humans[19], but rather in the rapidly growing bones of animals such as sheep and cattle. Woven bone does occur in humans, but only in response to overloading or during fracture healing (callus). Hence, under normal conditions only lamellar or Haversian bone is found in the cortex of health humans. Lamellar bone is an arrangement of tightly packed layers of bone material. Conversely, Haversian bone consists of concentric layers of bone material that are embedded into the lamellar bone. This is the result of intracortical remodeling (see below).

There is a dense network of canals that permit vessels and nerve supplies to penetrate the compact bone tissue. Because of their different genesis, we distinguish them as either Volkmann canals (in lamellar bone) or as Haversian canals (in Haversian bone).

Bone tissue, like all connective tissue, is rich in extracellular matrix and poor in cells. The only cells found within bone tissue are the **osteocytes**. Their cell body lies in a *lacuna* within the bone and has an oval shape. The longer axis (~20 μm) is in the plane of the lamellae, and the two shorter axes (~4 μm) perpendicular to it. Their number is ~50,000 per mm^2, but this value varies with different species, with the anatomical location and with age (Mullender *et al.* 1996, Qiu *et al.* 2002). Osteocyte cell bodies cause porosity within the bone material of around 1%.

[19] With the exception of some rare pathological states, e.g., paraneoplastic syndromes.

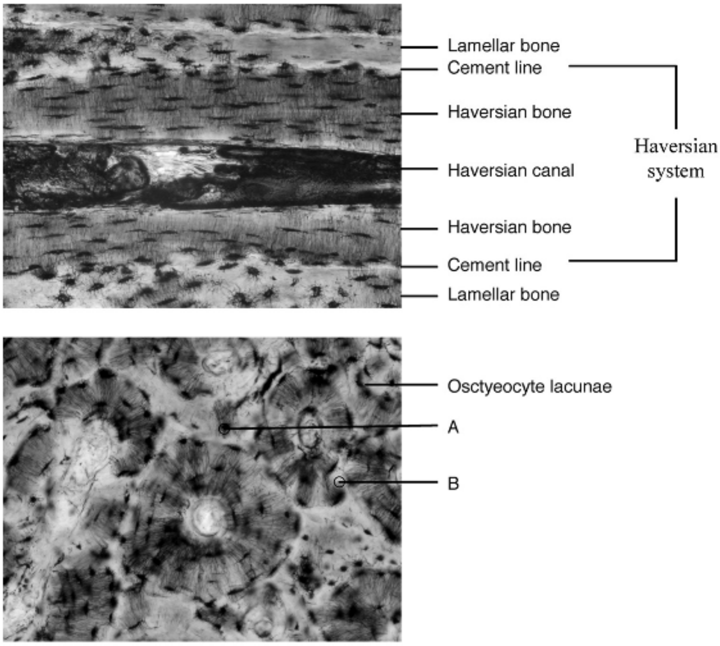

Figure 7-05. Compact bone. Upper panel: Longitudinal section of undecalcified human cortical bone, pneumatic staining, polarized light microscopy. A Haversian system runs horizontally across the image, engulfed by lamellar bone on either side. At the upper end note the regular layers of osteocyte lacunae in the Haversian bone, and the dense network of canaliculi emerging from the lacunae. The shape of the osteocyte lacunae and of the canaliculi network is different in the lamellar bone, due to a different orientation of the bone lamellae. Also note the grey levels differ between Haversian and lamellar bone, suggesting a different orientation of the bone matrix (for an explanation see Figure 7-03).

Lower panel: Cross section of human cortical bone, otherwise technical details as upper panel. Here, the Haversian systems impose as pseudo-circular shapes, with a central canal and a surrounding cement line. Note the intense network of canaliculi within the Haversian systems, but how few canaliculi connect to outside the system! An exception can be seen where two osteocytes on either side of the cement line are very closely neighboring (see mark "osteocyte lacunae"). Also, it can be seen that system B has eroded the outlines of system A. Hence, system A must be older than system B.

Each osteocyte maintains 60 dendritic processes (Boyde 1972) which are embedded in the so-called *canaliculi* (Figure 7-05). Via these processes and gap junctions at their ends, neighboring osteocytes interconnect to each other. Most of the gap junctions in bone consist of connexin 43, a "tunnel" protein, which allows for the flux of small ions such as Ca++ across neighboring cells (Schirrmacher *et al.* 1996). This trans-osteocytic traffic is enhanced by mechanical stretch in osteoblast cultures (Ziambaras *et al.* 1998), which leads to the hypothesis of a fundamental role of such trafficking in bone adaptation to mechanical stimuli.

Recent research supports this notion: bone adaptation to mechanical stimuli is mitigated in the absence of connexin 43 (Grimston *et al.* 2006). However, as it is not completely abolished connexin 43 gating is probably not the only pathway involved in bone adaptive processes. Other researchers hold that strain-induced fluid flow in the canaliculi plays a crucial role in the process of mechanotransduction[20] (Owan *et al.* 1997, Bacabac *et al.* 2004). This theory bears some relevance to space research, as interstitial fluid pressure with in the bone marrow is thought to enhance the process of mechanotransduction (Bergula *et al.* 1999). It has been speculated that, therefore, reduced interstitial fluid pressures in the lower extremity may contribute to bone loss during spaceflight (Turner 1999).

Moreover, there is evidence for the intracanalicular fluid space and the adjoining bone matrix to contain non-crystallized ions, which supposedly play an important role in ion homeostasis. Despite the physiological importance of the canaliculi, however, it should be kept in mind that the diameter of these canaliculi is tiny (~0.2 µm) (Cooper *et al.* 1966), and that the porosity caused by this network is estimated to be less than 2% of the total volume in compact bone (Frost 1960).

Osteoblasts (Greek for *bone* and *germ*) are the only cells with the ability to generate bone material. It is thought that during the process of bone formation, one out of seven osteoblasts differentiates to an osteocyte. For obvious reasons, osteoblasts can do their job only on existing surfaces. They always operate as large arrays of cells (Figures 7-10 and 7-11). Osteoblasts differentiate from the **lining cells** within the periosteum, or from precursor cells in the bone marrow or in other organs. After they have done their job, osteoblasts differentiate back into lining cells. Both lining cells and osteoblasts cover the bone surface like smooth a carpet, always connected to one another. As a consequence, bone surfaces are smooth after bone formation (Figures 7-10 and 7-11).

There are two steps involved in bone formation. Firstly, osteoid, i.e., a mixture of proteins is laid down. This process is similar to the secretion of extracellular matrix proteins by fibroblasts in tendons or fasciae. The major part (~90%) of the osteoid is collagen. Other mechanically important proteins are elastine and glycosaminoglykanes. However, there are also many other proteins found in bone (e.g., TGF-ß, osteocalcin). They are supposedly involved in regulatory functions.

In the next step the osteoid is mineralized. For some reason, it takes 10 days[21] or more for the mineralization to start. As a result of this

[20] Mechanotransduction is the sensing of mechanical stimuli and their translation into biological information.

[21] The mineralization lag is prolonged in osteomalacia, probably due to low serum levels of D-hormone and calcium.

"mineralization lag time", osteoid seams (Figures 7-10 and 7-11) can be recognized in biopsy samples. It is thought that osteoblasts are essential to start the mineralization. Alkaline phosphatase is a key enzyme in this step, and osteocalcin seems to be another crucial protein. Once mineralization has started it progresses more or less automatically. As result of this, the mineral density of the bone material increases steadily with its age.

Bone formation can be quantified with a technique called *dynamic histomorphometry* (Parfitt *et al.* 1987). In essence, a compound is given (tetracycline in the case of humans) which stains osteoid that is currently mineralizing (Epker and Frost 1966b). This generates a label that can later be recognized under the microscope. Ingesting the compound at two different times produces two such labels. A biopsy sample taken after that reveals the bone formation rate (based on the osteoid seams) and the mineral apposition rate (based on the distance between the labels).

The fourth type of bone cell is the **osteoclast** (from Greek for *bone* and *broken*), which is the only cell that can degrade and resorb bone material. To do so, osteoclasts first build up a tight seal with the bone matrix. They then secrete an "osteolytic cocktail", i.e., hydrogen ions and proteolytic enzymes (e.g., collagenase, cathepsin K) via their ruffled border into the sealed space. This cocktail erodes the surface, first dissolving the bone mineral by the acidity, and next digesting the proteins. The dissolved remnants can then be resorbed and transported transcellularly to a vein at the back of the osteoclast. The result is a hollow space that has been traditionally called *Howship lacuna*. Many of these lacunae constitute the scalloped surface which is typical for a bone surface on which resorption has taken place.

Osteoclasts can either have one nucleus (mononucleated) or many (multinucleated). Multinuclear cells depict a greater metabolic activity and are active during the early stages of bone remodeling (see below). On average, they live for about 12 days (Parfitt *et al.* 1996) after which the cells decay by apoptosis and leave the field to mononucleated cells. Osteoclasts have receptors and respond to parathyroid hormone, calcitonin and interleukin 6. Unfortunately, there is no technique, comparable to the assessment of bone formation and mineral apposition in order to directly measure bone resorption.

2.3 Bone as a Material

As alluded to above, bone as a material is a made up of two phases. The **organic phase** constitutes approximately two thirds of the volume of a bone, but only one third of its dry mass. Its main constituent is type I collagen, which in total accounts for a quarter of the protein mass in our body. Collagen has a remarkable tensile strength, which is largely down to the aminic bond. Every third amino acid of the peptide is glycine, and among the others many are proline or hydroxyproline. As a result of its amino acid sequence, there is little freedom of rotation and no α-helix is formed. Rather, three strands from a triple helix. Collagen is made up in several steps. Procollagen is synthesized within the osteoblasts and secreted into the extracellular matrix. Here, the procollagen I polypeptides (one at the C-terminus and one at the N-terminus) are cleaved off. The result is tropocollagen, which is integrated by cross-links to form protofibrils, which in turn aggregate to form fibrils.

The **inorganic phase** (or mineral phase) consists of bone apatite, a crystal of the calcium phosphate family. However, in about 5% of the crystals the phosphate group is replaced by carbonate, and calcium can be replaced by sodium, potassium and other cations. Bone apatite is therefore to be regarded as an impure crystal. Because the inorganic phase is rich in minerals of high atomic order, it generates a signal that X-ray based methods can distinguish from soft tissue[22]. In a simple experiment the inorganic phase can be dissolved with *hydrochloric acid* (EDTA). The result is a tissue with mechanical properties similar to tendons or other connective tissue. Conversely, ashing, i.e., the burning of the organic phase produces a material that appears to be "hard" but fractures quite easily. It thus seems as though the inorganic phase of bone provided rigidity and the organic phase toughness.

During the formation of bone, and also in the course of its resorption, substances are released into the blood and subsequently excreted with the urine, which can help to monitor bone metabolism, the so-called *bone markers*. Historically, bone metabolism has been first investigated by calcium excretion. The drawback of this approach is that calcium metabolism depends also on renal and intestinal absorption and secretion. It is possible to monitor all of these calcium fluxes by applying stable calcium isotopes (Yergey *et al.* 1987). However, that technique is extensive and expensive. Therefore, focusing on the protein phase is a more straightforward alternative. Initially, proline or hydroxyproline have been used in order to assess bone resorption (Lockwood *et al.* 1975). However, these amino acids are abundant in but not specific to bone protein. In that sense, the assessment of pyridinoline and desoxypyridinoline, as constituents of degraded collagen-I cross-links, was a step towards a more specific marker (Robins *et al.* 1986). Commercial kits are nowadays available that are specific to certain epitopes in the collagen cross-links (either *C-terminal*, CTX, or *N-terminal*, NTX). They can conveniently be user for measurements either from the serum or from the urine.

As to formation markers, alkaline phosphatase, ideally its bone specific (osteoblastic) isoform is mostly used. Procollagen I polypeptides, i.e., the tips of the collagen that are cleaved off intracellularly can assess the rate of collagen type I synthesis. Often, osteocalcin is also regarded as a bone formation marker, given its role in the mineralization process. However, as it

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[22] Hence the term bone *mineral* content or bone *mineral* density.

is a protein residing within bone, it is also set free in the course of bone resorption. Hence, osteocalcin levels are more informative when combined with measurements of other bone markers.

Assessment of biochemical bone markers has certainly enhanced our understanding of bone metabolism. Unfortunately, the markers reflect bone formation and bone resorption only in a semi-quantitative way. In the case of the alkaline phosphatase, the enzyme activity will depend upon local inhibitory and stimulating effects. Moreover, different markers have different pharmacological kinetics. It is therefore impossible to make inferences upon bone gains or losses solely on the grounds of these markers. Another drawback of bone markers is that they do not deliver anatomically specific information. This can, however, also be a strength, say when the overall effect of an intervention upon bone formation is of interest. The main role for bone markers, however, is to provide information regarding the rate of change (comparable to the mathematical differential) and that they therefore respond earlier than other techniques.

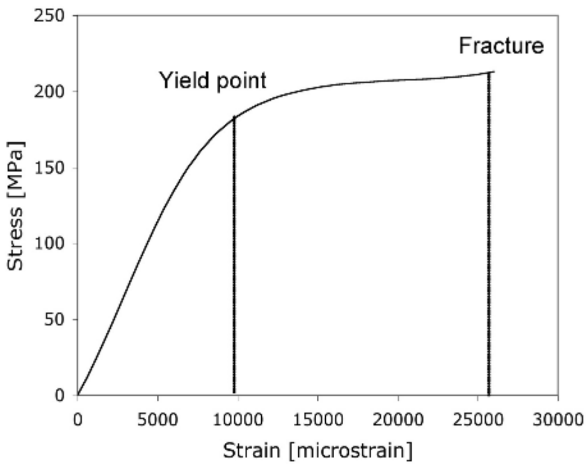

Figure 7-06. Stress strain diagram for human bone in compression. Up to the yield point the deformation is elastic, which means that mechanical energy is stored. The area under the curve unto this point is called resilience *and illustrates the capacity of a material to store recoverable energy. The total area under the curve (up to fracture) can be understood as the energy absorbing capacity. Between the yield point and fracture, the stress does not increase, but a considerable amount of energy is stored, the majority of which is in the form of little defects to the material and hence irrecoverable. Adapted from data by Cezayirlioglu* et al. *after Currey (2002).*

3 MECHANICAL FUNCTIONS OF BONE

Bone has exceptional material properties that make it one of the most rigid materials in our body. What does this mean? Material properties tell us how materials deform under the impression of force. When talking about material, dimensions should play no role. A material's deformation, measured as length change per original length is called *strain*. As the material's chemical bonds are strained, a resistive force is generated in the material. This force, normalized to the material cross sectional area, is the *stress*.

3.1 Strain and Stress

For each material, strain and stress are related to each other in a characteristic way (Figure 7-06). As the strain increases, so does the stress. Initially, this occurs in a linear relationship, the incline of which defines the elastic modulus (material stiffness). Obviously, the lower the stiffness, the easier it is to deform a material. With further increases in strain, however, there is a point from which stress does not progress as much as strain does. This is the yield point. Beyond it, some of the chemical bonds fail. Obviously, the energy involved in straining the failed bonds cannot be recovered. Luckily, however, the deformation energy up to the yield point can. Therefore, the first part of the stress-strain relationship is called the elastic region. Different materials have different capacities to store elastic energy (resilience), and a way to quantify this is to measure the area under the curve up to the yield point. Conversely, the total energy stored when a material is tested to fracture is the energy absorbing capacity or toughness of a material. Clearly, a material can be rigid (i.e., have a large stiffness) without being tough. Such a material is called a brittle material, and a well-known example for such a material is glass. Finally the material fails, and engineers note the stress at failure (ultimate strength) as a characteristic measure to quantify this.

Hence, in order to build solid structures, materials are required with large values for elastic modulus, ultimate strength and toughness. Bone is outstanding in that respect[23]. It is therefore an ideal material to resist compressive forces in the musculo-skeletal system.

Obviously, Figure 7-06 gives only a very incomplete introduction to the scientific field of the material properties of bone. In reality, these properties differ for compression, tension, and shear (Figure 7-07) in the same material. Elastic modulus and ultimate strength increase with strain rate (i.e., the speed at which a deformation takes place), and the elastic modulus increases with the degree of mineralization (Currey 1984, Rauch 2006). Even more importantly, bone is highly anisotropic. Its properties depend on the orientation of the lamellae, being 2-4 times greater along with the lamellae that perpendicular to it (Liu *et al.* 1999, Liu *et al.* 2000). For example, the ultimate compressive strain of bone is around 40,000 microstrain in line with the lamellae, but only 10,000 microstrain perpendicular to it. In compact bone, the lamellae are oriented in line with the cortical shell, and hence its normal loading axis is in line with the maximum stiffness and strength of the

[23] Teeth have similarly outstanding material properties, but unlike bones they cannot be repaired (see below, remodeling).

material. Cancellous bone, however, is made up of struts and pieces of bone with vastly diverging orientation (see Figure 7-03). It is therefore quite difficult to understand and model the mechanical behavior of cancellous bone.

An important material property worthy of mention is its resistance to fatigue. If a material does not fail at a stress somewhat lower than its ultimate strength, then experiences I gathered as a little boy tells me that a second go might break the stick. More seriously, increasing the number of loading cycles reduces the stress a material can resist. For example, Gray and Korbacher found the failure stress in bone to decrease from 180 MPa when loaded once to 140 MPa when loaded a thousand times, and to below 100 MPa when loaded a million times (Gray 1974). With repetitive loading of bone, irrecoverable strains accumulate (Cotton *et al.* 2005). They causing microdamage to the bone (Figure 7-07) and lead to a reduction in stiffness, strength and toughness. If not repaired by remodeling (see below), microdamage tends to enlarge and will eventually lead to fracture, often without severe mild trauma. The importance of microdamage accumulation for bone fragility and of "true" osteoporoses (Frost 1998b) has been recognized in recent years (Li *et al.* 2005, Diab *et al.* 2006).

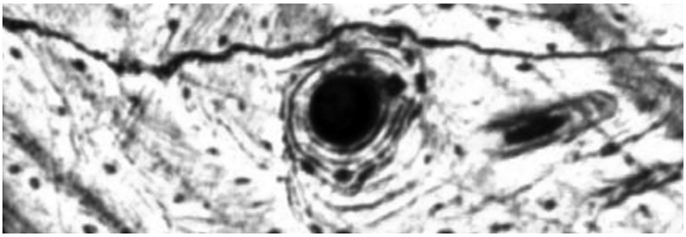

Figure 7-07. Photo of a microcrack in a human cortical bone. Image courtesy of Keith Winwood.

3.2 Aging

Aging is another factor that takes important effects upon bone material properties. With increasing age, the fraction of old and thus highly mineralized bone with greater elastic modulus values increases Moreover, there is an increasing variation in the biological age of adjoining struts of bone material as a result of ongoing remodeling activity (see below). Importantly, therefore, it is more the variation in material properties, rather than those properties themselves, which is altered with age (Zioupos and Currey 1998). This may have deleterious effects. Given the different elastic modulus of these struts of different age, there strains will vary under the same load, introducing large shear strains, which are particularly harmful to bone material. Finally, there is an accumulation of microdamage with age, and on top of that the rate at which microdamage accumulates is also accelerated with age (Zioupos *et al.* 1996). On top of this, the impact of microdamage upon material is increasingly detrimental with age (Diab *et al.* 2006).

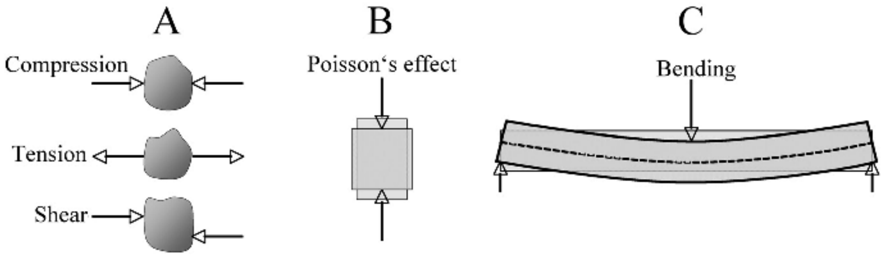

Figure 7-08. Different loading conditions. A: Uniaxial force vectors cause compression and tension, while in shear loading the force vectors are parallel shifted. B: The cross-expansion associated with shrinkage in compression (and vice versa in tension) is called Poisson's effect. It introduces shear strains that are maximal at angles 45 deg to the normal stress axes. C: Bending is a complex loading pattern. Here a simple 3-point bending pattern is given as an example. The loading leads to compression in the upper half of the beam, and to tension in the lower half. Note that the length of the neutral fiber (dashed line) does not change, hence strain and stress equals 0. One can therefore see bending as straining a structure around a rotational axis, which in this example would stick out of the figure plane.

3.3 Geometrical and Structural Properties

An engineer not only considers material properties, but also its geometrical and structural properties in order to judge whether a building (or organ such as bone) is bound to fail. Different loading conditions (Figure 7-08) have to be considered and met by adaptation of the structural measures. The uniaxial loading modes of compression and tension are straightforward. Structural adaptation is by increasing the cross section (orthogonal to the force vectors) in proportion to the force magnitude. Therefore, bone mineral content (i.e., the amount of bone per unit length) is a predictor of the compressive strength of a bone. Similarly, for shear loading, the cross section parallel to the force vectors must be enhanced in proportion to shear force magnitude.

For bending, however, the problem is a bit more complicated. As depicted in Figure 7-08, the neutral fiber in the centre of a bent beam does not change in length. Because strain causes stress, and this in turn causes the reactive force of materials, it follows that the neutral fiber does not contribute at all to the beam's resistance to bending. On the other hand, it is easy to see that the strain increases linearly within the material with increasing distance from the neutral fiber. Further assuming a linear stress-strain relationship as in Figure 7-06, one arrives at a mathematical description of the beams structural strength in bending which is called the *moment of resistance* (W)[24].

[24]Also known as the section modulus.

Size	*R = 1.13*	*r = 0.65* *R = 1.30*	*s = 2*	*h = 2.42* *b = 1.65*	
A (cm^2)	4	4	4	4	4
W_y (cm^3)	1.13	1.62	1.33	1.10	1.39
W_x (cm^3)	1.13	1.62	1.33	1.62	1.62

Figure 7-09. Comparison of four different beams and the human tibia. All structures were chosen to have identical cross sectional areas. Hence, with the same material properties they have the same strength in compression and tension. However, their strength in bending varies, as illustrated by the moment of resistance (W), which is given for bending in around the x and y directions. From a structural point of view, the tibia can be regarded as a combination of a hollow cylinder (distributing its material far from the central fiber) and a rectangular bean with W being axis-specific. Adapted from Rittweger et al. *(2000).*

W is affected by the *eccentricity*, i.e., its distance from the neutral axis of the material to the power of 2. Hence, locating material within a beam far away from its neutral axis is an efficient way to adapt it against bending. This is exemplified in Figure 7-09, where five different beams with identical cross sectional areas (and hence the same strength in compression or tension) are discussed. For circular beams, *W* is considerably greater in hollow as compared to massive circular cross sections. That is why flagpoles are designed in this way[25]. However, strength in bending critically depends on the plane in which bending occurs. Hence, there is a different *W* for each plane. This effect is also illustrated in Figure 7-09.

Daily experience tells us that failure in bending is more common than in uniaxial loading. Therefore, according to the concept of *tensintegrity*, nature and modern architects try to reduce loading modes to compression and tension wherever possible. However, bending does occur in musculo-skeletal systems (Biewener *et al.* 1983, Hartman *et al.* 1984) and our bones appear to be adapted to them (Rittweger *et al.* 2000). Making our bones larger increases their weight and would require larger forces to accelerate and decelerate them during locomotion. Therefore, the existence of some *marrow* factors (Frost 1998a) has been postulated which help to keep the long bones' design slender, and compromise between the required strength and the desired light-weight.

It should be mentioned here that, nowadays, bone strength can be indirectly assessed by *peripheral computed tomography* (pQCT) (Braun *et al.* 1998, Sievanen *et al.* 1998). Bone geometry, including the assessment of *W*

[25] Remember, the wind can come from all sides.

can easily be obtained and allow for an excellent estimation of bone strength (Ferretti *et al.* 1996, Ebbesen *et al.* 1997) and stiffness (Martin *et al.* 2004). Trabecular density, as assessed by pQCT predicts the compressive strength of trabecular bone fairly well (Ebbesen *et al.* 1997, Ebbesen *et al.* 1998). The latter relationship however, is a power function. Ebbesen found exponents around 2.7 for human iliac bone samples (Sievanen *et al.* 1996, Ebbesen *et al.* 1997). Other authors, may be for convenience, assume exponents of 2. So, for example, a reduction in trabecular density of 50% would lead to a reduction in strength of 75%.

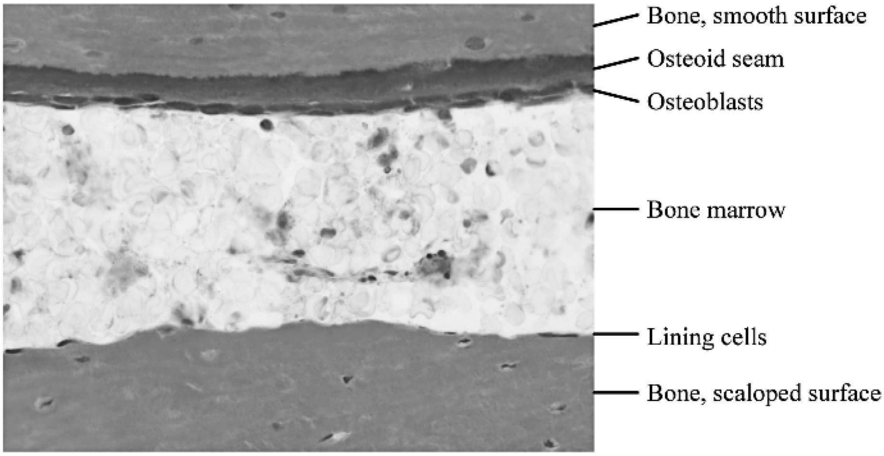

Figure 7-10. Modeling. Goldner trichrome staining of human trabecular bone from a pelvic biopsy in an 8-year-old boy. On the upper trabeculum, osteoid has been laid down on a smooth surface. Note that the osteoid surface itself has a smooth surface, and so will the bone after it has been mineralized. In the image, the osteoblasts are quite flat, suggesting that their secretory activity is only moderate. On the lower trabeculum, the scalloped surface indicates earlier resorption by osteoclast. Formation of the upper trabeculum and resorption on the lower trabeculum results in an overall drift towards the bottom of the image. Image courtesy of Rose Travers and Frank Rauch. See also color plate.

4 ADAPTIVE PROCESSES IN BONE

For the longest part of human history, bones have been regarded as "dead" material. Only recently has it been recognized that bones, which are fundamental to life on Earth, are living structures themselves. They metabolize and undertake adaptive processes, which we are beginning to understand. Most importantly, although there is meaningful variation in material properties across the bones of different species (Currey 2002), Nature does not alter these properties within a single individual[26]. Rather, she changes the design in order make bones stronger or weaker.

4.1 Modeling

Modeling results in the sculpting of bones by drifts of their surfaces (Frost 1990a). These drifts encompass bone formation on one envelope, and often resorption on the opposing envelope. As an example, consider the diaphysis of a long bone during growth. As the bone becomes longer, it also increases its outer (periosteal) and inner (endocortical) shaft diameters. The latter is caused by the simultaneous formation on the periosteal envelope and by resorption of bone on the endocortical envelope.

Microscopically, modeling implies large arrays of osteoblasts (Figure 7-10) working together on one envelope. Conversely, resorption is by several osteoclasts acting independently. The bone balance of modeling is usually positive, i.e., the bone structure becomes stronger as a result. However, it should be noted that modeling is not just a synonym for formation[27]. Rather, both formation and resorption help to shape the bone. Modeling is thought to optimize the structure of trabecular networks (Huiskes *et al.* 2000), and it can also help to straighten long bones after malunion[28] (Frost 2004).

4.2 Remodeling

Modeling prevails during skeletal growth. Conversely, once our skeletons have adapted to their final dimensions, bone turnover is predominantly by remodeling. Remodeling is the replacement of old bone by new material. It therefore can be seen as tissue repair, helping to avoid the accumulation of microdamage and thus preventing material fatigue (Frost 1960, Mori and Burr 1993). Remodeling follows the so-called *A-R-F sequence*, which involves the activation of osteoclasts, the resorption of old bone, and the formation of new bone (Takahashi *et al.* 1964).

This is done by the so-called *basic multicellular units* (BMU), which tunnel their way through bone. One or a few osteoclasts work their way through the bone, resorbing the old bone material. They are supplied with an artery, usually two veins, and a nerve ending. The blood supply reflects the high metabolic demands of the remodeling process. Too little, however, is known regarding the function of the neural supply (Chenu 2004). Closely behind the osteoclast, osteoblasts refill the resorption space layer by layer. Many authors believe in a physiological coupling between osteoblasts and

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[26] This is unlike tendon, where strength training increases the elastic modulus, and immobilisation decreases it (see the excellent work by Neil Reeves and Constantinos Maganaris).
[27] A misconception that is not unfrequent.
[28] Fracture healing with a “kink”.

osteoclasts. Ample *in vitro* evidence suggests that osteoclast activity is controlled by the osteoblasts (e.g., via RANK), and vice versa that osteoblasts are controlled through by-products of osteclastic resorption (e.g., TGF-ß). While such coupling would absolutely make sense to explain the co-operation of osteoblasts and osteoclasts during the remodeling process, sensible doubts exist as to effectiveness and relevance of such coupling as an omnipotent principle (for an excellent challenging review see Gasser 2006).

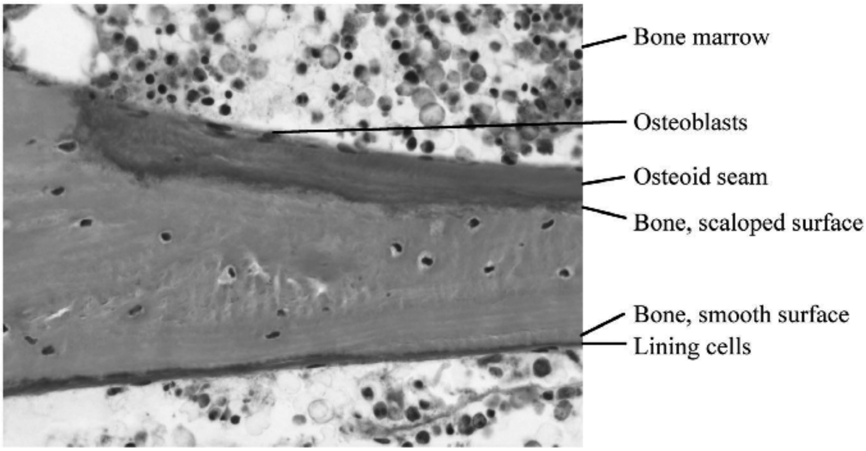

Figure 7-11. Remodeling. Goldner trichrome staining of human trabecular bone from a pelvic biopsy in a 12-year-old girl. The osteoid seam on the upper part of the trabeculum has been laid down on a scalloped surface. Osteoblasts are very flat, indicating that they are re-differentiating into lining cells, which may already have happened in the right part of the image. Note the continuity of the old envelope at the left end of the image with the surface of the osteoid seam, suggesting that the same amount of bone has been formed as had earlier been resorbed. Photograph courtesy of Rose Travers and Frank Rauch. See also color plate.

Microscopically, remodeled bone can be recognized by the scalloped surface on which it has been laid down (Figure 7-11). In compact bone, this scalloped layer has been called the "cement" line[29], and it confines what has been known as the *Haversian system*[30] since 1691 (Havers, 1691). In humans, a Haversian system is a couple of mm long and has a diameter of 50-100 µm. It is a result of BMU remodeling activity within compact bone.

There are about one million BMUs active in a human at any moment in time, and because the ARF sequence requires 90 to 120 days to complete[31],

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[29] Also called *reversal line*

[30] Also known as *secondary osteons*.

[31] Note that this is considerably longer than the lifespan of a multinucleated osteoclast. Hence, during the lifetime of a BMU the osteoclasts have to be replaced. Also importantly, the time to complete is prolonged with age.

the activation frequency, i.e., the emergence of new BMUs in the entire skeleton is three to four million per year. If the number of active BMUs increases, the overall resorption space will also increase. The result will be a temporary bone loss until the number of active BMUs returns back to normal. For similar reasons, a short-term decrease in activation frequency will lead to a temporary bone loss. Consideration of such transitory effects is crucial in interpreting study results. For example, increases in *bone mineral density* that level off after a year or so are likely to be due to change in activation frequency. They are indeed observed in drugs that inhibit osteoclast activity, such as bisphosphonates (Liberman *et al.* 1995).

Each BMU has a bone balance by itself, which has been termed ρ. Under normal conditions, in the conservation zone (Figure 7-12), ρ is slightly negative, i.e., remodeling leads to a mild bone loss. An estimation yields that for the 0.5 mm^3 that each BMU turns over, 0.003 mm^3 or 0.6% are not re-filled (Frost 2004). However, that value is increased under disuse conditions, where ρ can approach values of –100%.

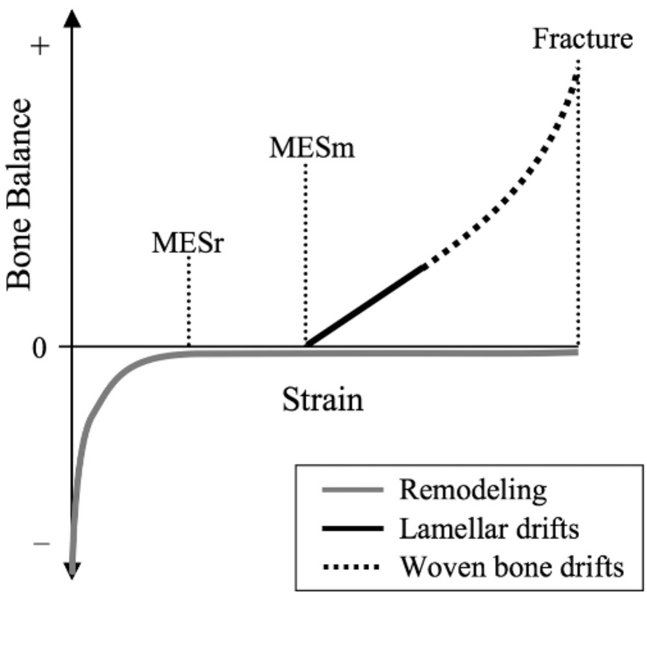

Figure 7-12. Frost's Mechanostat Theory (Frost 1987a, 2003). In this theory, modeling and remodeling are responsive to the strains that come with the habitual loading patterns. As strains are above the MESr threshold, remodeling restores the resorbed bone almost entirely. Below MESr, however, remodeling is associated with an increasingly negative bone balance. Modeling is turned on when strains exceed the MESm threshold. Modeling drifts in humans are usually by lamellar bone. However, above a certain threshold there is formation of woven bone. Because a positive bone balance will lead to a more rigid bone structure, thus reducing strains within the bone, the mechanostat theory describes a negative feedback loop. The range between MESr and MESm is also called the "conservation" mode or zone. For further explanation see text.

4.3 Mechanostat Theory

After the mechanisms of bone turnover by modeling and remodeling had been deciphered in the 1960's and 1970's, the question arose as to what governs these mechanisms. A plethora of observations suggested that mechanical influences are crucially important. Galileo Galilei was the first to recognize that bones are adapted to the loads they bear (Galilei 1638). Julius Wolf and D'Arcy Thompson progressed on towards a more mathematical description of that adaptation (Wolff 1870, 1899, Thompson 1917). However, it took until 1987 before the *Mechanostat Theory* was proposed (Frost 1987b), which is the first formal theory of bone adaptation. In essence, it maintains that modeling drifts are stipulated when strains within the bone exceed a certain threshold (*minimal effective strain* [or *stimulus*] *for modeling*, or MESm) (Figure 7-12).

Conversely, if the strains remain protractedly below a certain threshold (*minimal effective strain for remodeling*, or MESr), the formation by the BMUs is incomplete, thus leading to a negative bone balance. In other words, the theory proposes that exceedingly large strains lead to a strengthening of bone structures, while low strain levels lead to local bone loss. The mechanostat can therefore be understood as a control system with a negative feedback loop that keeps the strains within certain limits. The theory implies that bones adapt to the largest habitual loads, which from an engineer's point of view makes sense.

There has been quite some discussion regarding the actual values for MESr and MESm. For MESr, values around 50 to 100 microstrain have been proposed (Frost 2004), and for MESm values around 1000 microstrain (Schiessl *et al.* 1998, Frost 2004). While it is difficult to obtain empirical evidence for MESr, *in-vivo* strain measurements can give us some idea about MESm. Such measurements at the human tibia during vigorous physical activity yielded peak strains of up to 2000 microstrain (Burr *et al.* 1996). Moreover, in the leg bones of animals ranging from mouse to horse, i.e., covering 4 decades in body mass, peak strains have been found during locomotion that ranged only between 1000 and 2000 microstrain, i.e., they were independent of body mass (Biewener 1990). Given that bone fractures between 10,000 and 40,000 microstrain (see above), this implies that a safety factor of 10 or so seems to be universally found across species. Importantly, MESr and MESm can supposedly be modulated, e.g., by hormones (Schiessl *et al.* 1998, Frost 2004), and they may also be specific to the anatomical location (Skerry 2006).

4.4 Longitudinal Growth

In mammals and birds, by far the largest part of longitudinal growth occurs by endochondral ossification at the physes (therefore the name *growth* *plates*). Only a minor fraction of our longitudinal growth, but all of it in amphibians and reptiles is by endochondral ossification of the epiphysis, directly under the joint cartilage.

The physis is structured in layers, germinal cells give rise to chondroblasts, which proliferate and gradually differentiate into the chondrocytes of the hypertrophic zone. They are resorbed by chondrocytes. Next, woven bone is laid down on the remaining vertical columns. The result of this is the **primary spongiosa**. It has a bone fraction of ~50% and is readily remodeled into the **secondary spongiosa**, the bone fraction of which is usually half that of the primary spongiosa.

The cartilage layer within the physis, which runs horizontally across the long bones, entails the same problem to the transmission of forces as the joint cartilage (see above). Consequently, virtual all of the cancellous epiphysis is constant in cross section between the physis and the joint surface. Only towards the diaphyses is there a more slender design. Hence, longitudinal growth involves an inwaisting at the metaphysis. This is achieved by opposing modeling drifts on the periosteal and on the endocortical side, with resorption taking place at the periosteal envelope and simultaneous formation the endocortical envelope. There is no immediate need to remodel this bone, but as longitudinal growth progresses, and bending levers, but also muscle forces are augmented, modeling drifts enlarge the diaphyseal cross section in order to enhance its strength.

It is important to consider the complicated (and certainly not well understood) processes at the growth plate, and discern them from the secondary requirements that they impose upon the metaphyses and diaphyses. As a matter of fact the standard animal models in microgravity and other fields of research are growing mice and rats. Surprisingly, however, research is often undertaken without due consideration of the complexity of longitudinal growth. As an example, the distinction between primary and secondary spongiosa is a common mistake that can lead to tremendous misinterpretation when the effects of some agent or intervention upon *bone mineral density* are investigated.

4.5 Importance of Muscle Contraction for Bones

Within the musculo-skeletal system, our muscles work against poor levers, with a mechanical advantage[32] ranging between 1:2 to 1:10 (Martin *et al.* 1998, Özkaya and Nordin 1998). The consequences for the tibia of this are exemplified in Figure 7-13. Consider an elite long jumper, who can elicit a ground reaction force of 5000 N during a one-legged drop-jump. Accordingly, his calf muscle will generate 15,000 N (equivalent to 1.5 tons), and his tibia is subjected to a compressive force of 20,000 N (equivalent to 2 tons).

[32] From the muscle's point of view, it is rather a mechanical disadvantage.

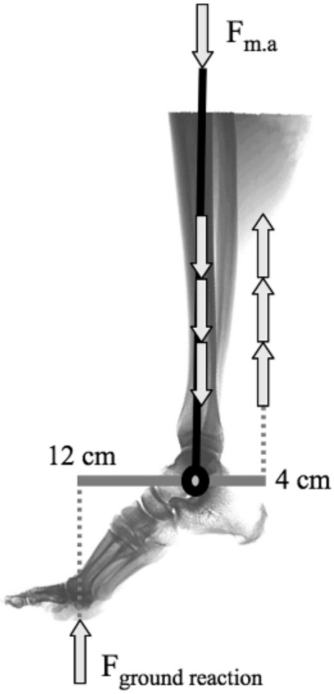

Figure 7-13. Nature of forces to which the human tibia is subjected. As the tibia is vertical, the ground reaction force ($F_{ground\ reaction}$) will generate an opposing force within the tibia propagating the acceleration of body mass ($F_{m.a}$). If we neglect the weight of the lower limb, then these two forces have the same magnitude. Due to the mechanical advantage at the ankle joint (4:12 = 1:3), the calf muscles have to generate a force three times as large as the ground reaction force when our heel is lifted from the ground.

Hence, the magnitude of forces within our musculo-skeletal system is strikingly large. Even more amazing is the contribution of muscle contraction to the loading, accounting for 75% of the tibia compression in Figure 7-13. In the forearm, for example, where there is usually no contribution of body mass times acceleration, muscle contractions will even account for 100% of bone loading forces.

Many authors have used the terms "weight-bearing" and "load-bearing" without a clear distinction, or even synonymously. As we can understand now, there is a fine line of distinction between these two terms. *Load-bearing* of bones should be understood as application of forces of any kind of origin, while *weight-bearing* includes a force component of body mass times acceleration. Hence, even if the tibia of astronauts under microgravity conditions were subjected to load bearing by some muscle contractions, there would be no weight bearing. This leads to a reduction in tibia force, even if the calf muscle contractions were as forceful as on Earth[33]. This point is relevant when designing countermeasures against muscle atrophy and bone loss under microgravity conditions. For the lower extremity, it follows that exercise paradigms need to involve a force component imitating $F_{m.a}$ in Figure 7-13 in order to be fully effective.

[33] Which most likely they are not.

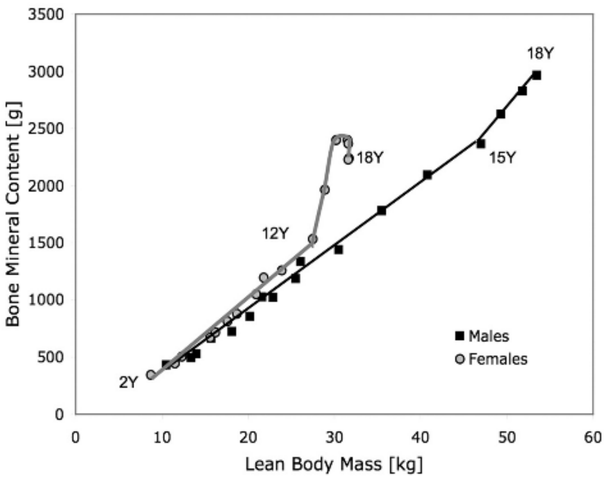

Figure 7-14. Muscle-bone relationship as demonstrated by Schiessl et al. *(1998). The total body bone mineral content is plotted against total body lean body mass, the latter being closely related to muscle mass. Both measures had been obtained by dual x-ray absorptiometry in 345 boys and 433 girls (Zanchetta* et al. *1995). Apparently, the relationship is altered at the age of 15 in boys and at the age of 12 in girls.*

However, the difference between weight bearing and load bearing being only 25% or so, it is crucial to consider muscle contraction as the main source of forces that bones have to adapt to. A beautiful illustration of skeletal adaptation to the musculature was devised by Schiessl *et al*. (1998), the main result of which are illustrated in Figure 7-14. The first striking feature to observe is the neat matching between bone mineral content and lean body mass (most of which is muscle mass) in the growing human body. In boys between the age of 2 and 15, a straight line relates both variables to each other. The second important point to note is the effect of puberty, which can be appreciated by the slight upward deflection in boys after the age of 16. More clearly, and more importantly, girls whose line is undistinguishable from the boys' line until the age of 12, accrue more bone per unit lean body mass than boys once they reach puberty.

The enhanced accrual of bone mineral in women supposedly constitutes a reservoir of calcium that can be used during lactation (Kalkwarf and Specker 1995, Kalkwarf *et al.* 1996) without compromising bone strength below the mechanical needs imposed by the musculature (Ferretti *et al.* 1998). Clinically, recognition of the "muscle-bone unit", validated with more advanced methods (Schonau *et al.* 1996, Ferretti *et al.* 2000, Schonau *et al.* 2002) and in more biomechanical detail (Rittweger *et al.* 2000), has helped to distinguish primary bone diseases from those that are secondary to muscular deficits (Schonau *et al.* 2002).

4.6 Effects of Exercise upon Bone

As outlined above, bone is readily lost under conditions of immobilization, when the habitual loading is reduced. What about the opposite? It seems pretty straightforward to increase the loading, say by some form of resistive exercise and then expect an increase in bone strength. However, the reality is more complicated than this.

There is no doubt that exercise before and during puberty increases bone mass (Bass *et al.* 1994, Kannus *et al.* 1994, Bass *et al.* 1998, Specker and Binkley 2003, Specker *et al.* 2004). The effects of exercise are site specific (Kannus *et al.* 1994, Kontulainen *et al.* 1999, Bass *et al.* 2002), and exercise modes involving large muscle forces seem to be more effective than others (Tsuzuku *et al.* 1998, Dickerman *et al.* 2000). If the exercise is adhered to, bone mass seems to remain constant even to very old age (Wilks *et al.* 2006).

However, all attempts to increase bone mass by exercise in adulthood have yielded either humbler results (Maddalozzo and Snow 2000, Vincent and Braith 2002) or no result at all (Rhodes *et al.* 2000, Milliken *et al.* 2003). In post-menopausal women, the best that could be achieved by exercise was to mitigate or equalize bone loss (Heinonen *et al.* 1998, Hawkins *et al.* 1999, Verschueren *et al.* 2004). However, this does not imply that one could not gain bone adulthood. As an example to the contrary, the amount of bone that is lost during bed rest is re-gained almost to the milligram (Rittweger, unpublished data). The inability of the adult skeleton to increase bone mass during adulthood therefore constitutes a puzzle. Nevertheless, it is now well documented that an adequate type of exercise can prevent bone loss during immobilization such as bed rest (Rittweger and Felsenberg 2004, Shackelford *et al.* 2004, Rittweger *et al.* 2005), suggesting that exercise is indeed effective for bone. Hence, the solution for our puzzle may lie in factors other than bone or muscle, e.g., the inability of tendon or joints to adapt to increased loads.

Hence, while the efficacy of exercise in general is well documented, there is comparatively little known as to which kind of exercise performed during which intervals elicits the optimal response. In young rats, five jumps per day have about the same effect as 100 jumps (Umemura *et al.* 1998), indicating that relatively few loading cycles are required to elicit maximal modeling responses. However, conservation of bone may be a matter that is different from bone accrual during growth. In a long-term bed rest study in Toulouse, 2-3 bouts of resistive exercise were able to maintain the thigh musculature (Alkner and Tesch 2004), but not bone mass at the femur, tibia, and spine (Watanabe *et al.* 2004, Rittweger *et al.* 2005). On the other hand, daily exercise successfully maintained bone in two independent studies (Rittweger and Felsenberg 2004, Shackelford *et al.* 2004).

In the past, research has focused (too much) upon bone mineral density and bone mass, as the available technology (e.g., dual X-ray absorptiometry) did not allow for a more detailed anatomical approach. With the advancement of computed tomography, we are currently gaining the first insight as to how bone geometry responds to exercise and disuse. In the epiphyses, there is evidence that the cortical area is more responsive to exercise and unloading than the central portions (Nikander *et al.* 2006, Rittweger *et al.* 2006b). With respect to the shaft geometry, it is well established from animal studies that its cross section assumes a more circular shape in conditions of (Allison and Brooks 1921, Carey 1929, Vigliani 1955b, 1955a) and the same turns out to be the case in humans (Rittweger, unpublished data). It is a tempting interpretation to directly ascribe this to the reduced muscle pull. As an exercise, contemplate the insertion of the calf muscles at the tibia for a while (Figure 7-09), which is in the plane for which the tibia's moment of resistance is the largest.

5 HOMEOSTASIS

Beyond its mechanical functions, bone is interlinked into the endocrine network providing the homeostasis of our *milieu intérieur*. Bone constitutes the major reservoirs of calcium and phosphate to our body. Approximately 1 kg of calcium in bone is confronted by 1 g in the extracellular and intracellular compartments. Calcitonin, *parathyroid hormone* (PTH), and the D-hormone[34] are the hormones involved in calcium metabolism. Calcitonin stimulates bone formation and thus helps to store calcium. D-hormone stimulates the uptake of calcium in the intestine and kidney. It also fosters bone mineralization and enhances function and proliferation of skeletal muscle (Boland *et al.* 2005). PTH has been regarded as a mere antagonist to calcitonin. However, while it is true that basic levels of PTH stimulate bone resorption, pulsatile levels of PTH can induce *de novo* bone formation in adulthood (Reeve *et al.* 1980). There is accumulating evidence that this is by modeling. Recently, recombinant PTH has been approved for the treatment of osteoporosis (Reeve 1996, Neer *et al.* 2001).

Traditionally, it has been thought that calcium homeostasis is regulated via these hormones, and that the exchange were solely by resorption and formation of bone (Heaney 2003). However, the mineralization lag time is around 10 days, osteoclast recruitment takes eight days (Eriksen *et al.* 1994), and hormones can modulate the activity of existing osteoclasts only in the range of minutes and hours. Calcium homeostasis exclusively by resorption and formation would hence be sluggish and latently risk hypercalcaemia. Therefore, and also for physico-chemical reasons of calcium phosphate solubility (Talmage 2004) and the balance of calcium fluxes

[34] The activated vitamin D (1,25 OH D).

(Parfitt 2003) it has to be expected that there be a rapid ion exchange mechanism independent of resorption and formation. Evidence for such a system has recently been put forward (Marenzana *et al.* 2005).

Bone could also be regarded as a (limited) reservoir of protein. It is evident that a diet poor in protein hampers skeletal growth (see Chapter 9). In adult rats, a low-protein isocaloric diet reduces bone formation, making the bone balance ρ of the BMU negative. That ensues bone loss and reduction in bone strength (Bourrin *et al.* 2000b). Suppression of the somatotropic axis and suppression of IGF-1 levels have been proposed as the mechanisms involved (Bourrin *et al.* 2000a). In female rats, amenhorrhea aggravates the problem, fostering also bone resorption (Ammann *et al.* 2000). Essential amino acids can set off the effects upon bone (Ammann *et al.* 2002), and so can the anti-resorptive treatment with pamidronate (Mekraldi *et al.* 2005). It seems thus that there be a physiological "starvation" program that spares protein in bone remodeling.

6 HYPERGRAVITY BONE RESEARCH

There is an established *in vitro* model of murine foetal long bones. Very interestingly, this model has been applied in hypogravity, normogravity and hypergravity[35] (Van Loon *et al.* 1995, Vico *et al.* 1999). The results show enhanced mineralization under hypergravity conditions as compared to normogravity, and reduced mineralization under hypogravity conditions. At first glance, this is suggestive of hypergravity being capable of preventing, or even reversing, the detrimental effects of microgravity upon bone, as though there was a continuum: microgravity–normogravity–hypergravity. Unfortunately, animal studies do not support this simplistic view. Hypergravity, depending on the magnitude of rotational acceleration, takes quite subtle effects upon bone. Trying to make sense of the published literature is therefore a difficult business and requires solid background knowledge.

To start with, two effects have to be considered in relation to artificial gravity. Firstly there is a centrifugal acceleration, A_c, given by

$$A_c = \omega^2 r, \qquad [1]$$

where r is the radius of centrifugation and ω is the angular velocity. Let us call this the **gravitational** effect of centrifugation. It is large as compared to the second one, namely the Coriolis acceleration[36].

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[35] Because of our obvious inability to carry out investigations in a true hypergravitational field, the term *hypergravity* in this chapter denotes centrifugation leading to a total acceleration higher than 1 g.

[36] For reasons of energy conservation.

This acceleration emerges when a mass shifts the radius of rotation, and it is given by

$$A_r = -2\ \omega\ v, \qquad [2]$$

where v is the velocity of the radial shift. This effect could be called the **rotational** effect of centrifugation, and it is responsible for the nausea that many people experience as an "adverse" effect.

As can be easily seen, the gravitational effect depends upon r, the radius of centrifugation, but rotational effects do not (see also Chapter 2). This circumstance has been taken advantage of in order to isolate both effects in scientific experiments (Smith 1975, Vico *et al.* 1999). In principle, two groups of animals are investigated with the same angular velocity, and hence identical rotational effects. However, one group is centrifuged with a short radius (and thus low gravity levels), and the other with a long radius (and high gravity levels). While that approach seems very elegant at first glance, it requires that the animal or human is still able to elicit radial shifts with unchanged velocity v under high gravity level conditions. Past research has failed to ascertain this. The reason why it is important to have a full account of rotation-related nausea is that it will have profound effects upon nutrition. As detailed above, however, nutrition in turn is crucial for bone metabolism, particularly with regards to longitudinal growth.

It must also be considered in how far animals or humans will actually behave when exposed to hypergravity. Emerging from mathematical scaling laws, an increase in typical length (L) is paralleled by an increase in typical cross section proportional to L^2, and by an increase in typical mass proportional to L^3. Muscle force is related to the muscle cross section (hence to L^2), but static and dynamic forces for posture and movement need to overcome body mass (hence to L^2). In that sense, small animals are advantaged because body mass is less crucial to them. Therefore, they are naturally designed to assume a crouched posture, where the long bones significantly deviate from the vertical axis. By contrast, the design of large land-living animals foresees an erect posture, with the long bones perfectly aligned to the vertical (McMahon 1975, Biewener 1983). However, under hypergravity conditions an erect posture will be easier to maintain than a crouched one – which smaller species may be unable to tolerate due to their design. Hence, we must be prepared to encounter differences across species in response to hypergravity that are related to behavioral constraints.

6.1 Past Research

The most consistent observation in hypergravity animal model is probably the loss in **body mass** (Smith *et al.* 1959, Wunder 1960, Oyama and

Zeitman 1967, Riggins and Chacko 1977). There seems to be a reduction in food intake during the first days of centrifugation (Feller and Neville 1965, Oyama and Platt 1965), and losses in body weight are particularly pronounced during this period. At the same time the behavioral patterns are altered (Oyama and Platt 1965). Most likely, these transitory changes are due to motion sickness, occurring as a result of rotational effects. One should expect that hormonal changes accompany this transitory adaptive phase. However, even when subjected to chronic or virtually lifelong (810 days) centrifugation, rats depict a marked reduction in body weight (Smith 1975), indicating that reduced food intake or energy expenditure may be more than a transitory phenomenon. As to body composition, hypergravity seems to reduce the musculo-skeletal mass in proportion to total body mass.

The second effect found in many studies is a reduction in **longitudinal growth** (Wunder *et al.* 1960, Smith and Kelly 1963, Jankovich 1971, Smith 1975, Jaekel *et al.* 1977, Smith 1977, Doden *et al.* 1978). It has been reported that the ratio of length/diameter was decreased in rats after centrifugation at 2 g (Smith 1975). The author interprets his findings in saying that hypergravity lead to an increased "robustness" relative to the shorter length of the bone. However, there is no relationship established between the length of bones and their diameter, and consequently any such conclusion is unjustified.

A more conclusive study compared rats exposed to hypergravity with weight and age-matched controls (Amtmann 1973). The femur length and also its diaphyseal cross section were comparable among hypergravity animals and their weight-controls. Moreover, when considering the basic rules of mathematical scaling (see above), it turned out that the reductions in femur length and cross section in the centrifuged animals were as they would be expected from their reduction in body weight. This suggests that the changes in bone dimensions are merely an effect of biological scaling, i.e., longitudinal growth was reduced in the centrifuged animals. However, the femur's geometry was systematically altered by centrifugation, leading to a more circular cross sections, confirming an earlier finding by Wunder in mice (Wunder 1960). As it was stated above, more circular bone cross sections can be a sign of reduced loading. Seemingly paradoxical for hypergravity conditions, forces elicited by the musculature may very well be reduced if the animals are unable to assume their normal posture and use their habitual muscles. Alternatively, the more circular cross section might constitute an adaptation to increased compressive loads (by body mass) with unchanged or reduced bending moments (by muscle pull).

Hence, both the reduction in body mass and the reduction in musculo-skeletal mass, as well as the smaller bone dimensions with centrifugation could be explained be a primary affection of the **growth plate**. Negative alterations of the growth plate are known to occur under conditions of microgravity (Jee *et al.* 1983). Conversely, the growth plate appears to become thinner as a result of centrifugation, and femoral ossification appears to occur at a younger age (Smith 1975). Moreover, Vico *et al.* report profound changes in the growth plates of young rats (Vico *et al.* 1999). Their study was one of the few to include both a gravitational (2 g) and a rotational (1.03 g) group. It was found, quite importantly, that micro trauma occurred in the hypertrophic zone of the tibia growth plate in 2 out of 10 animals in the gravitational group. In addition to that, the width of the physis was reduced by about 25% in the gravitational group, but not in the rotational group. This is strongly suggestive of direct mechanic damage by hypergravity of 2 g to the tibia growth plate in growing rats. Moreover, the authors found the width of the primary spongiosa[37] to be reduced both in the gravitational and in the rotational group (Figure 7-15). The magnitude of this reduction was only mildly larger in the gravitational group, suggesting that the reduction in longitudinal growth, at least within the first 4 days span covered by that study, is mainly related to rotational rather than to gravitational effects.

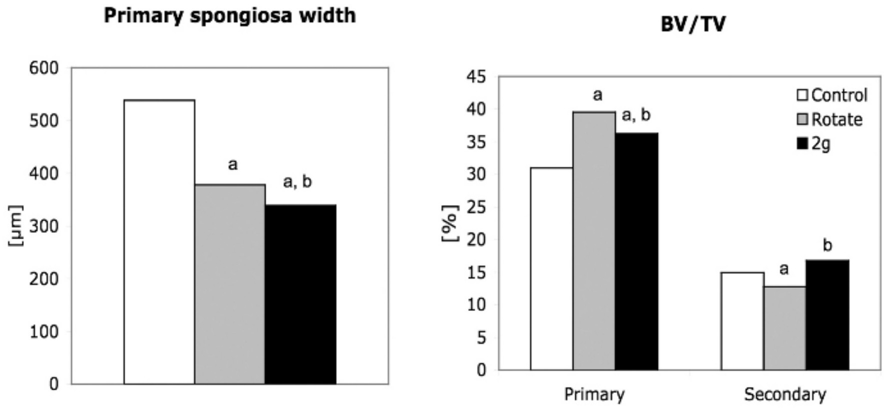

Figure 7-15. Primary spongiosa width and fractional bone volume (BV/TV) in young rats rotated for four days at 1.03 g, centrifuged at 2 g and controls. Data are for the proximal tibia epiphysis and are adapted from Vico et al. *(1999). a = different from control, b = different from rotate group. The width of the primary spongiosa, which can serve as a surrogate measure for longitudinal growth rate, is considerably reduced by rotation and further hampered by 2-g centrifugation. Conversely, the fractional bone volume (≈bone density) in the primary spongiosa is increased more by rotation than by 2 g. More importantly, however, there is a reduction in BV/TV in the secondary spongiosa by rotation, but no effect by 2 g.*

[37] Assuming a constant rate of turnover of the primary spongiosa, its width is an estimator of longitudinal growth rate.

The most intriguing issue with regards to hypergravity and bone, however, is bone strength or, where measures of it are unavailable, **bone mass**. The original publication by Wunder *et al.* suggested a comparative increase in outer diameter (Wunder *et al.* 1960). However, the first measurements of bone mass revealed quite the opposite, namely a decrease (Smith and Kelly 1963), albeit a reduction that was seemingly less than in proportion to body mass (Oyama and Zeitman 1967).

Clearly, the weight of entire bones is a crude method. More informative data stem again from Vico's study in rats exposed to 2 g for four days (Vico *et al.* 1999). Analysis of the secondary spongiosa in the tibia metaphysis showed a decrease in trabecular bone density with rotation, but no change with 2 g exposure. This suggests that bone loss induced by rotation could be set off by centrifugation at 2 g. However, results for the humerus diverge from the tibia results. Here, there was no change observed between groups. As Vico *et al.* argue, the reason for this could lie in the earlier closure of the growth plate in the humerus as compared to the tibia. However, evidence in their publications suggests that closure of the physes did not occur[38]. Moreover, although not reaching statistical significance, the metaphyseal changes in the humerus were opposite to those in the tibia, rather than being only mitigated. Therefore, another explanation might hold true. Possibly, the mechanical usage was affected differently in the humerus and in the tibia in the context of altered movement patterns under hypergravity conditions, and animals loaded their hind legs more than the forelegs.

Another interesting study is by Riggins and Chacko (1977). After centrifuging male chicken for 18 weeks up to 3 g, the tibia's strength in torsion, its relative ash weight, specific gravity and the histological examination were all unaffected. However, the outer diameter of the tibia shaft was reduced in the experimental animals, while cortical thickness was increased. In other words the tibia had gained mass, but also become more slender, but maintained overall its strength. Again, these results suggest that there is no "global" effect by hypergravity, but that more detailed analyses, including a biomechanical approach, are required to make sense of the skeletal effects.

While there has been some evidence put forward above to suggest that the skeletal effects of hypergravity are subtle or even detrimental, Oyama's study suggests clear cut positive effects in beagle dogs (Oyama 1975). By analyzing the circadian rhythms the author identified a 2-week adaptive phase to centrifugation at 2.5 g. In line with studies in smaller mammals, body mass was reduced in the centrifuged dogs. However, the length and diaphyseal cross sections of their long bones was comparable to the control group, and the fat free dry weight of the fore- and hind limb bones was even increased in

[38] As evidenced by the existence and width of the physis and primary spongiosa.

the centrifuged dogs. Photon absorptiometry showed that this increase in weight was due an increase in X-ray attenuation, and thus most likely caused by an increase in bone mineral content. This effect was not significant in the epiphyses but only in the meta- and diaphyses.

Besides other possible explanations, the positive skeletal response in this study is most likely species related. As discussed above, there is reason to assume that the musculo-skeletal system is able to tolerate higher gravity levels in larger species. It may therefore be questioned, in how far studies in rodents are informative for the search of countermeasures. As to humans there is to date only one study. Iwase *et al.* (2004) investigated young healthy males during 14 days of 6-deg head down tilt with and without bicycle exercise at 2 g every 1-2 days. Without giving much detail in their publication, the authors report that "urinary de[s]oxypyridinoline was suppressed in the countermeasure group, but not in the control group". This reported suppression of a bone resorption marker is an encouraging indication, but it can by no means prove the efficacy of hypergravity as a countermeasure for musculo-skeletal deconditioning in humans.

6.2 Research Questions

It is clear from the above that there is a huge gap between what we <u>could</u> and what we actually <u>do</u> know about bone and artificial gravity. The scientific literature is scant. That is due to having focused on a potentially tricky animal model (growing rodents), and also to a lack in understanding and technology at the time the studies were done. To date, Vico *et al*. (1999)'s study is the only one to apply methods that allow some basic understanding of the mechanisms involved.

Even still, some conclusions can be drawn from the past research:

a. Hypergravity effects upon the skeleton are not just opposite to those by microgravity.
b. Hypergravity leads to a reduction in body mass.
c. In rodents, this reduction is related to an inhibition of longitudinal growth. Evidence suggests a crucial role of the growth plate, which may be subject to mechanical damage (Vico *et al.* 1999). This may allude to a failure to cope with hypergravity.
d. Conflicting results are observed with respect to bone mass. In rodents it seems to decline with hypergravity, but data in dog suggest an increase (Oyama 1975).
e. Very interestingly, there seems to be a consistent alteration in long bone geometry, with the shaft assuming a more circular cross section in response to hypergravity exposure.

From a bone physiologist's point of view, the most pertinent question is, of course, whether bones can get stronger by hypergravity exposure. In fact, this very question was at the onset behind past hypergravity research (Wunder *et al.* 1960).

However, as we have seen in the present relation, there is no simple way to answer that question. If we wish to tackle it nevertheless, what would be the necessary steps involved?

a. Firstly, future research should assess the tolerable limits of hypergravity. It does not take much imagination to expect an animal centrifuged flat on its abdomen to lose bone from its legs. The question therefore is up to which g-levels the musculo-skeletal system operates in a meaningful way? Simple ways to test this would involve climbing, jumping and balancing tasks.
b. Similar arguments apply to the adaptation of tendons, joints and other connective tissue. As discussed above, they might constitute an unrecognized limitation to exercise effects upon bone and deserve due consideration in hypergravity research. To the best of my knowledge, there is no study so far that would have looked at those tissues.
c. Future research must clearly discern rotational from gravitational effects. Experiments should be designed in a way so that rotational effects are minimized (allow for adaptation), and nutrition needs to be controlled / monitored.
d. A spectrum of different species needs to be tested, covering a relevant range of body masses and designs. It will be easier to start with animals in which longitudinal growth has come to an end, rather than confounding the problems associated with longitudinal growth and bone modeling.
e. Finally, state of the art technology should provide valuable mechanistic insights into processes of skeletal adaptation. It is actually a scientific scandal that we do not have any information regarding bone formation rate or bone geometry under hypergravity conditions.

Considering these pre-conditions, hypergravity bone research may well develop into an extremely rewarding field that will help to enlarge our vision. For instance, will hypergravity affect the muscle-bone relationships? Does the maximum tolerable gravity level change with age? Will increased gravitational forces affect the structure and anisotropy in cancellous bone? Is the accumulation of microdamage (and hence the “aging” of bone material) accelerated under hypergravity conditions? Are there portions of bone that respond differentially to hypergravity loading? Comparing the effects by short-arm and long-arm centrifuges, will we be able to assess the effect of interstitial fluid pressure upon bone mechanotransduction and bone metabolism?

These and other research questions may lie on the path towards the use of artificial gravity as a countermeasure tool. There should be little doubt that normogravity (e.g., 1-g level in a centrifuge) will effectively maintain musculo-skeletal integrity, provided it is provided for 24 hours per day. But would 12 hours also do? Or even less? Going further down that road, artificial gravity in combination with (simulated) microgravity opens the field of hypogravity research. What would the skeletal adaptations be like if we were to live under 0.16 g (Moon) or 0.38 g (Mars) conditions?

The textbooks of bone biology will remain incomplete without the light of gravitational physiology.

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Chapter 8

INTERACTIONS AMONG THE VESTIBULAR, AUTONOMIC, AND SKELETAL SYSTEMS IN ARTIFICIAL GRAVITY

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1 INTRODUCTION

As gravity imposes a direct and permanent stress on body fluids, muscles and bones, it is not surprising that weightlessness has important effects on cardiovascular and musculo-skeletal systems. However, these harmful effects – detailed elsewhere in this book (see Chapters 5, 6, and 7) – do not result entirely from the removal of the direct stress of gravity on these organs, but are partially and indirectly mediated by the vestibular system. Besides its well-known crucial role in spatial orientation and postural equilibrium, it is now clear that the vestibular system is also involved in the regulation of other important physiological systems, including respiratory and cardiovascular systems, circadian regulation, food intake, and even bone mineralization. The neuro-anatomical substrate for these vestibular-mediated regulations is still poorly defined; however, there is much evidence that the vestibular system has strong impacts not only on brainstem autonomic centers but on many hypothalamic nuclei as well. As it is well known, although quite recently for bones, that the autonomic nervous system controls almost all body organs bringing into play the vestibular system by microgravity could virtually affects all major physiological functions.

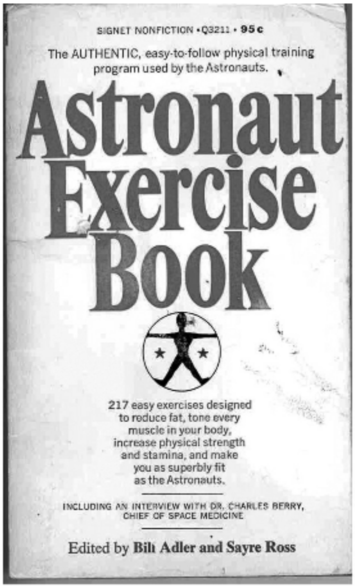

Figure 8-01. Adler and Ross recommend an integrated approach for exercise in this book published in 1967.

This chapter reviews what we know about vestibular-autonomic interactions, and more specifically, the vestibular influences on cardiovascular control and bone mineralization. Central neural circuits have been identified which enable the integration of vestibular and autonomic information. In particular, stimulation of the vestibular nerve, either through natural stimulation or via selective stimulation of vestibular afferents, is known to produce large effects on sympathetic neural reflexes and blood pressure. Recent studies have demonstrated that bilateral loss of the vestibular nerves in rats compromised the maintenance of blood pressure during changes in body posture and induced bone demineralization in weight-bearing bones. The implications of vestibulo-autonomic interaction on the use of artificial gravity as a countermeasure are briefly discussed in the end of this chapter.

2 CENTRAL VESTIBULO-AUTONOMIC PATHWAYS

The brain stem vestibulo-autonomic pathways can be broadly categorized into two components, namely **direct pathways** from the vestibular nuclei to brain stem autonomic output circuits for vestibulo-autonomic reflexes (Yates and Miller 1998), and bidirectional **indirect pathways** via the parabrachial nucleus (Balaban and Porter 1998). The influence of direct pathways on blood pressure and respiratory activity during postural changes is reviewed in Section 3 below. Furthermore, as described in Sections 4 and 5 below, the indirect pathways influence neuroendrocrine and affective responses via the medullary autonomic regions, hypothalamus, amygdala, and neocortex (Balaban 1996, Balaban 2004).

Direct vestibulo-autonomic reflexes are primarily mediated from pathways leading from the caudal medial vestibular nucleus and inferior vestibular nucleus. These direct descending pathways include projections to the *nucleus tractus solitarius* (NTS), the nucleus ambiguous, nucleus raphe magnus, dorsal motor vagal nucleus, the lateral medullary tegmentum, and ventrolateral medullary reticular formation to preganglionic neurons in the thoracic spinal cord (Yates 1992). The NTS plays an integral role (Onai *et al.* 1987), also receiving inputs from visceral afferents (Barron and Chokroverty 1993). The cerebellar modulation of vestibulo-autonomic reflexes appear to be mediated through the medial cerebellar cortex, including the medial uvula and anterior lobe regions (Balaban and Porter 1998, Ito 2006).

It is interesting to note synaptic inputs to the vestibular efferent neurons can be mapped from visual, somatic, and autonomic pathways (Metts et al. 2006). Yates and colleagues (Yates *et al.* 2000) observed a modulation of vestibular nuclei activity in cats following recovery from bilateral labyrinthectomy and vestibular neurectomy. The relative rapid recovery of autonomic function following peripheral vestibular lesions (Yates and Bronstein 2005) is consistent with the time course of recovery from orthostatic intolerance following spaceflight (Yates and Kerman 1998).

Therefore, in addition to vestibular influences on autonomic function, the central pathways provide insight on how visceral inputs may in turn contribute to spatial orientation illusions in altered gravitational environments (Mittelstaedt and Glasauer 1993).

3 VESTIBULAR INFLUENCE ON CARDIO-RESPIRATORY REGULATION

3.1 Cardiovascular Regulation

A simple change in posture, such as moving from a supine to a standing position (orthostatism), dramatically alters the intravascular pressures and "pools" blood in the lower extremities. The resulting transient decrease in venous return to the heart lowers cardiac filling pressures, cardiac output, and perfusion of the brain. This leads to hypotension that can result in fainting in the absence of correcting action. Mechanisms that provide protection from hypotension during standing include contraction of the leg muscles, which prevents an increase in venous capacitance and a decrease in intrathoracic pressure, and an increase in abdominal muscle contractions that force blood toward the heart. However, the most important short-term response to orthostatism is a generalized vasoconstriction induced by α adrenergic stimulation, the origin of which is a deactivation of cardiopulmonary receptors and a decrease in arterial baroreceptor activity when arterial pressure drops (Blomqvist *et al.* 1980). The increased sympathetic outflow to the splanchnic bed, the lower limb and more generally to the less necessary organs, maintains blood in the central circulation and restores blood pressure.

Whereas the cardiac response to carotid baroreceptor stimulation of the vagal origin is less than 0.5 s (Eckberg *et al.* 1976), the vascular sympathetic response is much slower. The peak of the muscular sympathetic activity in response to the carotid compression occurs 2 to 3 s after the onset of stimulation (Rea and Eckberg 1987). The delay between sympathetic activation and change in arterial pressure is about 5 to 6 s (Wallin and Nerherd 1982). Thus, this feedback mechanism does not appear to be appropriate to counteract the immediate consequence of a rapid change in posture. As a feedback mechanism, compensation originating from the arterial baroreceptors occurs only after blood pressure has dropped. An open-loop mechanism, detecting the change in posture before arterial pressure decreases would be more appropriate.

3.1.1 Animal Studies

Numerous animal studies have pointed to the vestibular system as a possible key controller of the cardiovascular system during movement and change in posture. In cats, electrical stimulation of the vestibular nerve elicits an increase in sympathetic outflow to visceral organs (Kerman *et al.* 2000). Vestibular stimulation induced by head movements modulates the sympathetic nerve activity, with an increase in splanchnic nerve activity and blood pressure when the animal is nose up (Yates and Miller 1996, Woodring *et al.* 1997). Response dynamics to sinusoidal pitch rotations are similar to those of vestibular otolith afferents, suggesting that the otolith organs are primarily responsible for the vestibulo-sympathetic response. The vestibular inputs to the rostral ventrolateral medulla, a major source of excitatory inputs to sympathetic preganglionic neurons, appear to come mainly from otolith receptors (Yates *et al.* 1993). Bilateral transection of the vestibular nerve in anesthetized and paralyzed cats decreases the ability of the cardiovascular system to compensate for hypotension induced by head or whole body-up tilt (Doba and Reis 1974, Wilson *et al.* 2006). In our laboratory, Etard *et al.* (2004) showed that there was no changes in heart rate and mean arterial pressure modulations depending on the gravity level during parabolic flight in restrained rats who had previously undergone bilateral labyrinthectomy compared to control rats.

During the first week after labyrinthectomy, head-up tilt in cats that are awake transiently decreases blood pressure. After several weeks, one fourth of the neurons in the vestibular nuclei are modulated by head tilt, suggesting that non-labyrinthine signals, presumably originating from muscle, skin or viscera, are able to substitute for vestibular inputs (Yates *et al.* 2000). In contrast, lesions of the central vestibular system (medial and inferior vestibular nuclei) can produce a prolonged impairment in posturally related cardiovascular responses (Mori *et al.* 2005). Such prolonged impairment occurs whether visual cues are present or not, suggesting that integration of visual information is achieved in the vestibular nuclei. Other structures are also implicated in shaping the vestibular signal: ablation of the cerebellar uvula prior to a labyrinthectomy results in a prolonged impairment of autonomic compensation during 60 deg head-up tilt (Holmes *et al.* 2002).

These results prompted Yates and Bronstein (2005) to propose a functional representation of the relationship between inputs signaling posture and sympathetic activation centered on the “autonomic” portion of the medial and inferior vestibular nuclei. However, even after vestibular nuclei lesions, most animals recover normal responses to head-up tilt after a few weeks (Mori et al. 2005), leaving open the possibility that other circuitry can compensate for vestibular signals.

Recent data obtained during rats in hypergravity complicates the picture. Gotoh *et al.* (2004) showed that the increase in arterial pressure elicited by hypergravity was abolished by vestibular denervation, but increased in animals with normal vestibular system and sino-aortic denervation. However, rats without both afferents exhibited no change in arterial pressure during hypergravity. The authors concluded that the vestibulo-sympathetic reflex is controlling arterial pressure by in a "predictive manner" and that the over-corrective error caused by this reflex is compensated by the baroreflex. Another explanation would be that hypergravity produced a "fear and fight" response originating from the vestibular afferent. Further investigation is required to elucidate the relationship between the vestibulosympathetic response and the direction of the gravitational stress.

The circuitry that mediates vestibulo-sympathetic reflexes has been extensively studied in cats (see Yates and Miller 1996 for a review). A limited portion of the medial (caudal) and inferior vestibular nuclei mediates the responses originating in the pitch-responsive otolith receptors. The descending pathway from the brainstem to sympathetic preganglionic neurons originates from the rostral ventrolateral medulla.

3.1.2 Studies in Humans

Demonstrating the vestibulo-sympathetic reflex in humans is far more complex than in animals. In subjects seated on a linear sled and facing the direction of movement, Yates *et al.* (1999) observed an increase in blood pressure and heart rate soon after acceleration. The effect was much smaller in labyrinthine-defective subjects.

Others authors have used the "head-down neck flexion" paradigm (Normand *et al.* 1997, Shortt and Ray 1999). When the head is moved from neck extension to neck flexion, with subjects on the side, only the neck mechanoreceptors are stimulated because there is no otolithic reorientation relative to gravity, whereas the otolith and neck receptors are stimulated when the subject is lying prone. Head-down neck flexion induces a decrease in calf and forearm blood flows with no significant changes in heart rate and blood pressure. This maneuver also increases *muscle nerve sympathetic activity* (MNSA). The alteration in blood flow is maintained, thus indicating that the effect is presumably of otolithic origin.

The interpretation of head-down neck flexion is, however, quite difficult. This maneuver might not be the best way to study the vestibular effects on the sympathetic system because, independently of vestibular or neck stimulation, neck movements modify baroreceptor response. This maneuver does not allow elevation of the immediate reaction to the stimulus precisely when it could potentially be effective in adjusting the arterial pressure.

Herault *et al.* (2002) studied femoral blood flow during parabolic flight microgravity in subjects lying supine with the neck passively flexed or aligned along the long body axis. Comparisons between 0-g and 1-g conditions are somewhat difficult because, even in supine subjects, microgravity induces a fluid shift away from the lower limbs that probably stimulates the cardiopulmonary receptors. However, comparisons among various neck positions in microgravity showed that neck flexion, in the absence of otolith stimulation, induced a decrease in femoral blood flow and an increase in femoral vascular resistance. This observation suggests that neck flexion *per se* is able to alter the cardiovascular activity.

Radtke *et al.* (2000) used the "head drop" paradigm in which the head is suddenly released into free fall to demonstrate an effect of vestibular stimulation on the cardiovascular system in humans. Head acceleration (about 0.8 g for 140 ms), which stimulated both otolith organs and semicircular canals, triggered R waves. It was found that head acceleration decreased the time delay between trigerring and the next R wave in normal subjects, but not in labyrinthine-defective subjects. By varying the delay between the R spike and the acceleration, the latency of this vestibulo-cardiac reflex was estimated to about 500-600 ms (Radtke *et al.* 2000). Kaufmann *et al.* (2002) used *off-vertical axis rotation* (OVAR) as a way to stimulate the otolith organs with no stimulation of the neck receptors. They showed that, when subjects were within ±45 degrees of the nose-up position, MSNA was closely related to gravitational acceleration, with a latency of 0.4 s. However such a response could as well originate from non-vestibular graviceptors. Yates and Bronstein (2005) suggested that labyrinthine defective patients should be studied with OVAR to validate the vestibular origin of this reflex.

3.1.3 Implications of the Vestibulo-Sympathetic Reflex for Artificial Gravity

From the above studies, it is hypothesized that multiple sensory inputs are integrated, possibly in the vestibular nuclei, to produce stable blood pressure during changes in posture. To determine the spatial orientation of the body, the CNS elaborates an internal representation of gravity using several sensory inputs (visual, vestibular, somesthetic) (see Chapter 4, Section 2). It is conceivable that in the same way, the sympathetic activation during orthostatism would be based on an internal representation of the intravascular pressure, previously built based on the same information as used for the internal representation of gravity. According to this model, an abrupt absence of or change in a given sensory input does not affect sympathetic activity or blood pressure control until a new representation is built up.

On return to Earth, postflight orthostatic intolerance, manifested by an elevated heart rate, narrowed arterial pulse pressure, unstable blood pressure, and often pre-syncope or syncope, occurs in about 30-40% of all astronauts (Blomqvist and Stone 1979, Bungo *et al.* 1985). As discussed in Chapter 5, postflight orthostatic intolerance is probably induced by multiple factors, including hypovolemia. In fact, the effects of a reduced blood volume are probably amplified by changes in the low-pressure venous system of the lower limbs and by impaired baroreflex function, as indicated by the results of bed rest studies (Convertino *et al.* 1992). Changes in the otolith signals, or their reinterpretation, may also be involved. Indeed, the removal of the normal head-to-foot gravity vector acts not only on fluid (loss of hydrostatic pressure gradient), but also on the otolithic system (see Chapter 4, Section 1). A central reinterpretation of otolith signals is presumably taking place during re-adaptation to Earth gravity (Parker *et al.* 1985). However, no data is available yet on the possible role of non-cardiovascular inputs controlling the activity of the sympathetic nervous system during or after spaceflight.

Because the otolithic control of the cardiovascular system is supposed to compensate for head tilt coupled with the observation that otolith tilt reflexes generally vanish during adaptation to microgravity (see Chapter 4), it can be hypothesized that the otolithic control of the cardiovascular system will be altered after spaceflight. This alteration would then participate in cardiovascular deconditioning. If this hypothesis is confirmed, it could have potential consequences for the design of countermeasures preventing cardiovascular deconditioning. In this context, providing artificial gravity by using centrifugation in supine subjects with the head off-center might be an effective means for maintaining otolith sensitivity and preserving vestibulo-sympathetic reflexes.

3.2 The Respiratory System

Whereas the cardiovascular deconditioning after spaceflight is obvious when considering the inability of astronauts or cosmonauts to stand up, the adaptive changes in the respiratory system do not compromise their daily life activities. This is because the effects of microgravity on the respiratory system depend more on its mechanical properties and its relationship with the abdominal wall and the intrathoracic blood volume, rather than on the central command. However, changes in posture can affect the resting length of the respiratory muscles and thus require a modification of the central command for producing an adapted ventilatory flow.

In cats, electric vestibular stimulation alters respiratory muscle nerve activity, including the phrenic, intercostal, abdominal nerves and upper airway muscle nerves (Yates *et al.* 1993). Otolithic stimulation during head rotations in the pitch plane alters respiratory nerve activity, while semicircular canal stimulation in the yaw plane seemed to have no effect (Rossiter and Yates 1996). Bilateral labyrinthectomy is followed by an increase in diaphragmatic and abdominal muscle activity (Cotter *et al.* 2001), whereas the reactivity of abdominal muscles to nose up tilt is diminished. However, the respiratory effects of labyrinthectomy decrease over a few days, illustrating the remarkable plasticity of the vestibular system. In contrast to this transient effect on respiratory muscles, the removal of labyrinthine inputs results in alterations in genioglossal responses to postural changes that persisted for about one month (Cotter *et al.* 2004).

In humans, very little is known about the physiological importance and functional characteristics of the relation between the otolith organs and the respiratory system. Natural and caloric stimulations of the semicircular canals appear to induce alterations in respiration (Thurrell *et al.* 2003) in normal subjects but not in labyrinthine defective patients. Monahan *et al.* (2002) found that the stimulation of the semicircular canal increased ventilation in humans, but the stimulation of otolith organs induced by head down neck flexion had no effects.

Kauffman *et al.* (2002) incidentally reports synchronization between breathing and linear stimulus frequency during OVAR in humans. However, OVAR stimulates both the labyrinthic and the non-labyrinthic (visceral proprioceptors) graviceptors. Therefore, the ventilatory modulation during OVAR might be due to the activation of one or both type of receptors. In a recent OVAR study (Normand *et al.* 2006), we measured the ventilatory flow in 21 healthy subjects with the head either turned 60 deg to the left or to the right. A cross correlation analysis showed that the maximum correlation between breathing and the linear stimulus frequency occurred for a phase shift of 20-40 deg, that is about one-fourth of what would be expected from a pure otolithic effect on respiratory timing (120 deg between head positions). This finding indicates that the synchronization of the respiratory cycle with a linear stimulus frequency appears to be mediated by the activation of both labyrinthic and non-labyrinthic graviceptors.

4 VESTIBULAR INFLUENCE ON BONE MINERALIZATION

It was recently shown that the sympathetic nervous system regulates bone remodeling (Bjurholm *et al.* 1988, Takeda *et al.* 2002, Togari 2002). Nerve fibers have been detected in bone in close vicinity to osteoblasts, particularly in the metaphysis and the diaphysis of long bones. Moreover, β-adrenergic receptors have been localized on osteoclasts and osteoblasts. Finally, β-adrenergic agonists activate mouse and human osteoblasts.

Because the sympathetic nervous system controls bone remodeling and given that there is much evidence from animal and human experiments indicating that the vestibular system influences the sympathetic nervous system (see Section 2, and Yates 1992 for review), Levasseur *et al.* (2004) hypothesized that the vestibular system could be involved in bone remodeling. Indeed, they found that 30 days after a bilateral vestibular lesion in rats there was a decrease in *bone mineral density* (BMD) in weight-bearing bones and more specifically in the femoral metaphysis. This site is the area with the maximum bone loss in situations known to induce bone remodeling such as ovariectomy.

To investigate the hypothesis that the modulation of BMD by the vestibular system is, at least in part, mediated by the sympathetic nervous system, Denise *et al.* (2006) examined the interaction on BMD between vestibular lesions and propranolol, an antagonist of the sympathetic nervous system. Their results confirmed that bilateral vestibular lesion induces a bone loss in femoral metaphysis: in untreated animals, 30 days after lesion, BMD of the distal femoral metaphysis was significantly reduced comparatively to control intact rats (Figure 8-02, left). However, in propranolol treated rats, there was no significant difference between intact and vestibular defective animals (Figure 8-02, right). Moreover, in vestibular defective rats, BMD is higher in treated than in untreated rats, whereas in intact rats propranolol was associated with a bone loss. Thus β-blocker prevents bone loss induced by vestibular lesion suggesting that the vestibular system controls bone mineralization partly via the sympathetic nervous system.

This bone loss cannot be attributed to a weight loss because in untreated rats there was no difference in weight between control and labyrinthectomized rats. Because it has been shown that muscle activity modulates bone volume, the effect observed in these studies could be mediated via non-specific alterations in motor behavior that is induced by vestibular lesion. Porter *et al.* (1990), however, showed that behavioral activities increase in rats with vestibular lesion. Likewise, only moderate or temporary alterations in muscle properties and in stance parameters were found after bilateral vestibular lesion (Inglis and Macpherson 1995, Kasri *et al.* 2004). Thus, it appears unlikely that change in the motor system is a significant factor for the alteration in BMD that was observed after bilateral vestibular lesion.

It is known that a decrease in blood flow induces bone loss; therefore, the sympathetic nervous system could possibly modify bone metabolism directly via osteoclastic and osteoblastic β-adrenergic receptors or indirectly via modifications of the vascularisation or both. The pathways by which the vestibular system modulates BMD are not known but, in addition to a direct activation of the brainstem autonomic centers, they could also involve a hypothalamic relay (see Section 4).

It is interesting to note that the bone loss induced by bilateral vestibular lesion has the same distribution as the bone loss induced by spaceflight. Thus, this could identify the vestibular system as mediating bone loss in weightlessness conditions. If this hypothesis is correct, it has two consequences for devising countermeasures for long-duration spaceflights. First, to be maximally effective on BMD, artificial gravity should stimulate the otolith system (see Section 5). Second, β-blockers, such as propranolol or β2 selective blockers, should be effective in preventing bone loss. On Earth, an epidemiologic study demonstrated that the use of β-blockers is associated with reduced risk of fractures (Schlienger *et al.* 2004). However, Bonnet *et al.*

(2006) found that the preventive effect of propranolol on bone loss in ovariectomized rats is dose-dependent with high doses being less effective than lower ones. Thus, before considering the use of β-blocker as a countermeasure of bone loss during spaceflight, preliminary studies in human are needed to find the correct dose.

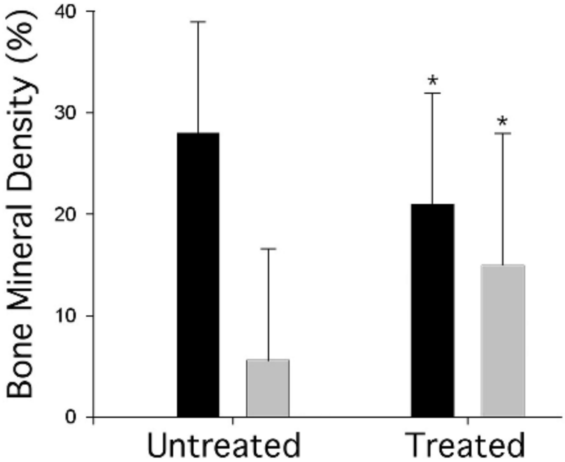

Figure 8-02. Effect of vestibular lesion and β-blocker treatment on bone mineral density in femoral metaphysis. The histograms compare the values measured 30 days after the lesion (black bars) and the values measured before the lesion (gray bars). In untreated animals, a vestibular lesion significantly decreases bone mineral density, whereas no significant variation is observed in animals treated with β-blockers.

5 VESTIBULAR INFLUENCE ON HYPOTHALAMIC REGULATIONS

Numerous animal and human studies have documented pronounced disruptions in circadian and homeostatic regulation during spaceflight and hypergravity (Alpatov *et al.* 2000, Fuller *et al.* 2002, Hoban-Higgins *et al.* 2003, Monk *et al.* 2001, Muraki and Fuller 2000, Samel and Gander 1995, Fuller and Fuller 2006). Likewise, neuroendocrine secretions in humans are altered during spaceflight (Strollo 2000) and hypergravity induces a loss of body mass and a transient anorexic response (Smith 1973).

Recently, the vestibular system was identified as a primary mediator of these circadian and homeostatic regulation responses to hypergravity (Fuller *et al.* 2002). Hypergravity induces a reduction in body temperature, amplitude of the circadian rhythm of temperature and food intake. These alterations are dramatically reduced in animals without functional macular gravity receptors (Figure 8-03). Inputs from the vestibular otolithic system modulate neural networks throughout the nervous system and more particularly regions involved in temperature regulation (anterior hypothalamus and preoptic nuclei), circadian rhythms (suprachiasmatic nuclei), feeding behavior (dorsomedial and other hypothalamic nuclei), and autonomic regulations (brainstem autonomic centers) (Fuller *et al.* 2004).

Thus, vestibular modulation of circadian and homeostatic regulation is probably mediated by hypothalamic and autonomic relays. Interestingly, it has been shown that molecular clock mediates leptin-mediated sympathetic regulation of bone formation (Fu *et al.* 2005). Thus, the vestibular system could modulate bone mineralization via a supra-chiasmatic nuclei relay.

However, these data were obtained during hypergravity experiments and even if they demonstrate that the vestibular system plays a major role in the physiological effects of hypergravity, it is not known to what extend the vestibular system could also be involved in the effects of weightlessness on circadian and homeostatic regulations.

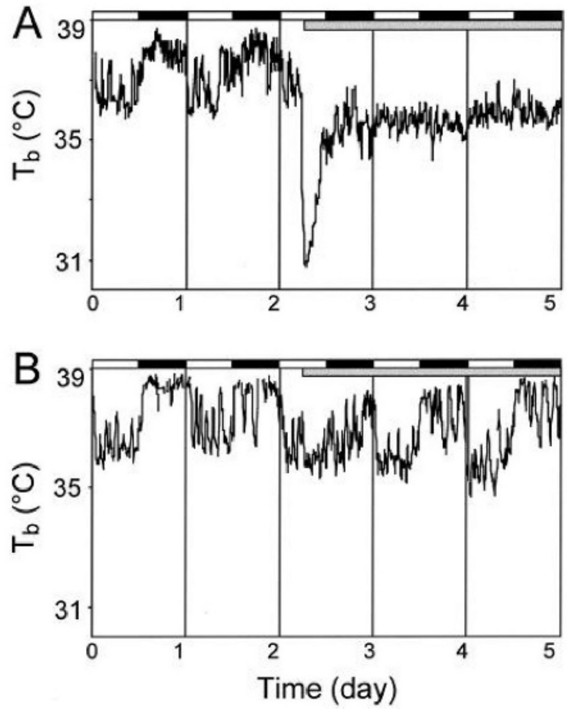

Figure 8-03. Effects of hypergravity on body temperature in mice. The first 2 days are at 1 g. The duration of the 2 g exposure is indicated by the horizontal gray bar at the top of the figure. In the normal mouse (A), there is a drop in temperature and a loss of its circadian rhythm at the onset of 2 g centrifugation. Mean body temperature rapidly recovers, but circadian fluctuation remains altered for several days. In the vestibular defective mouse (B), only small alterations in temperature are observed. Adapted from Fuller et al. *(2002).*

6 IMPLICATIONS FOR USING ARTIFICIAL GRAVITY AS A COUNTERMEASURE

The fact that some effects of weightlessness on biological systems are mediated by the vestibular system has an important implication for using artificial gravity as a countermeasure: artificial gravity should load not only bones and the cardiovascular system but the vestibular system as well. In short-radius centrifuges, the gravity level at the head level is low because the head is near the axis of rotation. If the vestibular system is implicated in cardiovascular deconditioning and bone loss during weightlessness, it would be more effective to significantly stimulate it and thus it would be necessary to place the head off-axis. In particular, positioning the subject so that the utricles would be stimulated, preferably within the plane of rotation to minimize motion sickness effects, may promote conditioning of vestibulo-sympathetic pathways reviewed in this chapter (Previc 1993), as well as other otolith-ocular reflexes (Moore *et al.* 2003).

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Chapter 9

INTERACTIONS AMONG ARTIFICIAL GRAVITY, THE AFFECTED PHYSIOLOGICAL SYSTEMS, AND NUTRITION

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1 INTRODUCTION

Malnutrition, either by insufficient supply of some nutrients or by overfeeding, has a profound effect on the health of an organism. Therefore, optimal nutrition is a necessity in normal gravity on Earth, in microgravity, and when applying artificial gravity to the human system.

Figure 9-01. A cosmonaut appears surrounded by food in the Zvezda service module on board the ISS. Photo courtesy of NASA.

Reduced physical activity, such as observed in microgravity or bed rest, has an effect on many physiological systems, such as the cardiovascular, musculo-skeletal, immune, and body fluid regulation systems. There is currently no countermeasure that is effective to counteract both the cardiovascular and musculo-skeletal deconditioning when applied for a short duration (see Chapter 1). Artificial gravity therefore seems the simplest physiological approach to keep these systems intact. The application of intermittent daily dose of artificial gravity by means of centrifugation has often been proposed as a potential countermeasure against the physiological deconditioning induced by spaceflight.

However, neither the optimal gravity level, nor its optimal exposure duration has been sufficiently studied to recommend a validated, effective, and efficient artificial gravity application. As discussed in previous chapters, artificial gravity has a very high potential to counteract any changes caused by reduced physical activity. The nutrient supply, which ideally should match the actual needs, will interact with these changes and therefore must also be taken into account. This chapter reviews the potential interactions between these nutrients (energy intake, vitamins, minerals) and the other physiological systems affected by artificial gravity generated by an on-board short-radius centrifuge.

2 ENERGY INTAKE AND MACRONUTRIENT SUPPLY

It is well known that astronauts, except perhaps during the Skylab missions, were and still are not optimally nourished during their stay in space (Bourland *et al.* 2000, Heer *et al.* 1995, Heer *et al.* 2000b, Smith *et al.* 1997, Smith and Lane 1999, Smith *et al.* 2001, Smith *et al.* 2005). It has also been described anecdotally that astronauts have diminished appetites during space missions. One possible explanation is that taste and smell sensations are altered. Although some early observations suggest that this is not the case (Heidelbaugh *et al.* 1968, Watt *et al.* 1985), data from recent head-down bed rest studies showed significant decrease in smell sensation (Enck *et al.*, unpublished data). This finding suggests that fluid shifts might have an impact on the decrease in the sense of smell. If this finding is confirmed during spaceflight, a decrease in smell could be responsible for lowered food intake, causing insufficient energy intake and subsequently insufficient supply of most of the macro- and micronutrients to the organism.

Other nutrients are, however, taken in excess, as it is the case for sodium. It is well known (especially from the companies that manufacture packaged food) that food with high salt content seems to be more palatable than food with low salt content. Salt also functions as a preservative, which is very important taking into account the food system limitations on board spacecraft, such as the limited amount of refrigerator and freezer space. The preference for food with high salt intake by astronauts might therefore very likely be caused by altered smell and taste sensations in microgravity.

2.1 Energy Intake

During most of the space missions in the past, astronauts have had an insufficient energy intake. On average their energy intake was about 25% less than their expenditure, thus leading to a loss in body mass (Bourland *et al.* 2000), including muscle and fat tissue. Although caloric intake in the recent

ISS missions has been slightly improved, it is still not optimal (Smith *et al.* 2005).

Energy expenditure consists of the *resting energy expenditure* (REE) plus the energy requirements for any activity (e.g., exercise, walking) plus the thermogenesis derived from the metabolism of protein, fat, and carbohydrates. As mentioned previously, voluntary energy intake by the astronauts in microgravity usually does not match the energy needs (Bourland *et al.* 2000, Smith *et al.* 2005). Experience with head-down tilt bed rest studies also shows that volunteers are rather reluctant to consume all the food prescribed to meet their energy needs.

Animals exposed to centrifugation increased their energy expenditure substantially. Wade *et al.* (2002) have shown that 2-week centrifugation of 24 hours per day at levels of 2.3 g or 4 g led to a 40% increase of REE in rats, independent of the gravity level. In another experiment wherein rats were continuously exposed to 1.25, 1.5, and 2 g for 14 days, the mean body mass was significantly lower than non-centrifuged controls, but no differences were found in food intake, which is expressed in 'g per day per 100 g of body mass', between the hypergravity group and the controls. Epididymal fat mass was 14 to 21% lower than controls in the centrifuged group. Plasma insulin was significantly lower (about 35%) in the hypergravity groups than controls, suggesting an improved sensitivity to insulin (Warren *et al.* 2000, Warren *et al.* 2001, Moran *et al.* 2001).

Decreased energy intake has a profound effect on the cardiovascular system (Mattson and Wan 2005). This has mainly been indicated in obese people during semi-starvation (Hafidh *et al.* 2005, Brook 2006, Sharma 2006, Poirier *et al.* 2006), in pilots during Ramadan (Bigard *et al.* 1998), and in a metabolic ward study in normal weight subjects during head-down bed rest (Florian *et al.* 2004). Hence, in the latter, moderate energy restriction of 25% of energy intake led to profound decrease in orthostatic tolerance, which was even greater than the effect of bed rest. Taking into account that centrifugation will lead to a fluid shift towards the lower legs, insufficient caloric intake and concomitant cardiovascular reactions might jeopardize the compensating effect of artificial gravity. This is because symptoms of pre-syncope might on one hand lead to an early termination of the centrifugation protocol and on the other hand might interact with any countermeasure effect to the cardiovascular system.

When total energy intake is less than total energy expenditure, endogenous energy stores (e.g., glycogen, protein, fat) must be mobilized. To provide sufficient energy for the body, these endocrine energy stores are used. After the glycogen stores are expended, muscle protein is used as an amino acid and energy source, thus leading to a decrease in muscle mass in addition to the muscle mass lost as a result of disuse. In microgravity or during bed rest, protein synthesis is reduced while protein breakdown remains the same, thus resulting in a loss of muscle mass (Biolo *et al.* 2004, Ferrando *et al.* 1996). Under these conditions, hypocaloric nutrition, even at moderate levels, will exacerbate muscle loss because muscle protein functions as an energy delivering nutrient (Lorenzon *et al.* 2005). A severe decrease in energy intake increases bone resorption, as shown in patients suffering from *anorexia nervosa* (Heer *et al.* 2002, Heer *et al.* 2004c) and in exercising women (Ihle and Loucks 2004). Moderate restriction in energy intake, however, seems to have no effect in male bed rest test subjects (Heer *et al.* 2004b).

The application of artificial gravity may have an anabolic effect on bone, and lead to an increase in bone modeling (see Chapter 7). Severe low caloric intake will lead to a suppression of osteoblast activity, if this activity is not stimulated by the mechanical loading induced by passive centrifugation (Heer *et al.* 2002, Heer *et al.* 2004c). Sufficient energy supply is therefore a prerequisite for using artificial gravity as a countermeasure to bone loss in immobilized subjects.

If increased REE during centrifugation occurs in humans as well and a combination of artificial gravity and exercise countermeasures is more effective for compensating cardiovascular deconditioning, maintaining muscle mass and strength, bone mass, and assuring optimal energy intake will be a critical co-factor for the success of artificial gravity as a countermeasure.

2.2 Protein Supplementation

Protein intake during spaceflight is about 102 ± 29 g per day (Smith *et al.* 2005) or 1.4 ± 0.4 g per kilogram of body weight daily. Therefore, protein intake in microgravity is a concern because of too much rather than not enough intake. As mentioned above, reduced physical activity leads to a decrease in protein synthesis, constant protein breakdown, and concomitant loss in muscle mass. Paddon-Jones *et al.* (2004) have shown that increasing protein intake to about 1.5 g per kilogram of body weight per day by using branched-chain amino acid together with carbohydrate supplementation preserves not only muscle mass but also muscle strength. In addition, Biolo *et al.* (1995b, 1997) have shown that increased protein intake combined with resistive exercise lead to an increased amount of muscle protein. Centrifugation of a passive subject lying on a short-radius device is equivalent to isometric resistive exercise. Therefore, supplementing protein during passive centrifugation might be a potential measure to keep up muscle mass and strength. However, the timing of this protein supplementation is very important. According to Biolo *et al.* (1997) protein must be supplemented shortly before or after the resistive exercise training in order to induce an increase in muscle protein synthesis.

An increase in protein supplementation, however, has some disadvantages for bone metabolism. As discussed in Chapter 7, immobilization *per se* leads to decrease in bone mass and strength in the lower legs. Increase in protein intake, however, might also have a bone resorption effect, which is highly dependent on the nutrients provided with the higher protein intake (Massey 2003). In this context, the intake of potassium seems to be very important. The effect of increase in bone resorption during rather low potassium intake together with high protein intake is even more important during immobilization where bone turnover is already increased. Our group has observed an increased relationship of animal protein intake to potassium intake during immobilization in bed rested healthy test subjects that exacerbated the effect of mere bed rest (Zwart *et al.* 2004). As previously suggested by others authors, this effect seems to be mediated by changes in the acid-base balance. High animal protein intake, together with low potassium intake, leads to a rather high potential of renal acid load. This might lead to mild metabolic acidosis. Mild metabolic acidosis has been shown to be a strong cause for increasing bone resorption (Meghji *et al.* 2001, Riond 2001, Bushinsky 1994, Bushinsky *et al.* 1999). Therefore, applying high protein intake plus artificial gravity might have a positive effect on muscle mass and strength. However, mild metabolic acidosis, which potentially increases bone resorption, must be counteracted by other countermeasures.

2.3 Insulin Resistance

The sensitivity to insulin has been shown to decrease in many bed rest studies (Mikines *et al.* 1989, Mikines *et al.* 1991, Shangraw *et al.* 1988, Smorawinski *et al.* 1996, Stuart *et al.* 1990, Yanagibori *et al.* 1994, Yanagibori *et al.* 1997, Blanc *et al.* 2000, Smorawinski *et al.* 2000, Stuart *et al.* 1988). Physical fitness and the training status of the subjects might have an impact on insulin sensitivity, according to studies carried out in trained and untrained test subjects (Wegmann *et al.* 1984, Smorawinski *et al.* 1996, Smorawinski *et al.* 2000). Furthermore, studies in trained and untrained test subjects have demonstrated that insulin resistance in untrained volunteers is due to a reduced sensitivity to insulin of their inactive muscles (Mikines *et al.* 1991, Stuart *et al.* 1988, Blanc *et al.* 2000). The effects of isometric, resistance exercise training on insulin sensitivity were tested in a prospective study by Tabata *et al.* (1999). Their data showed an improved glucose uptake of the muscles, indicating that resistance exercise training during bed rest could overcome the effect of inactivity (Tabata *et al.* 1999).

Besides its effects on glucose metabolism, insulin is also a regulator of protein metabolism. The synthesis of myofibrillar protein requires physiological levels of insulin. Hyperinsulinemia caused by insulin infusion, while holding blood amino acid concentrations normal, leads to increased rates of protein synthesis without changing protein breakdown in muscle in ambulatory healthy volunteers (Biolo *et al.* 1995a, Biolo *et al.* 1999). However, in the case of decreased insulin sensitivity, such an increased protein synthesis may not take place. Like in patients with type II-diabetes (Tessari *et al.* 1986), the insulin resistance in bed rest subjects might be responsible for a decreased muscle protein synthesis during immobilization.

Artificial gravity generated by a short-radius centrifuge in some way mimics isometric, resistance exercise so that one might speculate that artificial gravity would have a positive effect on insulin sensitivity. Thereby increased insulin sensitivity might also have a positive effect on muscle mass and strength. In order to distinguish between the potential effects of changed insulin sensitivity and resistive exercise on muscle mass and strength, further studies are mandatory to validate the effect of resistive exercise as well as artificial gravity.

3 VITAMINS AND ARTIFICIAL GRAVITY

3.1 Vitamin A

Vitamin A is a general term that refers to a family of fat-soluble compounds that are structurally similar to retinol and share its biological activity. Among these are retinol, β-carotene, and retinyl palmitate. Trans-retinol is the primary biologically active form of vitamin A. Many carotenoids, such as β-carotene, can be converted to trans-retinol and thus contribute to vitamin A activity. Collectively, these carotenoids are termed provitamin A carotenoids and are measured in retinol equivalents.

Vitamin A plays a role, albeit sometimes indirectly, in the function of almost all of organs of the body (Ross 1999). Vitamin A is directly involved in vision, bone growth, cell division, reproduction, and immunity. Vitamin A and β-carotene serve as biological antioxidants and have been shown in multiple studies to reduce the risk of cancer and coronary heart disease (Kohlmeier and Hastings 1995, van Poppel and Goldbohm 1995).

Deficiency of vitamin A leads to xerophthalmia, loss of appetite, drying and keratinization of membranes, or infection. Likewise, ingestion of large amounts of vitamin A are commonly associated with adverse skeletal effects (Dickson and Walls 1985, Hough *et al.* 1988, Scheven and Hamilton 1990). The mechanisms are thought to include suppressed osteoblast activity, stimulated osteoclast formation, and impaired function of vitamin D (Jackson and Sheehan 2005).

Serum levels of retinol and retinol-binding protein are decreased after long-duration spaceflight. One supporting animal study found that both serum retinol and retinol binding protein were decreased after prolonged immobilization (Takase *et al.* 1992), and the changes were thought to be related to a stress response.

Artificial gravity may induce changes in stress hormones (see Chapter 10), which may in turn affect vitamin A metabolism. Furthermore, care must be taken to avoid ingestion of large supplemental amounts of vitamin A during bed rest or artificial gravity studies due to its known toxic effects on the skeletal system.

3.2 Vitamin K

Vitamin K plays a role as a cofactor in the carboxylation of a limited number of proteins. The vitamin K-dependent carboxylase is an enzyme responsible for the posttranslational conversation of specific glutamate to *gamma-carboxyglutamate* (Gla) residues. Three carboxylated proteins, osteocalcin, matrix Gla protein, and protein-S, have been identified in bone (Hauschka *et al.* 1989, Vermeer *et al.* 1995). Osteocalcin is a protein synthesized by osteoblasts, and in its carboxylated form, osteocalcin exhibits strong calcium binding properties and is related to the bone mineralization process (Shearer 1995). In the event of a vitamin K deficiency, under-carboxylated osteocalcin, which lacks some or all of the Gla residues, is synthesized. Therefore blood concentration of under-carboxylated osteocalcin is a sensitive marker for vitamin K nutritional status (Knapen *et al.* 1989, Sokoll *et al.* 1997, Vermeer and Hamulyak 1991). The discovery of these vitamin K-dependent proteins in bone has led to research on the role of vitamin K in maintaining bone health. Epidemiological studies provide evidence for an association between low vitamin K intake and an enhanced osteoporotic fracture risk (Hart *et al.* 1985, Booth *et al.* 2000). A higher incidence of femoral neck (Vergnaud *et al.* 1997) and hip (Szulc *et al.* 1996) fractures has been observed in patients with high levels of under-carboxylated osteocalcin. Moreover, as a result of the vitamin K supplementation, the urinary calcium excretion was decreased by 30% in the fast losers (Knapen *et al.* 1989, Knapen *et al.* 1993).

While bone resorption can be counteracted (e.g., by bisphosphonates), there is no proven countermeasure for the decrease in bone formation. Vermeer *et al.* (1998) and Caillot-Augusseau *et al.* (2000) observed a profound effect of Vitamin K on bone formation in microgravity. During the 179-day Euromir 95 mission, one astronaut received vitamin K supplementation of 10 mg Vitamin K1 (Konakion®) for six weeks during the second part of the mission, as a countermeasure for spaceflight-induced bone loss. This astronaut showed a very promising effect in that while bone formation markers, PICP and serum *bone alkaline phosphatase* (bAP) had decreased in the first part of the mission (without Vitamin K supplementation), their concentration levels were comparable to preflight with vitamin K supplementation (Vermeer *et al.* 1998). In two other astronauts, under-carboxylated osteocalcin increased from preflight levels of 12-15% to 25% within the first five days in-flight. In one of these astronauts, a supplementation with 10 mg vitamin K 1 was able to decrease the levels of under-carboxylated osteocalcin into the preflight range. Moreover, Vermeer and Ulrich (1986) showed that the amount of Gla-residues is reduced by more than 50% in the postflight samples.

With regard to artificial gravity, the vitamin K status of the astronauts would need to be adequate to optimize the counteractive potential of artificial gravity. Resistive exercise leads to an increase in bone formation markers (Shackelford *et al.* 2004, Maimoun *et al.* 2005) and therewith to an increase in osteocalcin. If there is a lack of substrate, such as vitamin K, for carboxylation of osteocalcin, this under-carboxylated osteocalcin cannot bind to hydroxyapatite and therefore might not play its role in the mineralization process. A supplementation with vitamin K seems to have a very high potential to reduce the amount of under-carboxylated osteocalcin and, moreover, counteracts the decreased bone formation.

3.3 Vitamin B6

Vitamin B6 comprises a group of three compounds and their 5'-phosphates: *pyridoxal* (PL) and PLP, *pyridoxine* (PN) and PNP, and *pyridoxamine* (PM) and PMP. These vitamers of B6 serve as coenzymes in many transamination, decarboxylation, and trans- and desulfydration reactions involved in immune function and synthesis of several neurotransmitters (Institute of Medicine 1998, McCormick 2001).

Approximately 70% of vitamin B6 is stored in muscle tissue associated with glycogen phosphorylase (Coburn *et al.* 1988) with 10% stored in the liver and 60% is stored in the plasma pool (Institute of Medicine 1998). Because vitamin B6 is mainly stored in muscle tissue, a decrease in muscle mass could reduce the amount of the vitamin that is stored, or even influence vitamin B6 metabolism. Supportive of this, urinary excretion of 4-pyridoxic acid is indeed elevated after long-duration (17 weeks) bed rest when muscle mass is known to decrease (Coburn *et al.* 1995). Based on data from four to six month spaceflights, there is no change in red blood cell transaminase activation (Smith *et al.* 2005). However, plasma PLP has not been determined after long-duration spaceflight.

Vitamin B6 may also be involved with oxidative stress due to its role in homocysteine, cysteine, and glutathione metabolism (Kannan and Jain 2004, Mahfouz and Kummerow 2004). Vitamin B6 deficiency increases oxidative stress and decreases antioxidant defense systems (Taysi 2005, Voziyan and Hudson 2005). Furthermore, pyridoxamine supplementation can reduce oxidative damage in both animal and human studies (Anand 2005, Voziyan and Hudson 2005).

Because both oxidative stress and decreased muscle mass are observed during spaceflight and during head-down-tilt bed rest (Ferrando *et al.* 2006, LeBlanc *et al.* 2000, Zwart and Oliver 2006, Smith *et al.* 2005).

Vitamin B6 metabolism should be monitored during these instances. With respect to artificial gravity, we expect muscle mass may be maintained, and therefore artificial gravity may maintain vitamin B6 status.

4 MINERALS AND ARTIFICIAL GRAVITY

4.1 Calcium and Vitamin D

During most of the space missions, calcium intake and vitamin D supply were below the recommended values (Bourland *et al.* 2000). For example, although calcium intake has been improved recently, during the first eight increments on board ISS calcium intake was about 1000 mg per day (Smith *et al.* 2005, Heer *et al.* 1999, Smith and Heer 2002). Adequate calcium intake is a prerequisite to mineralize bone during life. Convincing evidence has emerged with respect to the effects of dietary calcium intake on bone health in all age groups. A number of reports led to a consensus view on the effectiveness of calcium together with vitamin D supplementation in postmenopausal osteoporosis (Chee *et al.* 2003, Lau and Woo 1998, Cumming and Nevitt 1997, Ilich and Kerstetter 2000, Prentice 2004). High calcium intake cannot prevent bone loss but can reduce the rate of bone loss in older women. Dawson-Hughes *et al.* (1997) showed that combined supplementation with calcium and vitamin D for three years significantly reduced non-vertebral fracture rates in men and women (mean age 71 years).

Astronauts in space have high serum calcium levels because of increased bone resorption (Smith *et al.* 2001). High serum calcium concentration and low 25-hydroxyvitamin D levels are also observed during bed rest (van der Wiel *et al.* 1991). One might argue that increasing calcium intake above the recommended levels, together with vitamin D supplementation, might counteract the microgravity-related and bed rest-induced bone losses. However, data from the Mir-97 mission and bed rest studies show that calcium absorption is reduced (Smith *et al.* 1999, Zittermann *et al.* 2000) and calcitriol concentrations are decreased (Heer *et al.* 1999, Rettberg *et al.* 1999), so that increased calcium intake above the recommended level is not absorbed.

In short-term (6-14 day) head-down bed rest studies it was shown that bone turnover was unchanged by increasing calcium intake from 1000 mg per day to 2000 mg per day (Heer *et al.* 2004a). Increasing calcium and vitamin D intake above the recommended levels appear to be ineffective as a nutritional countermeasure to maintain bone mass in bed rest without any mechanical loading. If artificial gravity acts as a form of isometric exercise, it might activate bone-forming cells. When bone formation is increased and bone built, all mandatory nutrients including calcium and vitamin D should be supplied in a sufficient amount in order not to limit bone formation because of malnutrition. In case of bed rest combined with centrifugation, the questions remains if calcium intake above the recommended level is necessary to maintain bone mass and strength.

In addition to its effect on calcium homeostasis, vitamin D also affects skeletal muscle (Bischoff-Ferrari *et al.* 2006). Vitamin D binds to specific receptors on skeletal muscle for 1,25-dihydroxyvitamin D (Bischoff-Ferrari *et al.* 2006). Investigations in the elderly showed that muscle strength is related to vitamin D status. Low serum 25-hydroxyvitamin D levels are related to lower muscle strength (Bischoff *et al.* 1999, Zamboni *et al.* 2002) and to a loss of muscle mass and muscle strength (Visser *et al.* 2003). Snijder *et al.* (2006) showed that low physical performance is associated with low serum 25-hydroxyvitamin D levels. With regard to artificial gravity, the supply of vitamin D in a sufficient amount might be preventive to achieve muscle strength as well.

4.2 Phosphorus and Magnesium

Phosphorus and magnesium are critical minerals for human health. Phosphorus is a critical element of many enzymes, cellular messengers, and carbohydrate fuels. Osteomalacia, a defect in bone mineralization, often occurs as a result of long-term phosphorus deficiency. Inadequate intake of phosphorus can cause the release of calcium from bone, impaired granulocyte function, and cardiomyopathy (Knochel 1999).

Magnesium is required as a cofactor for over 300 enzyme systems and serves as a substrate for phosphate transfer reactions in all cells. Adequate intake of magnesium is necessary to prevent hypocalcemia, resistance to vitamin D, and resistance to parathyroid hormone (Shils 2006). Magnesium is also critical for cardiovascular health.

There is evidence that magnesium and phosphorus are altered after long-duration spaceflight. Urinary magnesium and phosphorus were about 45% less after landing than before launch in 11 ISS crewmembers (Smith *et al.* 2005). Results of previous spaceflight studies are consistent with a significant decrease in urinary magnesium (Leach and Rambaut 1977, Leach 1992), possibly owing to a decrease in magnesium intake. Decreased urinary magnesium could be a point of concern for long-duration flights because of the role of magnesium in inhibiting calcium oxalate renal stones (Su *et al.* 1991, Grases *et al.* 1992).

The cause, extent, and impact of alterations in magnesium and phosphorus homeostasis during spaceflight are not well defined. However, it is quite possible that artificial gravity effects on musculo-skeletal health may help to reverse these changes. This too, remains to be proven.

4.3 Sodium

Sodium is the major cation of the extracellular volume and plays a major role in keeping up the membrane potential, nutrient absorption, as well as the maintenance of blood volume and blood pressure. However, as for the majority of people in the western world, sodium intake of astronauts in spaceflight is far above the recommended levels. We have shown that during the recent ISS missions (Increments 1-8) the average sodium intake was 4556 ± 1492 mg per day (Smith *et al.* 2005).

High *sodium chloride* (NaCl) intake affects most of the physiological systems, like body fluid regulation, cardiovascular as well as the musculo-skeletal system. We have recently shown that in space sodium intake mainly as NaCl leads to sodium retention without fluid retention (Drummer *et al.* 2000). In some metabolic balance studies we demonstrated that on Earth high NaCl intake also leads to sodium retention without fluid retention (Heer *et al.* 2000a) and may induce mild metabolic acidosis (Frings *et al.* 2005). Now, mild metabolic acidosis has a significant effect on release and function of several hormones including defects in growth hormone, IGF-1, insulin, glucocorticoids, thyroid hormone, parathyroid hormone and vitamin D (Mitch 2006). It also affects the musculo-skeletal system as described in the section on protein metabolism. For muscle, decrease in pH may inhibit protein synthesis, may lead to insulin resistance (which, as described above, is a risk because of immobilization already) and concomitantly may activate proteolytic mechanisms leading to protein breakdown. Application of artificial gravity by centrifugation as described above may act as a resistive exercise and if so might lead to anaerobic processes and consequently reduce pH by increasing lactate acid production (McCartney *et al.* 1983, Kowalchuk *et al.* 1984, Putman *et al.* 2003, Lindinger *et al.* 1995). The anabolic effect aimed at with applying artificial gravity might be at risk, in case of high salt intake because of induced mild metabolic acidosis. The prescription of artificial gravity should therefore be developed in such a way that all the impacting metabolic changes are taken into account.

It has been shown in studies in pre- and postmenopausal women (Nordin *et al.* 1993) and calcium stone-forming patients (Martini *et al.* 2000) that increasing sodium intake has also a profound effect on bone metabolism like increase in calcium excretion (Nordin *et al.* 1993) associated with lower area bone mass density (Martini *et al.* 2000). Nordin et al (Nordin *et al.* 1993) postulated that the rise in urinary calcium excretion is sodium driven. Increasing sodium intake by each 100 mmol (2300 mg) raises urinary calcium excretion by 1 mmol (40 mg). Taking into account that the average calcium excretion is around 120 to 160 mg per day, the rise in calcium excretion by higher salt intake is substantial. These findings were supported by Arnaud *et al.* (2000) in a seven-day bed rest study.

The mechanism by which high sodium intake exacerbates urinary calcium excretion is not fully understood. As mentioned above we have shown that high salt intake decreases blood pH bicarbonate and base excess levels (Frings *et al.* 2005). Concurrently, bone resorption markers were significantly increased. This supports the notion of Arnett (2003) who stated that even mild metabolic acidosis (pH-changes of less than 0.05) may activate osteoclasts and may cause appreciable bone loss over time in ambulatory conditions, and may exacerbate bone loss in bed rest. Application of exercise on top of high salt intake though has to be applied with caution. As mentioned above, exercise may increase blood lactate levels and reduce thereby blood pH. When applying artificial gravity as a resistive exercise training blood lactate levels should not lead to a strong metabolic acidosis in order to not jeopardize and bone forming process initiated by the mechanical loading.

4.4 Potassium

As the major intracellular cation, potassium has a significant role in many physiological processes (Preuss 2001). Potassium is critical to regulation of acid-base balance, energy metabolism, blood pressure, membrane transport, and fluid distribution within the body. It is also involved in the transmission of nerve impulses and cardiac function (Kleinman and Lorenz 1984). Disordered potassium metabolism because of excess or deficient circulating levels has negative consequences for cardiac, muscle, and neurological function.

Potassium levels cannot be maintained at intakes under 10–20 mmol per day (Perez and Delargy 1988). Moderate depletion of potassium in humans is associated with clinically significant cardiovascular risks (Srivastava and Young 1995). During long-duration spaceflight, serum potassium is decreased and potassium balance is negative, suggesting potassium loss from the body (Johnston and Dietlein 1975, 1977, Leach-Huntoon and Schneider 1987). One of the main concerns for decreased potassium status during spaceflight is related to the increased cardiovascular risks.

Potassium metabolism and status may also contribute to an individual's predisposition to orthostatic intolerance after exposure to microgravity or even tolerance to artificial gravity. In one study, subjects who failed a 60-min centrifugation on a short-radius centrifuge had higher salivary potassium than subjects who successfully withstood 60-min of centrifugation (Igarashi *et al.* 1994). The authors suggest that the potassium response may be due to the changes in autonomic nervous system function and stress response induced by centrifugation. Others show that orthostatic intolerant individuals during bed rest have higher baseline urinary potassium excretion (Grenon *et al.* 2004). Whether the differences in potassium metabolism are causes or effects in these instances are unknown.

While it is important to keep potassium intake at recommended levels for appropriate age groups (Institute of Medicine 2004), it is also important to monitor potassium status during artificial gravity experiments to minimize cardiovascular risks that may accompany changes in potassium status induced by stress responses. While potassium depletion is a concern during spaceflight, and this may in part be related to loss of muscle mass, artificial gravity may help to mitigate some of this concern.

4.5 Iron

Iron, while having multiple functions in the body, is critical for *red blood cell* (RBC) production and function. Maintenance of blood volume and RBCs has been of interest from the initial days of spaceflight, with concerns over a "spaceflight anemia". The mass of RBCs in the body is decreased during flight, and the rate of loss is slightly greater than 1% per day, and reaching a net loss of 10 to 15% of RBC volume after 10 to 14 days of launch. Further decreases do not occur with longer flight durations.

Experiments performed on the Space Shuttle showed that the release of new RBCs is halted upon entry into weightlessness, and furthermore that newly released RBCs are selectively removed from the circulation (Alfrey *et al.* 1996b, Alfrey *et al.* 1996a, Udden *et al.* 1995). These changes in RBC mass seem to be adaptive, and reach a new plateau after the first weeks of flight, as evidenced by long-term flight data (Alfrey *et al.* 1996a, Leach and Rambaut 1975).

One consequence of the change in RBC mass is the associated increase in iron storage. Serum ferritin, an index of iron storage, is increased after short- and long-term flights. All other indices also suggest increased iron storage and availability during and after spaceflight. Serum iron concentrations are normal to elevated during and after flight. The concentrations of circulating transferrin receptors, which are lower during conditions of iron overload, are decreased on landing day. The implications of this increased iron storage not known, but concern exists about iron overload during extended-duration spaceflight (Smith 2002).

Artificial gravity may have an impact on iron metabolism and red blood cell metabolism. The decreased RBC mass during flight is believed to be in part related to the loss of pooling of RBCs in the lower extremities related to gravity. When entering weightlessness, these cells become part of the circulating population of RBCs, and the body senses an excess of available oxygen carrying capacity. Artificial gravity might cause a transient (depending on the duration of artificial gravity application) restoration of the pooling effect, which in turn might stimulate erythropoietin and RBC synthesis. Whether this would be beneficial (or detrimental) requires further study. On the positive side, this might help to alleviate the iron storage issues associated with flight, it might also increase plasma and red blood cell volumes, which might improve muscle cardiovascular function. On the negative side, this might stimulate erythropoiesis during the application of artificial gravity, followed by a re-adaptation to microgravity afterwards.

5 IMPACT OF ARTIFICIAL GRAVITY ON GI-TRACT

Gastrointestinal (GI) function may be altered during weightlessness. However, this has not been systematically studied, but has been discussed in several reviews (Da Silva *et al.* 2002, Lane *et al.* 1993, Smirnov and Ugolev 1996). Fluid shifts, inadequate fluid intake, altered blood flow would be expected to decrease gastrointestinal motility. Bed rest studies have confirmed this, where it was noted that the mouth-to-cecum transit time is increased during head-down-tilt when compared to ambulatory periods. As discussed above (Section 3.2), vitamin K is a concern for space travelers, and might be part of the mechanism of spaceflight-induced bone loss. While difficult to study, it is possible that the production and absorption of vitamin K by the gastrointestinal microflora is impaired during weightlessness due to changes in gastrointestinal function.

Artificial gravity may help with gastrointestinal function, and the intermittent application may physically stimulate motility. This would help with anecdotal reports of constipation. What effect this would have on nutrient and drug absorption is yet to be determined, but depending on the frequency and duration of exposure, it might provide an effective countermeasure. It might also be possible (or necessary) to coordinate the timing of application of artificial gravity with either meal times or ingestion of medication, to ensure optimal absorption.

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Chapter 10

ARTIFICIAL GRAVITY AND THE IMMUNE SYSTEM FUNCTION

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Human space travelers experience a unique environment that affects homeostasis and physiologic adaptation. Spaceflight-related changes have been reported in the musculo-skeletal, neurovestibular, cardiovascular, endocrine, and immune systems as well as others. As humans prepare for longer duration missions to the Moon, Mars, and beyond, effective countermeasures must be developed, verified, and implemented to ensure mission success in light of these corporal effects.

Significant adverse effects on space travelers can be caused by various stressors, including isolation, confinement, anxiety, sleep deprivation, psychosocial interactions, and physical exertion. The spacecraft environment further subjects the traveler to noise, chemical and microbiological contaminants, increased radiation, and variable gravity forces (hyper- and hypogravity). Many of these stressors are intermittent, but some are relatively constant such as microgravity on long missions.

Figure 10-01. This photograph shows three astronauts confined in a tight space inside the Soyuz space vehicle. Photo courtesy of NASA.

Research on astronaut physiology in space is complicated by exposure to these, and other uncontrolled factors, and proceeds slowly because of the limited access to space and limited availability of microgravity-compatible technology for on-board analyses. High fidelity, validated ground-based analogs of spaceflight are therefore essential for studying the effects of spaceflight on human physiology, developing countermeasures, and testing the efficacy of countermeasures. Various ground-based analogs have been developed and used to model specific aspects of spaceflight. For example, bed rest has been successfully used to model the effects of microgravity on musculo-skeletal and cardiovascular systems.

The immune system is affected by multiple factors associated with spaceflight. Some ground analogs have been used to study cellular level immune function, and there has been some success in using specific animal models. Antarctic science stations and other isolated environments have been useful in study of the effect of stress on human immunity. Unfortunately, bed rest has not been demonstrated to be a highly useful spaceflight analog model for studying immune function. However, the immune system interacts with most if not all other physiological systems, and physical countermeasures, such as artificial gravity, which are increasingly being tested in human subjects deconditioned by bed rest, may impact some elements of immunity. From this perspective, measuring selected indicators of immune status during bed rest and spaceflight trials may be critical to understanding the overall efficacy artificial gravity countermeasures.

This chapter describes the effects of spaceflight and stress on the immune system, mechanisms by which stress could cause clinically important latent viruses to be reactivated, and suggests methods to be used to monitor the immune system in the artificial gravity studies.

1 EFFECTS OF SPACEFLIGHT

Numerous studies have demonstrated that dysregulation of the immune system occurs during or after spaceflight. Specific findings include altered leukocyte distribution and cytokine production after landing (Crucian 2000, Stowe *et al.* 1999) and latent viral reactivation during flight (Mehta *et al.* 2000, Mehta *et al.* 2004, Pierson *et al.* 2005, Stowe *et al.* 2000, Pierson, 2005, Stowe *et al.* 2001). Reviews of the human immune system response to spaceflight are available (Borchers *et al.* 2002, Sonnenfeld 2002). Although the cause of this dysregulation is unknown, multiple flight effects, such as radiation, physiological stressors, psychological stressors, and disrupted circadian rhythms are likely causal factors. Furthermore, microgravity itself may have a direct effect on the function of immune cells.

The efficacy of artificial gravity as a multi-system countermeasure to some of the untoward affects of spaceflight is beginning to be investigated. The immune system may be affected by artificial gravity, either through the direct effects of altered gravity levels (or gravity transitions) or indirectly through changes induced on other systems by exposure to artificial gravity. It is therefore imperative that immune system function be monitored during artificial gravity studies.

2 DESIGN OF THE IMMUNE COMPONENTS OF ARTIFICIAL GRAVITY STUDIES

The hypotheses to be tested with respect to the immune system during artificial gravity studies are related to the combined effects of hypergravity and stress and, if bed rest deconditioning is used, to modest changes in immunity and latent virus reactivation known to be associated with that model. The specific aims of immune system studies should be to evaluate stress levels through appropriate measures of psychological and physiological stress, to determine the status of the immune system and the function of virus-specific T-lymphocytes, and to quantify reactivation of latent herpes viruses.

2.1 Sample Collections

Blood, saliva, and urine samples should be collected from each subject at appropriate times during the study (Table 10-01). Blood samples are necessary to measure concentrations of stress hormones and titers of antibodies to viruses, as well as to conduct tests of immune system status, including measurement of varicella-zoster virus-specific T-cell levels and functions. Saliva and urine samples are necessary to measure shedding of viral DNA and excretion of stress hormones.

Pre Bed Rest					***During Bed Rest***														***Post Bed Rest***				
B									*B*				*B*						*B*				*B*
S	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*
U									*U*				*U*						*U*				*U*

Table 10-01. Proposed schedule for blood (B), saliva (S), and 24-hour urine (U) collection for immune assessment in a study of artificial gravity as a multi-system countermeasure to bed rest deconditioning. In this example, the duration of the bed rest is 21 days. Saliva collections (S) are performed every other day. Sample collection is performed every other day. Blood (B) and urine (U) collection is performed 9 days before the bed rest, then on bed rest days 8 and 15, and then on the first and eighth day after bed rest.

2.2 Psychological Stress Measures

Psychological stress can be measured using questionnaires, such as the *Perceived Stress Scale* (PSS) and the *Positive Affect and Negative Affect Scale* (PANAS). These questionnaires should be completed first thing in the morning when subjects' saliva is collected for measurement of stress-related hormones. The 10-item PSS (Cohen 1983) has been used to measure the extent to which participants perceived their recent life circumstances as stressful, that is, unpredictable, uncontrollable, and overloading. The rating scale is internally consistent and has demonstrated moderate correlations with other measures of appraised stress (Watson 1988).

During a 14-day undersea isolation study using these questionnaires (Mehta *et al.* 2004), patterns of increased positive affect were observed, but both the negative affect score and PSS subscales showed an overall trend indicating some negative psychological effects of the mission. A decrease in positive affect and an increase in negative affect were also observed during a 90-day bed rest study (Crucian *et al.* in press). In general, during a spaceflight, astronauts feel excited, strong, enthusiastic, and proud about their mission. Such feelings may increase positive affect scores during the mission. The impact of artificial gravity as a countermeasure to these psychological effects is currently unknown.

2.3 Physiological Stress

Major components of the physiological stress response include increased activity in the *hypothalamic-pituitary-adrenal* (HPA) axis and the *sympathetic nervous system* (SNS). Previous studies have monitored levels of hormones from these systems in plasma and urine of spaceflight crew members (Huntoon *et al.* 1994, Meehan *et al.* 1993). Probably the best-characterized stress response is the release of cortisol under the control of the HPA axis (Cohen *et al.* 2001, Vanitallie 2002, Yehuda 2002). Plasma concentrations of cortisol do not change significantly in response to spaceflight and may actually be lower at landing than before flight (Huntoon *et al.* 1994). In contrast, urinary concentrations of cortisol are higher at landing than before flight (Huntoon *et al.* 1994).

Plasma and urinary cortisol measurements provide different insights into regulation of the HPA axis. That is, one may obtain an indication of the total cortisol released by measuring its urinary excretion, and compare that with the response to an acute challenge as shown by a single blood collection. Plasma total cortisol includes both bound and unbound fractions of cortisol. Urinary cortisol is generally reported as unbound cortisol. Unbound cortisol is the physiologically active form. Acute stressors suppress binding of cortisol to *corticosteroid-binding globulin* (CBG) (Fleshner *et al.* 1995). Suppression of cortisol binding to CBG may elevate urinary cortisol after space missions while plasma total cortisol does not change. Only the unbound form of cortisol is biologically active. In two bed rest studies, physiological stress was assessed by determining cortisol concentrations (Crucian *et al.* in press). Plasma cortisol levels varied between subjects, and no bed rest-specific changes were detected in any of the subjects.

Because cortisol affects the immune system and the reactivation of herpes viruses, its concentrations in subjects during artificial gravity studies may change as an effect of the countermeasure. Thus, measurements of cortisol in blood and urine should be considered in subjects participating in artificial gravity studies.

2.4 Immune System Status

To understand the overall effects of artificial gravity on immune system function, it would be necessary to complete a comprehensive assessment of test subject immune system status. This could be accomplished using the following measures.

2.4.1 Peripheral Immunophenotype Analysis

An excellent indicator of the general health and status of the immune system is produced by using flow cytometry to determine the distribution of the various peripheral blood immune cell subsets, or immunophenotypes. Physicians routinely use immunophenotype analysis to monitor the immune system during specific clinical conditions. For artificial gravity studies, a four-color cytometry antibody panel could be used to resolve the major immune cell subsets commonly assessed in clinical medicine: leukocyte differential (granulocytes, monocytes, and lymphocytes), lymphocyte subsets (T-cells, B-cells, NK cells), T-cell subsets (CD4 vs. CD8), memory vs. naïve T-cells, and constitutively activated T-cell subsets. Changes in the relative percentages of specific immune cell subsets or in the expression of activation markers by immune cells can occur in a variety of pathological states, such as immune deficiency, infection, hematological disease, and physiological stress, and are therefore thought to be a reliable diagnostic measure of immune status. The specific cell surface antigens and the relevant immune cell subsets are shown in Table 10-02.

Surface Antigen Combinations	***Cell Types Evaluated***
CD45, CD14	*WBC differential*
CD3, CD16, CD19, CD45	*T-cells, B-cells, NK cells*
CD4, CD8, CD3	*T-cell subsets*
CD45RA, CD45RO, CD8, CD4, CD3	*Bulk memory/naïve T-cell subsets*
HLA-DR, CD69, CD8, CD3	*Early- and mid-activated T-cell subsets*

Table 10-02. Specific combinations of cell surface antigens and the immune cell subsets evaluated for these antigen combinations.

2.4.2 Assessment of T-Cell Function

Immune suppression may include a reduced capacity for certain lymphocyte populations to respond to stimuli, even though the relative peripheral distribution of immune cells is unchanged. In artificial gravity studies, the functional response of T-cells could be measured by performing whole blood culture in the presence of T-cell mitogenic stimuli, followed by measuring activation marker expression on T-cell subsets. T-cells could be stimulated by culturing them either in the presence of *Staphylococcus* enterotoxins A and B or in the presence of antibodies to CD3 and CD28. These molecules activate T-cells by triggering expression of T-cell surface molecules, requiring the full complement of intracellular signaling to be used. This is not required by pharmacologic stimulation such as with phorbol ester and ionomycin. T-cell progression through a full activation cycle can be monitored by culturing cells for 24 hours and determining the T-cell expression of cell surface markers CD69, an early activation marker, and CD25, which is the receptor for IL-2, a mid-activation marker that requires new gene synthesis. The use of whole blood culture most closely reflects the *in vivo* response capabilities of the cell populations because all soluble plasma factors are still present, and all relevant cell-cell interactions may still occur. This is not the case with use of purified mononuclear cell culture, which consists of artificially purified cell populations.

2.4.3 Assessment of Intracellular Cytokine Profiles

The particular direction or bias of the immune response as well as the magnitude of the response could then be identified by the assessment of cytokine profiles. Alterations in the cytokine response balance may reflect immune dysregulation associated with specific clinical scenarios. Two main types of T-cell-based immune responses, Th1 and Th2, are known. They are separate and polarized, and are distinguished by the cytokine secretion profiles of the individual T-cells. In general, Th1 immune responses (IFNγ, IL-2, and others) consist of cell-mediated inflammatory reactions and are largely responsible for controlling intracellular pathogens, such as viruses and mycobacteria. By contrast, Th2 responses (IL-4, IL-10, and others) encourage production of antibodies and are associated with strong antibody responses and allergic reactions. These two arms of the immune system usually operate in concert to protect the host, but decreased responses or an altered balance can be a significant health risk. This is of unique interest to the space medicine community, because a Th1 $\rightarrow$ Th2 shift has been postulated to occur during spaceflight, with potential serious health consequences.

2.4.4 Virus-Specific T-Cell Levels and Function

The simultaneous detection and quantification of antigen-specific $CD8^+$ T-cells has recently been made possible through the development of novel flow cytometry-based techniques. There are two current methodologies. The first is based on peptide-specific induction of cytokine synthesis in $CD8^+$

T-cells, followed by intracellular cytokine staining (of IFN-γ, for example) with fluorochrome-labeled antibodies and then by four-color flow cytometry. The peptides used to induce cytokine synthesis in artificial gravity experiments should include one encoded by cytomegalovirus and another encoded by Epstein-Barr virus. The second method involves directly staining $CD8^+$ T-cells *ex vivo* using *major histocompatibility complex* (MHC) tetramers and then performing flow cytometry. Tetramers are likely to provide the most complete antigen-specific response because they do not require functional responses (that is, cytokine synthesis). Moreover, MHC tetramers can be combined with other phenotypic markers to better characterize antigen-specific T-cells (Altman and Safrit 1998).

These approaches should be used to study the effects of artificial gravity on the number and function of virus-specific $CD8^+$ T-cells. This is an important approach that will allow correlation of this information with latent herpes virus reactivation (see the next section of this chapter). These same approaches are currently being used to assess viral immunity in astronauts flying on short- (Shuttle) and long-duration (ISS) missions.

3 LATENT VIRUS REACTIVATION

Spaceflight causes stress and diminished cellular immunity, and we have shown that reactivation of *varicella-zoster herpes virus* (VZV), *Epstein-Barr virus* (EBV), and *cytomegalovirus* (CMV) occurs in astronauts during short-term spaceflight (Mehta *et al.* 2000, Mehta *et al.* 2004, Pierson *et al.* 2005). Herpes virus reactivation increases the health risks for crewmembers during short-term spaceflights and on ambitious long-duration missions, such as those on the ISS and planned planetary exploration missions.

Stress and diminished cellular immunity favoring the reactivation of latent herpes viruses may also result from bed rest and artificial gravity. Reactivation of the following viruses should therefore be quantified during artificial gravity studies.

3.1 Epstein-Barr Virus

Latent virus infections are ubiquitous, and EBV, a DNA virus, infects over 90% of the population (Lennette 1991, Oxman 1986). EBV is highly infectious and can be transmitted by micro-droplets as well as by direct contact with saliva. When an acute infectious phase ends, EBV can become latent in B-lymphocytes. EBV is the causative agent of infectious mononucleosis and is associated with several malignancies, including Burkitt's lymphoma, nasopharyngeal carcinoma, and diffuse oligoclonal B-cell lymphoma (Brandwein *et al.* 1996, Henle and Henle 1974, Jordan 1986, Lennette 1991, Niedobitek *et al.* 1997, Simon 1997). Latent EBV may be reactivated by a range of physical and psychosocial stress factors and is generally shed in saliva (Glaser *et al.* 1985, Glaser *et al.* 1995).

In the first study on latent virus reactivation during spaceflight (Payne *et al.* 1999), a greater frequency of EBV DNA shedding was observed in saliva before Space Shuttle missions than during or after. In a subsequent study, EBV reactivation was characterized in 32 astronauts and 18 healthy age-matched control subjects (Pierson *et al.* 2005). The mean number of EBV DNA copies from samples taken during 10 Space Shuttle flights was 10-fold greater than the number of copies from the preflight and postflight phases, and the control group. No correlation was found between shedding frequency and amount of EBV DNA. Although the frequency of EBV shedding in saliva was highest before flight, the number of EBV copies in saliva was highest during flight, when it was 10-fold greater than before or after flight (Payne *et al.* 1999, Pierson *et al.* 2005).

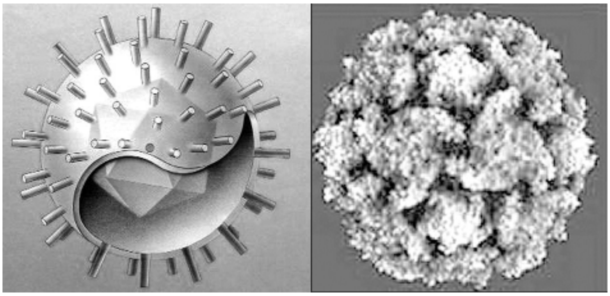

Figure 10-02. Schematic representation and electron microscopy photograph of Epstein-Barr virus (EBV). Photo courtesy of ESA.

The quantitative EBV DNA data (number of viral copies) indicated that the amount of EBV DNA shed in the saliva of astronauts during spaceflight increased as the number of days in space increased. Similar data from two cosmonauts on board the Russian space station Mir showed that EBV shedding in saliva occurred throughout the nearly three-month mission, a much longer time than the relatively short, less than 14 days, duration of the Space Shuttle missions. However, the number of EBV copies shed by cosmonauts on board Mir did not increase linearly as a function of the number of days in flight, as observed with astronauts on the Space Shuttle. The maximum number of EBV copies shed by cosmonauts on Mir was 1130/mL of saliva, and the maximum number of copies shed by astronauts on the shorter shuttle flights was 738/mL of saliva.

In addition to viral DNA, the titers of antibodies to EBV antigens, *virus capsid antigen* (VCA), and *early antigen* (EA) were measured in blood samples taken from astronauts at their annual medical exams (baseline), ten days before launch (L-10), a few hours after landing (R+0), and three days after landing (R+3). All 32 astronauts tested were seropositive. At L-10, the titer of anti-VCA antibodies was greater than the baseline value (Pierson *et al.* 2005, Stowe *et al.* 2000, Stowe *et al.* 2001), but at L-10 as well as after landing, the titer of anti-EBV nuclear antigen (EBNA) antibodies was less than its titer at the baseline (Stowe *et al.* 2001).

Increases in the number of EBV DNA copies and in the amount of anti-VCA antibody were consistent with EBV reactivation before, during, and after spaceflight. VCA is the structural antigen complex of proteins produced most abundantly during virus replication. Elevated amounts of antibodies to VCA and decreased or absent antibodies against EBNA are thought to reflect decreased cellular immunity against EBV (McDade *et al.* 2000, Preiksaitis *et al.* 1992). Kusunoki *et al.* (1993) have demonstrated a positive correlation between anti-EBNA antibody levels and precursor frequency of EBV-specific cytotoxic T-cells. The increase in anti-VCA antibodies before flight (L-10) may have resulted from stress-induced decreases in immunity to EBV.

3.2 Cytomegalovirus

Another latent herpes virus, human *cytomegalovirus* (CMV), may pose a similar kind of risk to astronaut health during spaceflight (Mehta *et al.* 2000). CMV infection is usually acquired asymptomatically during childhood. However, in individuals whose immune system is either immature or compromised, as by HIV infection, CMV can cause a number of serious diseases such as encephalitis, gastroenteritis, pneumonia, and chorioretinitis (Fiala 1975). Moreover, several studies have suggested that CMV infection may contribute to preexisting immunosuppression by directly infecting leukocytes as well as hematopoietic cells (Carney 1981, Rice *et al.* 1984, Simmons *et al.* 1990).

CMV reactivation and shedding was examined in urine samples collected before and after flight from 71 crewmembers on board 12 separate short-duration space missions (Mehta *et al.* 2000). Of the 71 crewmembers, 55 (77%) were seropositive for CMV. The frequency of CMV DNA shedding in either pre- or postflight urine samples from astronauts was significantly higher than that of the control population. CMV DNA was detected in 27% of the crew members studied. By contrast, only 1 of the 61 control subjects shed CMV during the sampling period. Blood and urine was also from two astronauts during a subsequent flight. Consistent with the earlier study (Mehta *et al.* 2000), CMV was shed in urine of one crewmember before, during, and after flight, and in urine of the other crewmember only during flight (on 2 days) (Stowe *et al.* 2001).

No significant changes in anti-CMV antibody titer occurred before or after flight within the group of 55 seropositive astronauts. However, when these subjects were divided into 40 non-shedders and 15 CMV shedders, an interesting difference was found. No significant change in CMV IgG antibody titer of non-shedders was found at any time point compared to the baseline values. In contrast, the anti-CMV antibody titer of the 15 shedders was significantly increased at all time points compared to their baseline values. In addition, antibody was significantly greater after flight than before (Mehta *et al.* 2000). Anti-CMV antibody titers of the two astronauts in the subsequent study (Stowe *et al.* 2001) were significantly greater during flight than before flight. No change occurred in anti-measles virus antibodies, confirming the specificity of CMV reactivation.

Figure 10-03. Electron microscopy photograph of a Varicella-zoster virus.

3.3 Varicella-Zoster Virus

Varicella-zoster virus (VZV) is an exclusively human neurotropic herpes virus that causes about 4 million cases of chickenpox annually. Varicella (chickenpox) is characterized by malaise, fever, and an extensive vesicular rash (Abendroth and Arvin 2000, Gilden *et al.* 2000). It is not always a mild disease. In 1994, an epidemic of chickenpox resulted in 292 cases and 3 deaths (Balraj and John 1994). In England, where VZV vaccination is not mandatory, about 25 people die from chickenpox every year (Rawson *et al.* 2001). Although VZV vaccine effectively prevents varicella (Arvin and Gershon 1996, Gershon *et al.* 1988, Gershon and Steinberg 1990, Gershon *et al.* 1992, Weibel *et al.* 1984) and reduces the severity of virus reactivation (Trannoy *et al.* 2000), breakthrough varicella (Takayama *et al.* 1997) and virus reactivation still occur (Krause and Klinman 2000, LaRussa *et al.* 2000). After chickenpox symptoms subside, VZV becomes latent in cranial nerve, dorsal root, and autonomic nervous system ganglia along the entire length of the central nervous system. Virus reactivation, which occurs mostly in elderly and immunocompromised individuals, produces zoster (shingles), characterized by severe sharp, lancinating, radicular pain and rash restricted to 1-3 dermatomes. In affected dermatomes, sensation is decreased, yet the skin is exquisitely sensitive to touch (allodynia).

In the U.S., more than 500,000 cases of zoster occur annually. Although varicella occurs mostly in spring, zoster develops at any time of year. The incidence of recurrent zoster in immunocompetent individuals is less than 5%. Thoracic zoster is most common, followed by facial lesions, usually in the ophthalmic division of the trigeminal nerve and frequently accompanied by zoster keratitis, a potential cause of blindness if not recognized and treated promptly.

Recently, VZV was identified as the causal agent in 29% of 3231 encephalitis, meningitis, and myelitis cases (Koskiniemi *et al.* 2001). In another study of 322 patients with acute encephalitis, VZV was shown to be the leading cause in patients aged 65 years or more (Rantalaiho *et al.* 2001). VZV is ubiquitous. A serologic study of 1201 U.S. military basic trainees indicated that 95.8% had been exposed to VZV (Jerant *et al.* 1998). A study of siblings in pre-vaccine Japan showed a 100% secondary attack rate (Asano *et al.* 1977). Reactivation of VZV results in shedding of infectious virus, which ensures its continual transmission.

Reactivation of VZV and *herpes simplex virus-1* (HSV-1) can result from dental treatment and orofacial surgery, which are examples of acute physical stress (Furuta *et al.* 2000, Kameyama *et al.* 1988). This is generally explained as resulting from local damage to nerve endings. Patients who have delayed facial palsy after orofacial surgery may have VZV DNA in their saliva and increased titers of antibody to VZV antigens in their blood.

The unexpected occurrence of thoracic zoster in an astronaut two days before spaceflight prompted a search for VZV reactivation in astronauts before, during, and after spaceflight. Using nested PCR and real-time PCR by Taqman 7700, 312 saliva samples were analyzed from 8 astronauts before, during, and after spaceflight. VZV DNA was detected in 1% of preflight, 28% of in-flight, and 31% of postflight samples. The number of copies of the VZV gene 63A was in the range of 10 to 4000 in the positive samples. No VZV DNA was detected in any of 88 saliva samples from 10 healthy control subjects. These results indicate that VZV, like CMV and EBV, reactivates during acute non-surgical stress in healthy astronauts after they are exposed to the stress or environmental factors associated with spaceflight (Mehta *et al.* 2004).

Levels of circulating anti-VZV IgG were also found to be two- to three-fold greater in astronauts than in control subjects. However, it was not possible to obtain samples that would demonstrate a significant change in antibody to VZV. A four-fold rise and fall in the level of antibody to VZV has been used as evidence of sub-clinical VZV reactivation in both immunocompromised and immunocompetent individuals (Arvin *et al.* 1983, Gershon *et al.* 1984, Schunemann *et al.* 1998). However, the combination of VZV DNA in saliva and a larger specific serum antibody response in astronauts than in control subjects further indicates sub-clinical reactivation of

VZV, adding VZV to the list of human herpes viruses capable of reactivation in response to acute non-surgical stress.

3.4 Quantification of Viral Reactivation in Artificial Gravity Studies

Viral load in blood, saliva, and urine samples can be measured using *polymerase chain reaction* (PCR) methodology (Mehta *et al.* 2000, Stowe *et al.* 2001, Tingate *et al.* 1997). DNA or RNA can be isolated from saliva, peripheral blood mononuclear cells, specific blood cell subpopulations, as isolated by magnetic beads, and urine using a modified quanidine-thiocyanate method (Tingate *et al.* 1997). For amplification of EBV DNA, primers can be made from the BamHI W repeat region of the EBV genome (Tingate *et al.* 1997). For amplification of CMV, a highly sensitive set of primers designed by one of the authors (patent applied 09/105,400) can be used to amplify a region of the viral polymerase gene (Stowe *et al.* 2001). For VZV, fluorescence-based simultaneous amplification and product detection can be performed using quantitative real-time PCR. Primers and probes for VZV gene 63 and for *glyceraldehyde 6-phosphate dehydrogenase* (GAPdH) DNA sequences have been described previously (Cohrs *et al.* 2000, Mehta *et al.* 2004). PCR products can be purified from agarose gel and directly sequenced to confirm the identity of each viral sequence. Subsequently, quantitative PCR can be performed on the virus-positive samples (positive by qualitative PCR) to determine the number of copies of viral DNA, as previously described (Mehta *et al.* 2000).

Standard techniques (immunofluorescence assay) can be used on blood serum or plasma samples to determine the titer of antibodies (immunoglobulins G and M) to EBV antigens VCA, EA, and EBNA, to CMV antigens (simultaneous detection of immediate early, early, and late antigens) (Mehta *et al.* 2000, Stowe *et al.* 2001, Stowe *et al.* 2001), and to VZV gene 63 product and GAPdH. Measurement of an irrelevant antibody (such as anti-measles virus) for an acute virus infection should be performed to confirm the specificity of titer changes for anti-EBV antibodies. It is expected that titers of antibodies to these viral antigens will be increased after bed rest and hypergravity, thus demonstrating a significant humoral immune response to lytic viral antigens.

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Chapter 11

MEDICAL, PSYCHOLOGICAL, AND ENVIRONMENTAL ISSUES OF ARTIFICIAL GRAVITY

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American astronauts and Russian cosmonauts have established a presence in space for approximately 40 years. Although most have spent several weeks in space, a few have logged a little over one year. Based upon this experience, flight surgeons have defined the adaptive (physiological and psychological) and maladaptive (medical and psychiatric) effects of microgravity and re-adaptation upon return to Earth. Although a number of countermeasures are being used, they only retard the effects of microgravity. None has proven to be truly effective. This chapter reviews the areas where artificial gravity could be beneficial from the flight surgeon perspective. It also examines the needs for medical monitoring and planned emergencies during studies on artificial gravity.

Figure 11-01. Contour couches were fitted for Mercury astronauts for performing physiological performance tests in the long-radius centrifuges. Flight versions of these couches were also used during spaceflight, for increasing tolerance to acceleration during launch and re-entry. Photo courtesy of NASA.

1 INTRODUCTION

Medical and psychological issues have been a concern for space travelers, even before the first living beings were thrust beyond 100 km, or 62 miles, above the Earth's surface[39]. More concerns were raised when proposals for space travel included altitudes of 120 km above the Earth's surface, especially with the speeds of orbital flights, because of the transition atmospheric thermal effects that are observed with the vehicular deceleration during re-entry. There were many "aviation medical experts", even as late as the 1950's, who felt humans were not adaptable to the space environment, and would become ill, be permanently impaired or even perish, if flown into space. Thus began the field of *space medicine*.

What is space medicine? To quote NASA space medicine leaders: *"Space medicine is the practice of all aspects of preventive medicine including screening, health care delivery, and maintaining human performance in the extreme environment of space, as well as preserving the long term health of space travelers. Space medicine must address numerous challenges to human health including environmental extremes, physiological responses to microgravity, and psychological considerations"* (Pool and Davis 2006).

Another definition espoused by the U.S. Institute of Medicine when reviewing the topic under a NASA-commissioned study states: *"Space medicine is a developing area of health care that has roots in aerospace medicine but that is focused on the health of individuals so that they can perform in, and return in good health from, increasingly distant extreme space environments, for example, from short-duration space flights, long-term space station flights, missions to the Moon, and in the next stages, exploration-class missions beyond Earth orbit, including missions involving planetary colonization"* (Ball and Evans 2001).

Notable pioneers in Space Medicine include Oleg G. Gazenko, Abram M. Genin, Andre Lebedinsky, Vasily Parin, V.I. Yazdovsky in the former U.S.S.R. and Russia. P. Marbarger, P. A. Campbell, Ashton Graybiel, W. Randolph Lovelace, Harry G. Armstrong, and Charles A. Berry were leaders and pioneers in aviation and space medicine in the U.S.A. (Pool and Davis 2006) The same issues that these early space medicine practitioners faced in the 1950's and 60's, current flight surgeons face today. However, since the 50's we have learned a significant amount about the human body's tolerance to the extremes of the space environment. Consequently, we now have a much

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[39] 100 km is also known as the *Karman line*, established as boundary between atmosphere and space by the *Fédération Aéronautique Internationale* (FAI), the standard setting and record-keeping body for aeronautics and astronautics, founded in 1905. The U.S. definition of space is 80 km (50 statute miles), approximately where Mesosphere ends; travelers beyond this altitude are called *astronauts*.

more robust evidence base, from which to pursue a universal countermeasure to microgravity such as artificial gravity.

The description of the environmental hazards of space and the practice of space medicine are described in Section 2. The rationale behind and requirements for medical monitoring of both research and operational utilization of artificial gravity as a spaceflight countermeasure are discussed in Section 3.

2 SPACE MEDICINE

This section is a review of the effects of physiological, medical and psychological factors on crew health, well being, behavior, and performance. This knowledge is helpful for evaluating the hazard of providing continuous or intermittent artificial gravity in deconditioned subjects.

Hazard	***Acute Risk***	***Chronic Risk***
Radiation	*Acute radiation sickness*	*Cataracts, cancer*
Vacuum	*Ebullism, decompression sickness*	*Death*
Microgravity	*Space adaptation syndrome*	*Muscle atrophy, bone loss, neurovestibular dysfunction*
Micrometeoroids/ Orbital debris	*Trauma*	*Plasma*
Toxic exposure	*Acute respiratory distress syndrome (ARDS), confusion, burns, sensory loss (sight, smell)*	*Fibrosis, dementia*
Surface regolith (dust)	*Allergic reaction*	*Pulmonary fibrosis*
Hypoxia	*Confusion, lethargy*	*Acute motion sickness (AMS), loss of consciousness, death*
Hypercarbia	*Headache, dyspnea*	*Confusion, coma, death*
Temperature	*Chilblains, pernio[40], heat exhaustion*	*Frostbite, loss of conciousness, heat stroke*

Table 11-01. Hazards and risks associated with the spaceflight environment.

[40] Chilbains or pernio are inflammatory skin conditions that appear after exposure to extreme cold.

2.1 Environmental Hazards of Spaceflight

The hazards that are unique to the extreme environment of space are summarized in Table 11-01. They include hypoxia, insufficient oxygen and hypercarbia, elevated carbon dioxide in the cabin or spacesuit atmosphere due to impaired performance or failure of the life support system. The life support system is essential for life in space and other planetary surfaces, due to an insufficient atmospheric pressure and oxygen supply for human existence.

2.1.1 Hypobarism

The relative vacuum of space poses a risk of ebullism should the crew be exposed to it, hence the need for a spacesuit while performing *extra-vehicular activity* (EVA). However, in order for crewmembers to perform efficiently in the suit, the pressure should be as low as possible, yet still maintain adequate oxygen tension to avoid hypoxia. Whenever the body undergoes transition to lower pressure environment, there is always a risk of developing *decompression sickness* (DCS) or illness, also known as "the bends". The larger the pressure difference in a nitrogen-rich atmosphere, the higher the risk of DCS developing, unless adequate time is dedicated to pre-breathing 100% oxygen to wash out the nitrogen from the body. The risk of DCS may be lower in microgravity than in 1-g conditions, possibly due to changes in large muscle group shear forces or differences in bubble dynamics. At least the number of observed cases of orbital DCS is less than would be expected based on terrestrial models (Balldin and Webb 2002, Pilmanis *et al.* 2004, Webb *et al.* 2005).

2.1.2 Toxic Compounds

A large number of potentially toxic compounds may be on board the transit and habitation vehicles for a wide variety of functions. Design engineers must trade the use of toxic compounds with a performance track record versus less toxic compounds with potential performance issues, especially in the area of propellants, cooling system, and in-situ resource utilization hardware. For example, fuels for reaction control jets often employ hypergolic components that spontaneously react or burn when mixed together and are effective in the vacuum of space, such as monomethyl hydrazine and nitrogen tetroxide, both of which are highly toxic when inhaled or when contact is made with the mucous membranes. Another example is in the cooling loops where ammonia or ethylene glycol is often effectively used; however, both of these substances have leaked into space station compartments and both have serious effects when breathed or ingested in significant quantities.

As has been experienced on both transit as well as habitation vehicles, e.g., Apollo, Salyut, and Mir combustion events can produce toxic compounds such as hydrogen cyanide, hydrogen chloride, and carbon monoxide. The acute and chronic effect risks of large dose exposure to lunar or Martian regolith dust has also not been fully elucidated, although the topic is under evaluation by NASA toxicologists and physicians.

Both acute and chronic diseases may result from toxic exposures, depending on the duration and magnitude of exposure. These induced conditions range from ocular or respiratory irritation, to unconsciousness and death. The effects of microgravity on the cellular and immune response to toxic compounds has yet to be completely defined, but some evidence would suggest that immune function will be diminished during long-duration spaceflight, and may result in increased risk of secondary microbial infections in tissue damaged by toxic substances (Kaur *et al.* 2004, 2005, Stowe and Pierson 2003). Artificial gravity, intermittent or continuous, could play a role in maintaining immune function, if it is determined that diminished gravity exposure produces alterations in leukocyte gene expression (see Chapter 10, Section 1).

Toxic substances countermeasures include personal protective equipment such as quick-don and portable breathing masks, which protect the crew's mucous membranes and respiratory system, in case of fire or rapid de-pressurization. Known antidotes for likely toxins will be components of medical kits and will include agents such as pyridoxine for hydrazine toxicity, and nitrites with thiosulfate for cyanide poisoning. Eyewashes will be included in the kit for removal of debris or chemicals from ocular tissues.

2.1.3 Radiation

Two classes of radiation pose a hazard to crewmembers, especially while on EVA: ionizing and non-ionizing.

Ionizing radiation can produce damage to human tissue through direct molecular interaction or via the production of free radicals and reactive oxygen species. This damage, depending on the severity and location within the cell can produce cellular lethality or mutation, especially if the radiation affects the nucleic acids. If the dose is high enough in a short exposure period, ionizing radiation can produce *acute radiation syndrome* (ARS), which is divided into three categories: hematologic, gastrointestinal, and central nervous system forms of ARS. Doses high enough to cause ARS are possible from large solar storms (Figure 11-02), especially if the crewmember is not protected by vehicular or habitat shielding. Potential long-term effects on the body resulting from lower doses or more prolonged exposures include cataracts, cancer, microvascular fibrosis, and dementia (Prasad 1995).

Crew defense against ionizing radiation hazards will lie mainly in the form of shielding. This is especially true for protection against the high dose concentrated over a short time interval, which could result from a large and energetic *solar particule event* (SPE) (Figure 11-02, left). The solar protons are much more amenable to shielding than is *galactic cosmic radiation* (GCR) (Figure 11-02, right). Having transit vehicle or habitat shielding that can provide a "storm shelter" in the event of a major SPE, will be an essential design feature (Wilson 1997, Simonsen 1997). Shielding GCR may come in the form of planetary regolith or natural terrain features, which additionally may aid with micrometeroid protection.

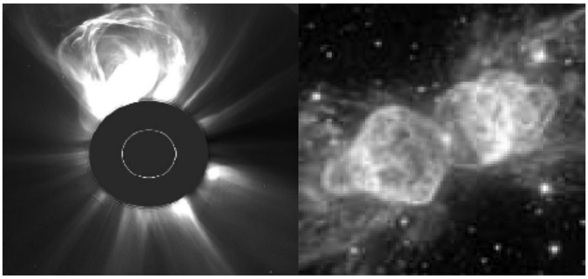


Figure 11-02. Left: Coronal mass ejection from the sun, at the origin of solar protons. Right: Colliding galaxies spewing galactic cosmic radiation.

The development of radioprotectant formulations, or agents that may reduce oxidative damage, which could be administered orally or parenterally, may augment the crew's defense against some of the ionizing radiation (Stanford and Jones 1999, Lupton 2001, Taylor 1992). Recent studies suggest that microgravity may affect cellular gene expression, and thus may alter the cell's natural radiation defense and repair systems (Boonyaratanakornkit *et al.* 2005, Purevdorj-Gage and Hyman 2006). This would most likely be a negative way synergy, such that the combination of ionizing radiation and microgravity may produce more biologic impact than ionizing radiation alone. If the observations in these studies prove to be correct, then artificial gravity may play a role in reducing these biological effects, by suppressing the changes in gene expression.

The sources of non-ionizing radiation are chiefly solar, but also include man-made equipment such as lasers and communications antennae, which can produce various forms of electromagnetic radiation. The solar light, ultraviolet, and infrared radiation can be near instantly hazardous to the retinas of crewmembers if their eyes are not protected by special visors which absorb or reflect the harmful wavelengths. This is also true of laser devices flown to assist in range finding during rendezvous and docking of space vehicles as well as exterior inspection, and other applications. The energy density of the laser beam has a large influence of the potential time and severity of biological effects of the laser.

Other forms of electromagnetic radiation, such as microwaves, can produce local tissue heating and thermal injury, if the radiation is of high enough intensity and the crewmember's body is placed directly in the path of transmission.

2.1.4 Impact

Micrometeoroids and orbital debris constitute a risk of not only hypobarism (DCS and ebullism) but also trauma to the crewmembers, whether they are conducting EVA in space or on the planetary surface. The kinetic energy contained by these small meteoroids can be quite significant, especially at typical velocities of up to 20 km/s, and therefore they can inflict serious harm. Vehicular and space suit design is likely to include energy absorbing strength layers which can resist penetration of micrometeoroids and should have a self-sealing type material in the inner pressure bladder, in case of non-lethal micrometeoroid strike (Jones *et al.* 2004).

2.2 Environmental Hazards Inside the Habitat

2.2.1 Atmospheric Composition

The partial pressure of oxygen must be provided to the crew to prevent development of hypoxic symptoms, and the partial pressure of carbon dioxide must be scrubbed to prevent development of hypercarbic symptoms. A challenge for exploration missions will be the development of *in-situ resource utilization* (ISRU)-based life support technology, and possibly even bioregenerative approaches to atmospheric control. Swing-bed technology with molecular sieves are likely to be used early in maintaining metabolic carbon dioxide at acceptable levels, as this approach does not consume the scrubbing material as is the case with lithium hydroxide used in Apollo and Shuttle environmental control systems.

The atmosphere must also be filtered of particulates and trace contaminants to prevent respiratory irritation. *Spaceflight maximal allowable contaminants* (SMAC) are established to limit levels low enough to prevent development of biological effects of the contaminants.

A unique potential atmospheric contaminant of the lunar or Martian surface will be dust from the planetary regolith. This dust will differ from terrestrial dust in size distribution, shape and chemical reactivity, therefore making it potentially a larger hazard than the nuisance variety found commonly in terrestrial vehicles and living spaces. Some speculate that lunar and Martian dust may have characteristics similar to freshly fractured silica or coal, which can produce not only acute respiratory reactions secondary to deposition in the bronchioles and alveoli of the lung inducing oxidative damage, but also potentially pulmonary fibrosis associated with prolonged exposure.

2.2.2 Water Chemical Contamination

Water chemical contamination will be kept within water quality standards, to prevent ingestion of potentially harmful agents. There have been several incidents during space station missions of water becoming contaminated with elevated concentrations of harmful substances, e.g. cadmium leaching from water system valving and ethylene glycol being accumulated in the water reclamation system from a cooling system leak.

2.2.3 Microbial Content

Vehicular and habitat air, water, and surface microbial content must be kept below standards, as microbes pose a hazard of infectious disease, that is mitigated through the use of biocide and filtration.

2.2.4 Thermal stress

Temperature control will be important not only in the transit vehicle and habitat, due to large temperature excursions during lunar and Martian day-night cycles, but especially in the EVA spacesuit, where slight perturbation in heat loading can rapidly increase thermal stress to the crewmember unless promptly controlled. The use of suit insulation and liquid-type cooling undergarments will likely play a large role in reducing the risk of thermal injury and performance deficits in EVA crewmembers (Waligora 1975). An active thermal control system with connections to heat radiators will assist in maintaining a cabin temperature and dew point.

2.2.5 Noise

Elevated sound levels usually emanating from onboard equipment, can pose hazards to the hearing and psychological well-being of the crew. The best means of reducing these risks is via engineering solutions, to muffle the sound emissions, however when the engineering approaches are not satisfactory, noise attenuation hardware, either active or passive may be employed.

2.2.6 Vibration and Acceleration

Flight vibrations and acceleration are usually only significant during dynamic phases of flight, i.e., launch, orbital maneuvering, transit burns, atmospheric re-entry, and landing. Design limits for vibration and acceleration, specific for the axis of load onto the crewmember should reduce the risk of critical task performance errors. However an important countermeasure for both the neurovestibular and orthostatic adaptations during g-transition phases of flight could be artificial gravity.

2.3 Psychological Hazards

2.3.1 Chronobiology

Due to the rapid sequence of light/dark cycling in LEO, there is a transition every 45 min for orbital periods of 90 min, the crewmembers natural biorhythm is interrupted. Interruption of usual chronobiology will also be expected during lunar surface stays, especially if permanently lit regions of the lunar south pole are chosen for the outpost habitat. Without the natural dark-induced timing of melatonin release of the environment, the vehicle may need to provide dark quarters to allow normal sleep patterns to be acquired by long duration crewmembers. In addition, vehicle docking, relocation and timing for orbital maneuvers, often force crewmembers to be awake during their chronobiologic nadirs, increasing the risk of fatigue-induced crewmember errors. Flight rules have been written in attempt to reduce the risk of fatigue-related task errors, but these rules are often overcome by operational drivers. Supplemental melatonin as well as short-acting benzodiazopines have been used during both Shuttle and ISS flights to not only induce sleep but to re-establish shifted sleep entrainment. Light therapy especially in the blue wavelengths, has been employed to help reduce fatigue during sleep shifting and assist in the establishing new wake-sleep schedules.

2.3.2 Isolation

Long-duration spaceflight places the crew in isolation from their family, friends, and most of their colleagues for months, and in the future for perhaps years. This isolation, as well as the heavy work schedule without effective opportunities for rest and relaxation, can take a toll on crewmember morale and well being (Nicogossian *et al.* 1994, Kanas and Manzey 2003). Risks for depressive symptoms and crew-crew and crew-mission control interaction difficulties increase with the duration, as well as stress-level, of the mission. Countermeasures that have been shown to be effective for long-duration crews include weekly family private conferences, biweekly private psychological conferences with a trained space psychologist or psychiatrist, recreational and personal hardware including musical instruments, DVD players and photo albums of family and friends. Artificial gravity is not likely to have a significant impact on psychological issues during spaceflight.

2.4 Microgravity

Multiple chapters of this text have discussed the changes in human physiological systems associated with the microgravity environment. These changes are expected physiological adaptations to the lack of gravity loading and are not in themselves pathological. Some of the symptoms associated with adaptive changes, such as *space motion sickness* (SMS), require pharmacological intervention, to limit mission impact of the symptoms, especially in first time space fliers (see Chapter 4, Section 3). Typically promethazine administered parenterally is used to treat SMS during the first 48 hours of flight, especially if the nausea and vomiting that are characteristic of the syndrome are severe. Other symptoms such as headache and nasal stuffiness are treated with additional pharmacological intervention as required.

However these adaptive physiological changes to microgravity are not diseases and are not usually treated medically (Nicogossian *et al.* 1994, Clément 2005). Instead, countermeasures are used in attempt to maintain 1-g conditioning so that the transition back to 1 g will be less challenging. Countermeasures for the muscle, bone, and neurovestibular changes are prescribed by the flight surgeons during both short- and long-duration spaceflight, and may include modalities such as exercise (aerobic for cardiovascular protection, resistive for musculo-skeletal protection), lower body negative pressure, fluid loading, anti-g suit, and pressure garment (for orthostatic hypotension protection).

This is where artificial gravity may provide the largest impact to protecting functionality for the crew upon return to a gravity field after prolonged periods in microgravity. Artificial gravity may be particularly effective in preserving the capability to response to an off-nominal landing event whether it be during the landing phase, or the need for emergency response or egress of the vehicle after landing. Additional risk reduction in the area of reduced postflight musculo-skeletal injury may also be conferred by artificial gravity use during flight, especially during the return trip.

2.5 The Role of the Flight Surgeon

The flight surgeon is the "space medicine practitioner" during space mission operations. From the medical perspective, space missions are commonly divided into three major phases: preflight, in-flight, and postflight. Let's examine the duties of the surgeon during each of these phases, so it will become clear how a surgeon's prescription for artificial gravity use may influence the crewmember's health throughout the mission.

Prior to beginning preparation for a space mission, the flight surgeon as part of an aeromedical board of physicians, will assess an astronaut applicant's health for selection to the astronaut corps, according to the medical standards. Each year following selection, the health of each astronaut will be evaluated for medical retention, which includes medical certification for training and flight in training aircraft. Prior to assigned spaceflight, each astronaut will be medically certified for duty on that vehicle. Crewmembers flying to the ISS will be certified by the *Multilateral Space Medicine Board* (MSMB) composed of representatives from the major partners of the ISS program.

2.5.1 Preflight

During the preflight certification process, the crewmembers are tested biochemically and microbiologically, and appropriate preventive measures are taken including immunizations and treatment of any infectious conditions. The *Astronaut Strength, Conditioning, and Rehabilitation* (ASCR) team will work with the crew during the 6-12 months prior to flight to optimize their physical conditioning and prepare muscle groups that our prone to fatigue during flight task like EVA.

During the preflight training period, the flight surgeon serves as the medical monitor and support for any physiologically stressful training activities. This includes training in the neutral buoyancy laboratory or hydrolab, where weightlessness is simulated for EVA, vacuum chamber runs, water and winter survival training. If artificial gravity is adopted as an in-flight countermeasure, then the preflight training and familiarization will also be supported by the flight surgeon.

The mission's assigned crew surgeon is also responsible for training the *Crew Medical Officer* (CMO) on the contents and operations of the medical system. Training also includes reviewing the procedures within the medical checklist, how to perform a private medical conference while in-flight, and how to handle a medical contingency should it arise.

A period of health stabilization and maintenance is entered approximately 10 days to two weeks prior to launch, to remove the crew from large vectors of infectious diseases as well as protect their time to focus on specific preflight preparation activities.

If the launch window or flight operations require the crew to be awake during nominal sleep periods, then the crew's sleep must be shifted in advance and a new anchor sleep time established prior to launch, to allow the crew's in-flight performance to be maintained at an optimal level. This process requires more advanced implementation if the magnitude of sleep shift is large. Sleep shift aids such a light therapy and melatonin may be employed, depending on the direction of the time shift.

The medical flight certification process also includes review and concurrence with the engineers that the medical hardware and kits are also ready to support the mission.

2.5.2 In-Flight Health Maintenance

The crew and deputy crew surgeons and biomedical engineers are on console at both the launch control and mission control centers for launch activities, and have communication networks open with search and rescue forces, provided by both NASA and the department of defense, in case of a launch abort or contingency. The surgeon is a front control room console position and provides a Go/No-Go recommendation for various phases of launch, landing and flight activity to the flight director.

The surgeon is responsible for enforcing the aeromedical flight rules concerning the crew health and safety concerns during flight, which includes responses to off-nominal space environment, such as atmosphere and water. The surgeon also enforces many of the ground rules and constraints, especially related to crew scheduling, to prevent jeopardizing crew safety secondary to mission overload.

Private medical conferences are conducting with the crew daily during short duration flight and on a weekly basis during long duration missions. The surgeon and biomedical engineer will be on console to medically monitor all EVAs and onboard medical or life science research activities, in which the crew is acting as a subject. During EVAs the medical team will receive biomedical telemetry from sensors worn underneath the cooling garment, so that they can track not only the level of carbon dioxide and thermal loading, but also heart rate and rhythm, metabolic rate based on oxygen utilization, carbon dioxide or heat production, and in some cases, like when Russian space suits are used, respiratory rate and body temperature. Future seats may build such sensing equipment into the cooling garment or maybe even a subcutaneous chip to allow these parameters to be monitored without overhead. Perhaps during Mars missions, the biomedical information will be locally processed with software algorithms which allow prediction of remaining consumables such as oxygen or water, to feed back to the crew for optimization of task performance or ambulation rate, or to caution the crew when off-nominal or life-threatening situations arise.

During long-duration flights in LEO, currently there are regularly scheduled periodic health assessments, consisting of monthly or bi-monthly examinations and laboratory tests of the urine and blood. A portable clinical blood analyzer and urinalysis testing hardware is flown to provide diagnostic and biochemical status information. Periodic fitness evaluations are conducted monthly to evaluate effectiveness of the in-flight countermeasures program. The crew surgeon, working with the ASCRs as mentioned above, provide exercise and other countermeasures prescriptions to the crew during the flight (Figure 11-03), and tailor the prescription based on in-flight assessment tools like the *pulmonary functional evaluation* (PFE), or, in the future, blood tests or imaging. Future countermeasure prescriptions for missions to Mars may include pharmaceutical agents, like bisphosphonates, or physical agents, like artificial gravity, if the results from current research prove promising.

The flight surgeon, working with nutritionists and food systems experts, reviews the content of the planned crewmember's diet as well as preflight nutritional testing to ensure adequate levels of nutrients are supplied to maintain health and to resist disease (Lane 2000, Watson 1996). Due to several factors, e.g., lack of sunlight exposure, prior long-duration crews have had reduced levels of vitamin D found in postflight measurements, so levels of this nutrient may need to be supplemented (see Chapter 9, Section 4.1).

The medical team is also responsible for environmental monitoring, and along with the environmental control team and specialists in toxicology, radiation, and water quality. There are periodic or continuous assessments of the vehicle environmental parameters. If these parameters should be found to be outside of acceptable limits, then the surgeon may need to invoke a flight rule, which could require the initiation of on-board corrective actions.

Figure 11-03. Expedition 13 Astronaut Jeffrey N. Williams, equipped with a bungee harness, gives a "thumbs-up" signal while exercising on the Treadmill Vibration Isolation System *(TVIS) in the Zvezda Service Module of the International Space Station. Photo courtesy of NASA.*

2.5.3 In-Flight Medical Events

Despite the rigorous screening and preventive medical approach to spaceflight, medical events occur very commonly, as was discerned from a review of the Space Shuttle flights between 1981 and 1998, comprising 89 missions and 508 crewmembers (439 men, 69 women), in which 98% of crew reported some medical symptom during their flights. A listing of symptoms affected during short duration missions is as follows: 67% headache, 64% respiratory complaints, 58% facial, nasal and ocular complaints, 32% gastro-intestinal complaints, 26% musculo-skeletal complaints, 12% injuries, 10% genito-urinary symptoms. In addition, 79% of the crew suffered from SMS within the first few days of entering microgravity (Jones *et al.* 2004).

The experience for long-duration crewmembers is not dissimilar from short-duration fliers. However, difficulties with skin rashes and abrasions, foreign bodies in the eye, sleep disorders, and interpersonal issues occur at a higher rate. Also during long-duration flight there is a higher rate of musculo-skeletal symptoms and equipment discomfort issues associated with the use of countermeasure hardware. Dental symptoms have arisen on several long-duration missions, especially when preflight dental issues existed.

Medical conditions with an expected incidence of greater than 50% include skin rash, irritation, foreign body, eye irritation, corneal abrasion, headache, backache, congestion, gastrointestinal disturbance, cut, scrape, bruise, musculo-skeletal strain, sprain, fatigue, sleep disturbance, space motion sickness, post-landing orthostatic intolerance, post-landing neurovestibular symptoms (Davis 1998, Jones *et al.* 2004).

There have been three medical evacuations during spaceflight from Russian space stations. These evacuations occurred: (a) during Salyut-5 in 1976 the station was abandoned 49 days into a planned 54-day mission for intractable headaches; (b) during Salyut-7 in 1985, there was one crewmember evacuated at 56 days into a 216-day mission for prostatitis-induced sepsis; and (c) on Mir in 1987 a crewmember was evacuated 6 months into a 11-month mission for a cardiac dysrhythmia.

There have also been multiple close calls occurring near evacuation or mission termination in both U.S. and Russian programs. For example, there have been spacecraft fires in 1967 (3-U.S. fatalities in Apollo 1), 1971, 1977, 1988, and 1997 (the latter occurred on board Mir due to an oxygen generator); a urinary stone in 1982 on Salyut-7, which passed spontaneously just prior to an evacuation; hypothermia during EVA in 1985; psychological stress reaction in the mid 90's; spacecraft depressurization in 1997, with collision of a Progress vehicle with the Spektr module of Mir; toxic atmosphere on two occasions in 1997 with inhalation of smoke during the fire and later an ethylene glycol release from the cooling system (Jones *et al.* 2004).

Radiation sickness has not occurred in-flight. However on August 4, 1972, i.e., less than four months after Apollo 16 returned from the Moon and three months before Apollo 17 launched, there was one of the highest magnitude SPEs on record. If a crew had been in interplanetary space during that SPE, with the limited shielding on the Apollo command module, estimates are that they would have experienced acute radiation sickness, possibly severe (Townsend 2003). The treatment requirements for a crew in the case of a high dose and rate radiation exposure is significant, and possibly beyond space medicine's ability to treat, unless new protective strategies are developed.

The occurrence rate of medical conditions requiring urgent medical intervention from expeditions in remote environments, analog simulations, and in the highly medically selected and maintained U.S. astronaut corps, both terrestrial and in-flight, have been compiled by Dr. Smith Johnston and others, looking at the medical requirements for crew rescue vehicles like the

Crew Return Vehicle (CRV-X38) and the Orbital Space Plane. This analysis reveals a 7% (5-10%: 90% CI) probability of a serious medical event per man-year. More crewmembers and missions of longer durations cumulatively increase that probability (Jones *et al.* 2004).

The very nature of exploration, especially on a minimally explored planet, has taught us that traumatic accidents will be highly likely, even with the best of precautionary procedures and safety algorithms. The real possibility of blunt and penetrating trauma, crush injuries, deceleration injuries, hypobarism injuries, and burns cannot be underestimated. Treatment protocols and capabilities should be expanded beyond the current advanced cardiac life support on board the ISS, to include advanced trauma life support for lunar outpost and Mars missions.

In order to maintain readiness to respond to a medical condition, there will be medical computer-based training and skills maintenance tools flown Examples include medical and surgical procedure simulators with realistic feedback on performance.

- *Potential illnesses and problems*
  - *- Musculo-skeletal problems*
  - *- Infectious, hematological, and immune-deficiency associated conditions*
  - *- Dermatological, ophthalmologic, and ENT problems*
  - *- Dental*
  - *- Psychiatric conditions- stress reaction, interpersonal conflict*
- *Acute medical emergencies*
  - *- Wounds, lacerations, and burns*
  - *- Decompression Sickness (DCS)*
  - *- Surgical emergencies - e.g. appendicitis*
  - *- Acute Radiation Sickness (ARS)*
  - *- Toxic exposure and acute anaphylaxis*
- *Chronic diseases*
  - *- Radiation-induced sequelae*
  - *- Responses to dust exposure, pneumonitis*
  - *- Chronic hypersensitivity skin reactions, possibly fungal*
  - *- Urinary calculi – can manifest acutely*
  - *- Latent virus reactivation*

Table 11-02. Summary of potential Moon and Mars expedition medical contingencies.

To summarize the medical events discussion, there is a high likelihood that each crewmember will have minor medical complaints that will need attention to minimize discomfort and maximize crewmember performance. There is a strong probability that a significant medical event requiring urgent intervention to prevent an unfavorable outcome will occur, including morbidity and even mortality. The medical support program for exploration missions should provide for health maintenance, acute condition diagnosis, and treatment for a wide range of medical conditions, trauma, and environmental exposures.

Figure 11-04. Medical contingency simulation at Haughton Crater, in the high arctic.

2.5.4 In-Flight Medical Hardware and Supply

The exploration medical hardware can be classified as ambulatory or emergency. The **ambulatory medical hardware** will include a data management and archiving analytical computer for recording all health-related information, including all preflight test data, and baseline images, for computer analysis and comparison. Diagnostic assist software will be programmed with algorithms for diagnosis and management of many symptoms and signs to assist the crew surgeon in medical and psychological complaint evaluation, in other words, a virtual consultant. This computer will also have a communication package for relay of medical information from field sites, possibly in a pressurized EVA rover to the planetary habitat and to Earth for telemedical consultation with Earth-based specialists.

The diagnostic suite will likely include a telemedicine instrumentation unit for electronic capture of all examination vital signs and photography of relevant anatomy. Other examination hardware may provide for electronic data file stowage, e.g. from a stethoscope, blood pressure cuff, which will facilitate computer-assisted diagnostic review and comparison to baseline information. Medical imaging may include a portable ultrasound unit, or perhaps more advanced imaging devices will have been miniaturized to reduce power and mass requirements and allow placement in the habitat. There will be ambulatory treatment medications for all commonly occurring, non-urgent conditions, including SMS treatment.

Emergency medical hardware to support full resuscitation protocols will be on-board providing the capability to perform defibrillation, suction, rapid fluid or blood replacement infusion, and other critical functions. A reduced gravity operating area, possibly with robotic assistants, will provide basic surgical therapy in both the transit and surface vehicles. Due to the potential for DCS, especially with gravitational ambulation on the lunar and Mars surface, hyperbaric treatment capability will developed, although not likely to provide terrestrial standard of care. Remote medical evaluation capability may be built into the surface rover vehicle, to allow the "away EVA team" to send back medical data to the crew surgeon who may be at the base camp. Figure 11-05 shows a concept for remote medical assessment station, with robotically controlled scanning and visualization hardware.

Despite all of the medical capability and training that will go into preparing for medical contingencies, the crew will need to be prepared both physically and psychologically for the possibility of the death of one or more of their crewmates. A means to contain a deceased crew, which will include a seal from air and fluid exchange, may be included to allow body stowage and transport; however, the possibly of a non-terrestrial burial may be considered because of logistics reasons.

Figure 11-05. Artist Pat Rawling's rendition of a Mars medical assessment station.

2.5.5 Postflight Rehabilitation

There will likely be no quarantine for crewmembers returning from the lunar surface, based on the Apollo experience and the lack of microbes found there. However a successful return of crews from Mars will be a milestone event in history, yet will require a detailed protocol for both quarantine and reverse quarantine of these crewmembers. This will be the case at least for the first crew, who will return to a level-5 containment facility, to prevent back contamination of potential Martian microbes. The crewmembers will also need to be protected from terrestrial bacteria and viruses until their immune systems are functionally nominally again.

After an extensive program of postflight medical and psychological testing, which will provide data for both the crewmember's flight surgeon and for medical research, the crew will embark on a three to six month long rehabilitation program, which will likely include massage, hydrotherapy, and progressive ambulation. Activities of daily living assistance may be employed during the first week. Subsequently, after medical clearance, they will begin a progressive program of increasing loads for both aerobic and resistive exercise to bring their strength, endurance, and bone mineral levels back up to baselines. Due to the social and political importance of the event, there will be extreme pressure from the media for commentary from the crew. The first interviews will need to be conducted from the quarantine facility. It will be challenging to meet the demands of media event requests while simultaneously protecting the crewmember's health and time for postflight debriefs and rehabilitation.

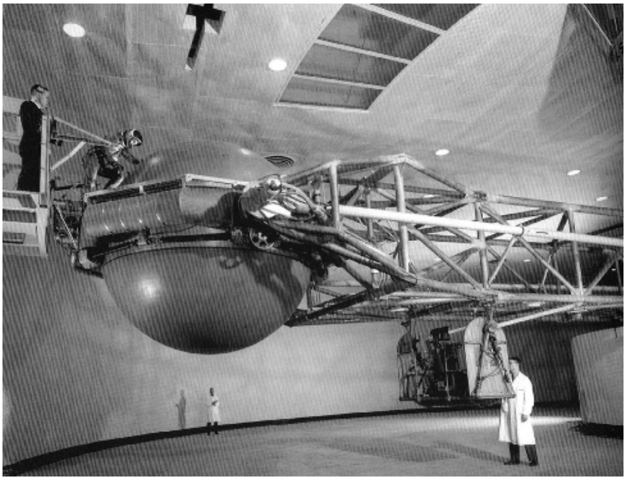
The requirements for the medical support program for space missions flow from medical standards documents such as the *Spaceflight Crew Health Standards Document* and the *Astronaut Medical Evaluation Requirements Document*. These documents supply the medical levels of care and fitness for duty standards that space vehicle program managers must comply with to ensure that the crewmembers occupying and operating those vehicles are healthy and safe to perform their mission tasks.

Even the best medical support and countermeasure system cannot mitigate all of the health risks of spaceflight. In 2001, a committee of the U.S. Institute of Medicine was tasked to create a vision for space medicine during travel beyond Earth Orbit. This committee concluded its report by stating that: *"Space travel is inherently hazardous. [...] The risks to human health of long-duration missions beyond Earth orbit, if not solved, represent the greatest challenge to human exploration of deep space. [...] The development of solutions is complicated by lack of full understanding of the nature of the risks and their fundamental causes"*. The main objective of the space medicine organization of tomorrow may well be to develop and validate all of the countermeasures required to enable human exploration of the solar system. Artificial gravity may be a key component to that countermeasure system for exploration-class missions.

3 MEDICAL MONITORING DURING ARTIFICIAL GRAVITY STUDIES

Continuous medical monitoring is necessary for centrifuge operations that expose subjects to high g and high g-onset stresses, such as those that are commonly used in training pilots for air combat maneuvers (Figure 11-06). While subjects in artificial gravity studies are generally exposed to less severe accelerations, many of the potential medical issues are the same and the approach to medical monitoring is similar. Most test protocols require the presence of a monitoring physician and have predetermined test termination criteria, which may vary somewhat depending on the specifics of the study. Vigilant monitoring and a timely response are necessary to effectively intervene for the most common problems resulting from the physiologic stress of centrifugation, including motion sickness, pre-syncope, and cardiac arrhythmias. In addition, centrifuge personnel must possess the appropriate training and equipment necessary to provide effective initial care to injured test subjects and those who develop any unforeseen serious medical issues.

Figure 11-06. The first long-radius human-rated centrifuge used in Mercury astronaut training program at the U.S. Navy Aviation Medical Acceleration Laboratory, Johnsville, Pennsylvania. Mercury Astronaut Walter M. Schirra prepares to enter the gondola of the centrifuge. Photo courtesy of NASA.



3.1 Syncope

For a subject on a centrifuge, presyncopal symptoms and syncope are usually caused by venous pooling in the lower body as a direct consequence of the gravity gradient along the subject longitudinal axis (Gz). Venous return is inhibited, resulting in reduced cardiac output and cerebral hypoperfusion. The gradient necessary to induce syncope on a short-radius centrifuge varies according to individual tolerances, the specific centrifuge configuration, and the onset rate. One study with supine subjects on a short-radius centrifuge revealed that cardiovascular responses to the gravity gradient becomes significant when gravity level at the feet (Gz) is about 1.5 g (Hastreiter and Young 1997). In this study, subjects had the tops of their heads at the center of rotation and the authors reported that syncope occurred in some subjects when as little as 2 g was applied to the feet. A previous validation study of a centrifuge design in which supine subjects had their legs flexed and their heads 66 cm from the rotation axis showed that as much as 6.4 g was tolerated (Burton and Meeker 1992). This same study showed that a gradual onset rate (0.1 g/s) was better tolerated than a more rapid onset rate (1 g/s).

It should be noted that the mechanism of orthostatic stress-mediated syncope seen in subjects on short-radius centrifuges is different than that of

G-induced loss of consciousness (G-LOC). G-LOC is an important issue in high performance and military aviation and has been extensively investigated in high performance centrifuges. The mechanism of G-LOC is thought to be primarily due to a sudden hydrostatic pressure drop associated with rapid onset high-Gz acceleration, because venous pooling is limited by the use of anti-g garments (Self *et al.* 1996). In short-radius centrifuge, the onset acceleration does not exceed a fraction of g/s. Despite differences in mechanism and the usual rate of onset, the resulting decrease in cerebral blood flow causes essentially the same neurologic symptoms in both cases. Therefore, the medical monitoring modalities are essentially the same as those used for high-performance centrifuge operations.

3.2 Prodromal Symptoms

Prodromal symptoms[41] may include a narrowing of the visual field (tunnel vision), pallor, weakness, light-headedness, impaired hearing, nausea, yawning, and a feeling of warmth or cold. Continuous communication with the subject via an audio communications loop is the most effective means for assessing symptoms of pre-syncope (Figure 11-07). Subjective numerical scales may be used to rate nausea and general well being. Video monitoring may be useful by allowing the medical monitor to directly assess diaphoresis, pallor, or repeated yawning.

The onset of tunnel vision can be recognized by using a simple assessment tool known as a light bar. This device has been used in high-g centrifuge operations to detect imminent G-LOC. A typical light bar configuration has two green lights located 35.5 cm laterally to either side of a single central red light. The central light is positioned at a fixed distance (76 cm) from the subject's face. The subject is instructed to focus on the central red light and note any subjective decrease in brightness of the green lights, indicating the onset of peripheral vision loss.

3.3 Heart Rate

Other helpful monitoring modalities include continuous *electro-cardiography* (EKG) tracings and blood pressure measurements. In addition to monitoring for arrhythmias, the EKG is a reliable means to continuously monitor the heart rate. A sustained baroreceptor-mediated increase in heart rate is expected during centrifugation. The percentage increase compared to that for a supine subject can easily be 40-60% and is dependent on the applied g level (Vil-Viliams *et al.* 2004, Miyamoto *et al.* 1995). This is a similar

[41] *Prodromal symptoms* are symptoms symptomatic of the onset of a medical event or a disease.

response to that observed for long-arm centrifuges (Vettes *et al.* 1980) and is presumably associated with a comparable decrease in stroke volume.

An anticipatory increase in heart rate just prior to centrifugation is sometimes seen, particularly for novice subjects. While tachycardia in the 100 to 140 beats/min range may be tolerated for 30 to 60 min or more by many subjects, those who experience progressive increases in their heart rate should be monitored closely for signs of decompensation.

The phenomenon of bradycardia that is occasionally seen during sustained high-g exposure may not be as common during artificial gravity centrifugation because anti-g straining maneuvers and anti-g suits are generally not used (see DeHart and Davis 2002 for review). However, most protocols appropriately call for termination of a test if sudden-onset bradycardia is noted. Such a rapid decrease in heart rate during centrifugation would likely be associated with a significant and abrupt decrease in cardiac output and syncope. The medical monitor should keep in mind that a rapid deceleration (1 g/s) and the associated sudden increase in venous return and reduction in sympathetic tone may actually exacerbate sinus bradycardia by slowing conduction through the *Atria-Ventricular* (A-V) node (Zawadzka-Bartczak and Kopka 2004). Therefore, a moderate deceleration may be more appropriate.

Figure 11-07. Close-up view of Astronaut M. Scott Carpenter, primary pilot for the Mercury-Atlas 7 mission, during centrifuge training at the U.S. Navy Aviation Medical Acceleration Laboratory, in Johnsville, Pennsylvania. Photo courtesy of NASA.

3.4 Blood Pressure

Blood pressure is usually monitored intermittently with an automated sphygmomanometer system. Photoplethysmography has been successfully used to measure blood pressure on a continuous basis during centrifugation (Serrador *et al.* 2005, Vil-Viliams *et al.* 2004) and the use of a tonometry device (Jentow®, Colin) has been reported (Iwasaki *et al.* 1998). However, these devices are generally less reliable than traditional sphygmomanometry and a traditional blood pressure cuff system should be used as a backup device. Invasive methods of blood pressure monitoring have generally been considered inappropriate for this application.

Published reports of blood pressure changes with the onset of short-radius centrifugation have shown a somewhat inconsistent pattern. For example, the study by Miyamoto *et al.* (1995) showed an increase in mean arterial blood pressure that paralleled the increase in gravity level during onset and rose from about 70 mmHg to 90 mmHg with the application of 2.2 g along Gz. Another study reported very small decreases in systolic blood pressure along with slight increases in diastolic blood pressure (Vil-Viliams *et al.* 2004). A third study showed a statistically significant but small decrease in pulse pressure that was primarily attributable to increased diastolic blood pressure with the application of Gz acceleration (Hastreieter and Young 1997).

Figure 11-08. A technician reaches across the arm of a high-g centrifuge to prepare two subjects for a test run.

For medical monitoring purposes, it is probably sufficient to check that the measured blood pressure remains fairly stable after the centrifuge reaches a constant speed. Formal termination criteria generally include a lower limit on systolic blood pressure (e.g., 70 mmHg) and may add a combination of other conditions to define hypotension (e.g., systolic blood pressure below 90 mmHg and tachycardia as greater than 140 beats/min, or a fall of systolic blood pressure by 25 mmHg). In general, it is difficult to detect a sudden fall in blood pressure with intermittent measurements before presyncopal symptoms are apparent. Continuous blood pressure monitoring may be somewhat more helpful, provided the measurement device is sufficiently reliable.

In all centrifuge operations, the signs and symptoms of pre-syncope should ideally be recognized early enough to prevent progression to syncope. Rapidly worsening symptoms are a clear indication for test termination. Mild or slowly progressing symptoms can sometime be ameliorated by muscular contractions of the lower extremities. This can often be accomplished by having the subject perform shallow knee bends or push his or her toes against a footplate. The rationale for this approach is supported by results showing that lower body exercise at least partially protects venous return (Caiozzo *et al.* 2004).

If the subject experiences syncope before a test can be terminated, recovery should occur rapidly, either during or shortly after deceleration. It should be remembered that myoclonic jerks often occur both in cases of G-LOC and neurally mediated syncope (DeHart and Davis 2002, Kapoor 2000). Therefore, it is not necessary to begin an extensive workup for underlying issues unless the subject has a focal neurologic deficit, headache, some other finding consistent with a seizure (e.g., post-ictal confusion), or the concurrent presence of a dangerous arrhythmia.

3.5 Motion Sickness

Motion sickness symptoms generally progress in a predictable order from lethargy to apathy, stomach awareness, nausea, pallor, cold sweats, retching and then vomiting. Other possible symptoms may include salivation, headache, eructation, warmth, flatulence, and anorexia. The traditional theory explaining the mechanism of motion sickness is that it results from a conflict in sensory inputs. The relevant issue here is the fact that in an artificial gravity environment Coriolis forces act on the endolymph in the vestibular system when the semicircular canals are moved into or out of the plane of motion. This creates illusory tilt sensations and nystagmus that can then trigger motion sickness (See Chapter 4, Section 3). Pitch head movements are apparently more provocative of symptoms than yaw movements (Young *et al.* 2001). Transient heart rate increases have been noted to occur after head movements (Hecht *et al.* 2001, Young *et al.* 2001).

In order to avoid provocation of symptoms, subjects should be reminded to avoid head movements whenever possible while the centrifuge is in operation. If movement is necessary, it should be done as slowly as possible. Subjects who are participating in protocols that require repeated centrifugation should be expected to experience some adaptation to the rotating environment (Young *et al.* 2001). A subjective numerical assessment scale is often useful in gauging the severity of symptoms. Progressive or severe symptoms require test termination. A relatively slow deceleration is often more comfortable for the subject. Rapid decelerations should be reserved for subjects who have progressed to emesis and for whom aspiration may be a concern.

3.6 Cardiac Arrhythmias

In addition to rate monitoring, the continuous monitoring of an EKG will give an indication of rhythm or conduction disturbances. Lead systems that use two mutually perpendicular leads, such as biaxillary leads and a sternal lead or a modified chest lead configuration, have proven to be adequate for monitoring purposes. Although it was not a requirement early on in the history of centrifuge training, electrocardiographic monitoring of subjects in high performance centrifuges has become standard because the publication of a study that documented the high frequency of arrhythmias in normal subjects exposed to standard Air Force training profiles (Whinnery 1990). Subsequent studies have confirmed that high-g-induced dysrhythmias are very common, with more than 90% of fighter aircrew exhibiting some sort of rhythm disturbance during high-g training profiles. Sinus arrhythmia, defined as a rate variation corresponding to more than 25 beats/min between successive beats, is the most common dysrhythmia and occurs in approximately 50-80% of aircrew at some time during standard high-g centrifuge training. Isolated *premature ventricular contractions* (PVCs) are the second most common arrhythmia, occurring about 60% of the time. Other arrhythmias, such as *premature atrial contractions* (PACs), sinus bradycardia, ectopic atrial rhythms, junctional rhythms, bigeminy, trigeminy, and A-dissociation are also commonly seen (DeHart and Davis 2002, Hanada *et al.* 2004).

Most arrhythmias occur during simulated air combat maneuvers or rapid onset +Gz exposure. Because the profile usually used in artificial gravity studies are much less severe and do not involve anti-g straining maneuvers, the overall frequency of arrhythmias is much less. However, it is still important to distinguish benign arrhythmias from those that may either indicate underlying cardiac disease or increase the risk for such dangerous rhythms as prolonged sinus arrest, A-V dissociation, ventricular fibrillation, or sustained ventricular tachycardia. A recent article by Hanada *et al.* (2004) analyzed data from the centrifuge training records of 195 male fighter pilots that was accumulated during a two-year period by the Japan Air Self-Defense Force Aeromedical Laboratory. Using their accumulated clinical experience and other considerations, such as a modified version of the Lown criteria to rank the clinical risk associated with ventricular ectopy, this group proposed some criteria for suspending high-g training on the basis of arrhythmias. They grouped the arrhythmias into three broad categories, as shown in Table 11-03.

This approach is similar to that used in many protocols for artificial gravity studies (see, for example, Iwasaki *et al.* 1998). In terminating a centrifuge run, the medical monitor should determine the rate of deceleration appropriate for the specific arrhythmia. Many of the critical arrhythmias, such as ventricular fibrillation, may require basic or advanced cardiac life support interventions. In those cases, a rapid deceleration to avoid delay in treating the subject is appropriate. A rapid deceleration may also be helpful in breaking the re-entry circuit of *paroxysmal supraventricular tachycardia* (PSVT) (Zawadzka-Bartczak and Kopka 2004), but will likely exacerbate sinus bradycardia.

Category	***Action Required***	***Type of Arrhythmia***
Normal physiological response	*Continue centrifuge protocol*	• *Sinus Arrhythmia* • *Occasional PVCs* • *Occasional PACs*
Borderline	*May require discontinuation of centrifuge training*	• *Frequent PVCs* • *Frequent PACs* • *PVCs in pairs or triplets (bigeminy, trigeminy)* • *Non-sustained VT* • *Mobitz type I AV block*
Critical	*Centrifuge training contraindicated*	• *Atrial fibrillation* • *Atrial flutter* • *PSVT* • *Sustained VT* • *Ventricular fibrillation* • *Sick Sinus Syndrome* • *Mobitz type II AV block (or higher)* • *Cardiac Arrest*

Table 11-03.Criteria used for suspending high-g training on the basis of arrhythmia. PVC: Premature ventricular contraction, PAC: Premature contractions in the atria, PSVT: Paroxysmal supraventricular tachycardia, VT: Ventricular tachycardia. Adapted from Hanada et al. *(2004).*

It is useful to set predetermined termination criteria for some of the borderline findings, such as defining more than 30 PVCs per hour or more than 6 PVCs in a single minute as frequent, for the purposes of a study. Other termination criteria based on EKG findings should include ST elevations or depressions and PVCs that fall on the T-wave of the previous beat (R on T). A maximum limit on tachycardia (e.g., greater than 180 beats/min) should also be set. It should be noted that T-wave changes, including flattening, inversion, and the appearance of biphasic T-waves are often seen at the beginning of high-g runs and generally disappear later in the run (DeHart and Davis 2002). These are generally not considered to be termination criteria for high-g centrifugation. This phenomenon has not been reported in artificial gravity studies and it is unclear if this should be considered a benign finding in that setting.

4 EMERGENCIES

Adequate planning for emergencies must be done in advance. While the likelihood of a cardiac or respiratory arrest may be low for adequately screened subjects, centrifuge personnel should be prepared to provide at least basic life support care and defibrillation. The need for advanced cardiac life support capability would depend on the immediate availability of emergency medical services. Advanced planning for evacuation of the subject from the facility and possible transfer to a hospital setting should be carried out. Frequent drills involving all responsible personnel should be a part of the regular schedule.

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Chapter 12

SAFETY ISSUES IN ARTIFICIAL GRAVITY STUDIES

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Artificial gravity is generally achieved by spinning humans in rotating devices (human centrifuges) that can present substantive safety hazards to subjects, operators, and facilities. In this chapter, the safety issues related to centrifugation are presented by scientific, engineering, safety, and medical experts having decades of experience spinning people at Brooks Air Force Base in San Antonio, NASA Johnson Space Center in Houston, the University of Texas Medical Branch in Galveston, and on board the Space Shuttle. We begin with an overview of general safety principals that must be considered when designing human-rated devices and facilities and continue on to specific safety issues associated with design and operation of centrifuges to be used in artificial gravity research and their support facilities.

Figure 12-01. The large-radius centrifuge at Brooks Air Force Base in San Antonio exposes the astronauts to the accelerations they will endure during launch. Photo courtesy of NASA.

1 GENERAL SAFETY PRINCIPLES

1.1 System Safety

System Safety Analysis provides a means to systematically and objectively identify hazards, determine their risk level, and eliminate or control them. The governing philosophy of system safety is to identify potential hazards as early as possible, eliminate as many hazards as possible through good design, and control any hazards that cannot be eliminated. The system safety process is an interactive process that begins in the conceptual design phase and extends through preliminary design, detailed design, manufacturing, and operations. The functions supported by the analyses are shown in Table 12-01.

- *Provide a foundation for the development of safety criteria and requirements*
- *Determine whether and how the safety criteria and requirements are included in the design and operations phases*
- *Determine whether the safety criteria and requirements created for design and operations have provided an acceptable level of risk for the system*
- *Provide a means for pre-establishing safety goals*
- *Provide a means to demonstrate that the safety goals have been met*

Table 12-01. Functions supported by the system safety analyses.

The system safety process should combine management oversight and engineering analyses to provide a comprehensive, systematic approach to managing the system risks. As with any problem, the first step is define the boundary conditions and analysis objectives. That is, determine the scope or level of protection desired. One must understand what level of safety is desired and at what cost. The Project Team needs to answer the question: How safe is safe enough?

1.1.1 Hazard Identification and Analysis

Hazard identification is crucial to the system safety process because it is impossible to safeguard a system and control risks adequately without first identifying the hazards. The hazard identification process is a form of safety brainstorming to identify as many credible hazards as possible. Through this process the Project Team develops a *Preliminary Hazard List* (PHL). Some or all of the following methods used in this process are listed in Table 12-02.

- *Survey of the site and facility*
- *Interview facility personnel*
- *Convene a panel of technical experts*
- *Analyze and compare similar systems*
- *Identify applicable codes, standards and regulations*
- *Review relevant technical data (e.g., electrical and mechanical drawings, analyses, operations manuals and procedures, engineering reports)*

Table 12-02. Methods used in the hazard identification process.

Once identified, each potential hazard needs to be analyzed to determine the potential causes and consequences. This allows one to understand how each hazard affects the system. How likely is it to occur? If it occurs, what are the consequences? Are they catastrophic? Critical? The hazard analysis will allow the Project Team to determine which hazards pose significant risk. With this information, the risks can then be ranked and Project Management can determine which warrant controls.

1.1.2 Hazard Control

After evaluating the risks and ranking their importance, the Project Team must either design them out of the system or control their effects. Controls fall into two broad categories: engineering controls and management controls. Engineering controls are the preferred solution because they use hardware or software changes to completely eliminate or reduce hazards to an acceptable level. Examples of engineering controls include: adding a relief valve to a pressure system, providing interlocks to terminate centrifuge runs if a door is opened, and adding mechanical sensors to detect over-speed conditions. Management controls are usually procedural changes imposed on the organization itself to minimize the likelihood of a hazard occurring. Developing and implementing a centrifuge safety plan is a good method of applying management controls. Some other examples are: developing standardized procedures for nominal and emergency operations, assigning signature authority to safety engineers for all engineering change orders and drawings, and requiring middle management approvals for any centrifuge or facility modifications.

Once controls are in place, they need to be verified to ensure that they actually control the hazards and reduce the risks to an acceptable level. An effective method of hazard control verification is the use of a closed-loop tracking and resolution process (Table 12-03).

Step #	***Action Required***
1	*Define objectives*
2	*Describe system*
3	*Identify hazards*
4	*Analyze hazards*
5	*Evaluate risks*
6	*Control hazards*
7	*Verify controls*
8	*Accept remaining risks?* *If yes, go to step #9* *If no, modify system and return to step #3*
9	*Document risk acceptance and rationale*
10	*Review system (periodically)*

Table 12-03. System safety process.

1.2 Safety Analysis Techniques

Safety Analysis is an umbrella under which a project team performs other standard engineering analyses. The purpose of the safety analysis is to assist the project team in identifying what further types of analysis is needed. Many safety analysis techniques are available to centrifuge project teams for application at different phases of the system life cycle. Some are complex, while others are simple. Some are quantitative, others qualitative. Following are examples of common, proven tools and process to assess, control, and mitigate risks in mechanical systems.

1.2.1 Hazard Analysis

The *Hazard Analysis* process is a systematic, comprehensive method to identify, evaluate and control hazards in a system. Traditionally, the Hazard Analysis process operates as shown in Table 12-04.

- *Define the System*
  - *Define the physical and functional characteristics and understand and evaluate the people, procedures, facilities and equipment and environment*
- *Identify the Hazards*
  - *Identify hazards and undesired events*
  - *Determine the causes of hazards*
- *Evaluate the Hazards*
  - *Determine hazard severity.*
  - *Determine event probability*
  - *Determine whether to accept the risk or eliminate/control hazard.*
- *Resolve the Hazards*
  - *Assume the risk, or*
  - *Implement corrective action*
  - *Eliminate*
  - *Control*

Table 12-04. Hazard Analysis process.

1.2.2 Process Hazard and Operability Analysis

A *Hazard and Operability* (HAZOP) study is a systematic group approach to identify process hazards and inefficiencies in systems. A team of engineers methodically analyzes a system, and through a series of guided words, asks how the process could deviate from its intended operation and what the effects would be.

1.2.3 Fault Tree Analysis

Fault Tree Analysis (FTA) is a graphical method commonly used in both reliability engineering and system safety engineering. It is a top-down, deductive approach that is very powerful as a qualitative analysis tool. The engineer postulates a top event then branches down from the top event, listing systematically the various sequential and parallel events or combinations of faults that would lead to an occurrence of the undesired top event.

1.2.4 Failure Modes and Effects Analysis

The *Failure Modes and Effects Analysis* (FMEA) identifies all the ways a particular component can fail and what consequences such a failure would have on the system. The FMEA does the exact opposite of an FTA: it is a bottom-up approach that begins with the components of a system, identifies potential failure modes of that component, and analyzes how each failure mode would affect the overall system.

1.2.5 Human Factors Safety Analysis

The objective of the *Human Factors Safety Analysis* is to identify and correct human error situations that could lead to significant hazards. The analysis can be either qualitative or quantitative depending on the level of detail desired.

1.2.6 Software Safety Analysis

Software Safety is the newest member of the system safety field. With the incredible proliferation of computers and microprocessors their safety control becomes both paramount and difficult. At a minimum the software safety analysis process should include the functions listed in Table 12-05.

- *Software requirements development*
- *Top-level systems hazards analysis*
- *Detailed design hazard analysis*
- *Code hazard analysis*
- *Software safety testing*
- *Software user interface*
- *Software change analysis*

Table 12-05. Software safety analysis process.

1.2.7 Energy Trace Barrier Analysis

The purpose of the *Energy Trace Barrier Analysis* (ETBA) is to identify hazards by tracing energy flow into, through, and out of a system. A hazard is defined as an energy source that adversely affects an unprotected or vulnerable target.

1.2.8 Sneak Circuit Analysis

Sneak Circuit Analysis is a formal analysis conducted to determine every possible combination of paths and process a signal or energy (electric, pneumatic, etc) could take. The intent is to identify all paths in the circuit that are designed in and not created due to failures.

1.2.9 Cause Consequence Analysis

Cause Consequence Analysis uses symbolic logic trees similar to fault trees. The engineer starts with an accident or failure scenario that challenges or adversely impacts the system then develops a bottom-up analysis. Failures probabilities are calculated and incorporated into each step of the analysis to quantify the tree.

1.3 General Safety Summary

In conclusion, System Safety can best be achieved when all failure modes and risks associated with those failure modes are analyzed early in the design process. It needs not be expensive, highly technical, or time consuming. The complexity of the system will mandate what level of scrutiny is required.

2 HAZARDS IN CENTRIFUGE SYSTEM DESIGN

2.1 Mechanical Hazards

2.1.1 Sharp Edges and Pinch Points

Centrifuge system designs should avoid sharp surfaces, edges, points, burrs, wire ends, screw heads, corners, brackets, rivets, latches, etc, which could present dangers to operators and subjects and could cause equipment failures from abrasion of wires or cables. Equipment should be mounted or installed so that it does not interfere with subject or operator movements. Items that must be grasped with bare hands must be free from potential pinch points and sharp edges. All free-moving hardware should be inspected frequently throughout long-term operations to check for wearing that may lead to sharp edges and hardware failure. Equipment and components of equipment that cannot be rounded should be covered or shielded to prevent inadvertent exposure.

2.1.2 Mechanically Stored Energy

Mechanical devices capable of storing energy (springs, levers, and torsion bars) should be avoided in centrifuge design. The dynamic nature of centrifuge operations can shift objects or load devices and provide potential energy situations not expected by subjects, operators, or maintenance personnel.

When stored energy devices are necessary, safety features such as removal tabs, locks, protective devices, and warning placards should be provided. Spring-loaded devices should provide a means for releasing stored energy sources. Stored energy sources should not generate a backlash. All stored energy sources must be provided with a means to lock-out or tag-out the source for maintenance personnel.

2.1.3 Moving or Rotating Parts

To protect subjects and operators from moving or rotating parts the designers should provide mechanisms (guards) to protect personnel from contact hazards created by point of operation rotating parts or in-running nip points. The guards must prevent subjects and operators from having any part of the body in the danger zone during the operating cycle of the equipment.

For most operations, adequate protection can be afforded by a single guard or guarding device as long as it is properly designed, installed, maintained, and most importantly used. The most common methods of machine guarding are: enclosing the operation, providing interlock devices, employing remote control, using two-hand tripping devices, electronic safety devices, removal devices, or moving barriers.

Providing and maintaining a safe work environment for the operators during centrifuge operations is imperative. It is common practice to employ several of the methods outlined in Table 12-06.

- *Door interlocks that terminate centrifuge operations when opened*
- *Warning lights, audible alarms, and posted signs*
- *Remote operator's consoles isolated from the centrifuge by structural barriers (walls). When designing or specifying these barriers, careful consideration must be given to the energy imparted should a mounting structure fail and a component be released at the maximum operational limit of the centrifuge*

Table 12-06. Examples of methods used for providing a safe work environment around a centrifuge.

2.1.4 Touch Temperatures

Tissue burns can occur when skin temperatures reach 45ºC (113ºF). Objects at temperatures in excess of this can be touched safely, depending on the duration of the touch, degree of thermal control (surface finish, contact force, contact area), and diffusivity of the surface material.

2.1.5 Acoustics

While maximum acoustic levels may be driven by science constraints, noise levels in the workplace should not exceed an average of 85-90 dbA for an eight-hour day. If noise levels exceed this maximum, exposure to the noise should be reduced with feasible administrative controls such as limiting duration of exposure, or engineering controls such as enclosing noisy equipment. If such controls are not feasible hearing protection must be provided to reduce exposure levels.

2.1.6 High Pressure Systems

Hydraulic or pneumatic actuators may be required for centrifuge braking systems or other moveable equipment on board a centrifuge. The hazards of high-pressure systems arise largely from failures caused by leaks, pulsation, vibration, and overpressure. Besides the damage that can be expected from the release of high-pressure gases, if a vessel or pipe ruptures, fatal injuries can result from the blow out of high-pressure gases as well as from debris and the whiplash of broken high-pressure tubing, pipe or hose. Pressure system safety is achieved through careful engineering: ensuring the structural integrity of the components, regulating pressures and flows, and providing pressure relief.

Specific countries, territories, states, and municipalities have detailed rules and regulations pertaining to the design and operation of pressure systems and pressure vessels. All pressure systems should be designed so that the lowest-rated component in the system has a design safety factor of at least 4.0 at the *Maximum Allowable Working Pressure* (MAWP). To ensure that the MAWP is not exceeded, pressure relief devices must be provided. The *Maximum Operating Pressure* (MOP) of any system should be 10% to 20% below the MAWP. Pressure relief valves and rupture disks must be set at no more than the MAWP.

Pressure systems must be constructed of components rated for the intended service. Typically, this means metal ductile tubing and rated pressure fittings that are compatible with the contents of the system. Hoses and flexible tubing may be used, but additional protective measures may be required. Non-rated components, such as Tygon tubing, surgical rubber tubing, and hose bibs are unreliable for pressure use and must not be used where their failure could create a hazard. However, such components may be used with low-pressure inert gases. Pressure systems must also have a reliable means of pressure regulation. All systems should be equipped with industry standard regulators. It is highly recommended that all pressure regulators be on a standard preventative maintenance program. All pressure vessel systems must be tested to assure their integrity. The local authority having jurisdiction may mandate specific testing requirements.

2.2 Control of Hazardous Energy Sources (Lock-Out/Tag-Out)

Mechanical energy can be either kinetic energy (energy of motion) or potential energy (stored energy of position), and can arise from electrical, pneumatic, hydraulic, thermal, and mechanical sources. When maintenance and servicing is required on equipment all energy sources must be isolated and locked out and tagged out. The term zero energy state or zero mechanical state has often been used to describe machines with all energy sources neutralized.

A *Lock-Out/Tag-Out* (LO/TO) program establishes the minimum requirements for the application of energy-isolating devices whenever maintenance or servicing is done. It should be used to ensure that the equipment is stopped, isolated from all potentially hazardous energy sources, and locked out before employees perform servicing and maintenance during which the unexpected energizing or start-up of the equipment or release of stored energy could cause injury (Table 12-07).

Individual organizations or facilities will have established LO/TO programs for their institution. Individuals not familiar with the local process should contact the facility engineering or safety department for program specifics and training.

- *Process to notify users that maintenance and servicing will be conducted*
- *Basic understanding of the hazards associated with the equipment to be serviced*
- *Activation of energy-isolating device(s) so that the equipment is isolated from energy source(s)*
- *Means to apply locks to the energy isolating device*
- *Means to dissipate stored or residual energy*
- *Process to verify that the equipment is ready to be restarted when work is complete*
- *Process to ensure that all individuals have completed work and removed their individual locks*
- *Verification that all controls are in neutral*
- *Process to remove locks and reenergize equipment*

Table 12-07. Minimum comprehensive LO/TO program.

3 SAFETY IN CENTRIFUGE DESIGN

Rotators (centrifuges) used in artificial gravity research vary in both design and complexity. Some are powered by electric motors while others require that the subject provide the power to run the machine by some sort of exercise device. Some accommodate a single test subject while others accommodate multiple subjects simultaneously. Each design presents its own hazards, safety concerns, and challenges to risk reduction. This section addresses some of the design safety elements that are common to all centrifuges.

3.1 Structural Design

The design of the centrifuge structure entails important safety considerations. Any significant fracture or deformation of the structure could have disastrous effects on the test subjects, the operators, or the facility. Most centrifuges have three structural components in common: the motor hub assembly, the rotating arm(s), and the subject station(s). The design strength of the motor hub assembly is determined primarily by the inertial mass of the structure and the performance requirements of the system, that is, the maximum rotation rate (peak gravity level), which applies a tensile load at the arm attachment, and the angular acceleration (gravity onset), which applies a torsion load to the hub assembly. These requirements also apply to the design of the attachment of the motor hub to the facility floor structure, because that interface must transmit and counteract all static and dynamic inertial loads from the centrifuge. The strength requirements for the arm are usually dictated more by the angular acceleration requirements of the system, which apply a bending moment to the arm structure, than by the tensile loads applied during steady-state operation. Although the ramp-up angular acceleration requirements for centrifuges are usually low, the emergency braking angular deceleration rate requirements are often much higher and may drive the "design case" for structural loading.

Designs, and therefore safety requirements, for the human subject station in centrifuges vary widely, from complex gondola designs that are computer controlled to align the subject's spine with the acceleration vector, to much simpler designs such as the "hanging cage" in which the subject stands upright, or the "sled" designs on which the subject lies supine. The subject station design must provide a comfortable platform for subjects of widely varying sizes and weights and must adequately restrain the subject from being ejected from the centrifuge at high angular velocities or accelerations. Adequate wind protection may also be necessary to prevent buffeting of the subject or discomfort from cold. If the gravity load on the body is to be borne by the legs, alone, the subject station must be free to move some distance along the radial axis to eliminate load transfers through shear forces generated between the body and the subject station. At the same time, care must be taken to keep the mass attached to the subject (such as the back support, peripheral devices, and data equipment) to a minimum to avoid overloading the subject. If exercise or subject movements are required during the spin, adequate support for the subject must be provided, and the subject station design must include consideration for the effects of Coriolis forces. Any movement of the subject out of the plane of rotation can produce forces on the limbs that could cause discomfort or injury, and movements of the head out of the plane of rotation can cause cross-coupled stimulation of the vestibular system that can quickly induce nausea.

The structural safety factor requirements for centrifuges usually follow the standard requirements established for aircraft. For load-bearing components, that is 2.0 times yield strength (the load at which the component bends or deforms) and 3.0 times ultimate strength (the load at which the deformation is permanent). Some critical components may require higher safety factors. The structural design of complex centrifuge systems is often done using *Finite Element Analysis* (FEA), a computer design tool for calculating structural loads and stresses. When an FEA is performed, it is often useful to install strain gages at critical locations during dynamic testing to validate the stress predictions of the FEA and further assure the structural safety of the system.

The natural frequency of the system must also be considered in its design. To prevent unwanted oscillations or vibrations from being transferred to the subject's body during centrifugation, the natural frequency of the centrifuge structure should exceed the 4-5 Hz natural frequency of the human body (Rainford and Dradwell 2006).

3.2 Drive System

In the past, human-rated centrifuges were powered by hydraulic systems, gasoline engines, and multiple electric motors operating through a "bull gear" system. The most common method used today is a single, computer-controlled electric motor connected directly to the hub-and-arm assembly. This method is quite simple and has very few inherent safety implications. A variant of this method is a motor coupled to the hub-and-arm assembly through a gearbox. In this case it is possible for the gearbox to "lock up" and cause an unsafe or disastrous stop. This danger has been reduced in some cases by the use of a clutch assembly or shear pin system that would release and provide acceptable stopping rates in the event of a gear system lock up.

The motor should be selected to provide an adequate performance margin, "power" or torque being the primary consideration, because although the onset rate requirement for the system may be very low, requiring minimal torque, the motor may also be used for system braking and a much higher torque capability will be required for short-duration emergency stops.

For most systems designed for artificial gravity research the maximum rotation rate will be in the order of 50 rpm or less. Almost any electric motor providing sufficient power for a centrifuge system will be capable of providing much higher rotation velocities, making over speed protection a principal safety concern.

3.3 Control System

Accuracy of the commanded profile (times, angular acceleration, and rate) is an important research factor, but from a safety standpoint, prevention of over-speed is most critical. Many centrifuge installations, particularly those used to train military pilots, feature onset rates as high as 10 g/s. In these cases, loss of control for only a few seconds could put the subject in extreme danger. Even though the centrifuge systems designed for artificial gravity studies usually do not have a high angular acceleration capability, an independent device must be installed to monitor the gravity level or rotation rate and shut the system down if the commanded level is exceeded. This device should be a redundant system not dependent on the centrifuge-operating computer in any way. An accelerometer connected to a relay system, which terminates power to the motor, is often used. Because the occurrence of an over-speed condition is an indication that the control system has failed in some way and may be unreliable, system shutdown must use an independent method, coasting down or a separate braking system, to stop the centrifuge.

Protection from excessive angular accelerations can usually be accomplished by either placing torque limits on the system or by making comparisons of actual versus commanded angular acceleration rates within the control system itself. Indications that these rates are being exceeded should also initiate an independent stop sequence.

The human-machine interface between the system operator and the control system is an important safety aspect in system design. Adequate safeguards should be designed into the system to prevent any inadvertent operation (start, stop, or change) of the system dynamic state. As an example, arming or enabling the system to initiate a run should take, at a minimum, two separate actions, such as operating a switch or button and issuing a computer command. The control panel or computer screen should be designed using good human engineering practices. Controls should be laid out so that their purpose is clear and that inadvertent operation is highly unlikely. Emergency controls, such as the control for an independent braking system, should be large, isolated from other controls, and made available to more than a single person in the control room. Most systems use some form of computer control so that the run profile (ramp up, peak angular velocity, time at peak angular velocity, and ramp down) is displayed in some sort of active graphical representation or plot on the operator screen. This display must be closely monitored during a run and the system must be shut down manually if any significant deviation from the commanded profile is observed. A well-trained and alert centrifuge operator is the best first level of defense against accidents, making the interface design one of the most important aspects of centrifuge safety.

3.4 Independent Brake System

Most electrically-driven centrifuges rely on the drive motor to control stopping rates by using what is called *regenerative braking*. Regenerative braking essentially uses the motor as a generator, but requires that the control system and motor be operational for the braking system to function. If the control system or motor has failed, it is necessary to have a secondary stopping system to bring the centrifuge to a safe stop. A pneumatically-operated caliper or disk brake is typically used for this function. Usually this device is connected to emergency stop switches on the operator and medical monitor consoles as well as at other strategic locations. In some cases, certain interlocks will also trigger this device.

These braking systems usually provide relatively short stopping times (high negative angular acceleration rates) and therefore apply higher loads to the subject and structure. In order to avoid exposing the subject to potentially harmful levels of acceleration the maximum stopping rate should be limited to 1 g along the subject y-axis (side to side acceleration, ±Gy) or less.

A pneumatic caliper or disk brake can also serve as a convenient "parking brake" to hold the arm in position when the centrifuge is not in operation. This can provide additional safety by automatically holding the arm in a stable position for rapid removal of the subject in an emergency situation.

3.5 Electrical System

Design of the electrical system must meet all local and national standards, which in the U.S. includes NFPA 70 (National Electric Code), and all medical devices must meet similar standards, which in the U.S. includes UL-6060-1 Section 3 (Medical Electrical Equipment, Part 1: General Requirements for Safety).

3.6 Audio and Video

The ability to communicate with and monitor the subject during a centrifuge run is important to operations safety. At a minimum, the system should support voice communications with the subject from the system operator or monitor and the physician. The subject's microphone should be open at all times to allow immediate "hands free" communications. Closed-circuit television of the subject is important in assessing the subject's condition during a run.

3.7 Interlock System

The numerous potential hazards to operators, test subjects, and maintenance personnel associated with a large rotating device, such as a centrifuge, require that a system of interlocks be designed which will prevent the machine from starting or continuing to operate unless a number of safety conditions are met. The design of this system will depend on the specific system and facility, but typically will include the requirements listed in Table 12-08.

- *Any doors to the centrifuge room are closed and locked*
- *Any doors or hatches to the subject compartment are closed and locked*
  Note: Usually these locks can be overridden if emergency access to the subject is required and the lock has failed closed
- *All motor and drive systems are within normal operating limits*
- *All control system functional requirements have been met*
- *The independent braking system is operational*
- *At some facilities, the subject and one of the operators must each hold a switch closed for the centrifuge to operate*

Table 12-08. Requirements for starting or continuing operations of a man-rated centrifuge.

3.8 Emergency Egress

The ability to reach and remove the subject from the centrifuge quickly and safely is crucial in the event of an emergency. In most cases it would be impossible for the subject to safely egress the centrifuge without assistance. It is necessary, therefore, for the system to be designed so that the operations crew can quickly and safely remove the subject from the subject station and render aid or medical treatment. Because artificial gravity research data collection often requires that a number of wires or leads be attached to the subject, the system must be designed to allow the rapid removal of these attachments. The same requirement exists for the restraint harness and any other devices that could interfere with rapidly removing a deconditioned, incapacitated, or unconscious subject from the subject station. Because the subject could be deconditioned or otherwise incapacitated, a stretcher, gurney, or other suitable transportation device is also required. Procedures for transporting the subject to safety in the event of facility emergencies such as fires or severe weather must also be developed and the operations crew trained in their use.

4 FACILITY SAFETY CONSIDERATIONS

The construction of new centrifuge laboratory buildings and the renovation of existing buildings to support artificial gravity research require close communication between the laboratory users, project engineers, architects, construction engineers, and safety and health personnel. Among the multitude of needs to be addressed, all too often safety and health conditions are overlooked, and significant safety issues are noted after laboratories are built. Appropriate coordination of all disciplines during the design and construction phase, appropriate analysis of anticipated hazards and risks, and consideration of issues unique to human-rated centrifuges early in the process will eliminate last-minute changes in building design and construction that can be both costly and time-consuming.

4.1 Building Spatial Organization

While the optimal building enclosure configuration is being designed, concepts for the internal organization of the building spaces must be generated. The internal organization comprises three major patterns of spatial definition: (a) Circulation of people and materials; (b) Centrifuge laboratory module; and (c) Distribution of mechanical equipment and services. These patterns are examined in details thereafter.

4.1.1 Circulation of People and Materials

A major determinant of spatial definition is the circulation of people and materials within the building and around it. Circulation health and safety issues are primarily concerned with emergency egress and access to the building and its internal parts by emergency personnel, such as firefighters and police. Special attention must be paid to emergency egress and accessibility to the facility by individuals with disabilities.

Artificial gravity research will include research subjects who are deconditioned through bed rest or other methods. This deconditioning could prevent subjects from effectively egressing the building during an emergency. All emergency egress walkways and doors should be free of steps, and ramps should be provided when changes of level are required. Hallways and doors inside the laboratory intended to be used for non-ambulatory research subjects should be designed in a manner to allow the safe passage of gurneys or other subject transportation devices, that is they should be provided with such features as double doors, and wide hallways.

4.1.2 Centrifuge Laboratory Module

Formulation of the internal organization of the centrifuge laboratory begins with a decision on the dimensions of the module. This should direct the planning focus down from the scale of the total facility to the small scale of a single laboratory. At this point in the design process, architects and engineers must have established a working relationship with the scientist to ensure that the laboratory as designed will meet the researcher's science needs.

4.1.3 Distribution of Mechanical Equipment and Services

Laboratory buildings require a great amount of energy to supply, condition, and exhaust ventilation air. For equipment safety and science requirements, a specific number of air exchanges and humidity levels should be mandated. Vertical chases for distribution of mechanical services show where major penetrations in slabs will occur. From data collected on equipment that has been identified through the building and design process, the spaces that pose structural or construction problems can be determined. For centrifuges, special design and construction could be required because of the weight of the equipment, vibration issues, and electromagnetic interference. Visual stimulation of research subjects on the centrifuge should also be considered. All duct works, pipes and electrical services should be installed above the finished ceiling, below the floor, or within the room walls. Lights should be installed so they are not in the general field of vision of the research subject undergoing centrifugation.

4.2 Heating, Ventilation, and Air Conditioning

Heating, Ventilation, and Air Conditioning (HVAC) requirements for a controlled environment room depend on the temperature and humidity conditions to be maintained, as well as on the activities to be performed. Outside air volume rates should he kept to a minimum, particularly when close humidity control is required. A minimum of 1.4 m^3 (50 cubic feet) per minute of outside controlled air is recommended when people must work inside the controlled environment room regularly for prolonged periods. Supply and exhaust air volumes will depend on room size and the activities to be conducted inside the controlled-atmosphere room.

4.2.1 Temperature Control

The recommended room temperature in the centrifuge laboratory is in the range of 16-24ºC (60-75ºF). Room temperature controllers and other instrumentation should be designed to control room temperature over the full temperature range on a precise demand basis. The control mode should be fully modulating with proportional action from 0 to 100% of total condensing unit capacity of the full-rated temperature range. The main controller should include a means for direct setting of the control point, input, and output meters to display the proportional action of the control unit, a temperature indicator to permit monitoring room temperature conditions with a set point accuracy of not less than 0.5% of the full-rated temperature span, and a proportional band not less than 1% above the central point. A recorder with a 30.5-cm (12-inch) circular 7-day or 24-hour chart should be installed in a central control panel to assist in monitoring the stability of the set conditions.

4.2.2 Room Humidity

Active humidity control is required for equipment safety as well as subject comfort. Recommended humidity ranges for a centrifuge lab fall above 30% (to reduce static electricity) to less than 70% (to reduce condensation). When humidity control is required a mechanical method or providing humidity or dehumidifying supplied air must be provided in response to a proportional control system. The controller should be fully calibrated and include and electronic sensing unit and an integrated recorder with a set-point accuracy of not less than 0.5% for the full humidity span.

4.2.3 Emergency Alarm and Control System

A safety control and alarm system should be mounted on an outside wall of the centrifuge room adjacent to the exit door. It should consist of independent electrical low and high temperature as well as humidity control sensors that will alert laboratory personnel when temperature or humidity goes below or above the accepted range.

4.3 Emergency Electrical Considerations

The primary electrical feed to the laboratory should be as reliable as possible. For example, separate and distinct feeds connected to a common bus and then to two separate transformers with network protectors should be installed and each transformer should be large enough to carry the laboratory load so that loss of any one line will not interrupt laboratory power. Even with this type of reliable service, it is highly recommended that emergency electrical power be provided because any one of the primary electrical service components (e.g., transformers, main feeders) may fail and emergency power would be required. The laboratory should have a dedicated emergency power source that is required for emergency lighting, life safety requirements and provides the ability to safe the centrifuge in a manner that protects the test subject (Table 12-09).

- *Fire alarm and detection systems*
- *Centrifuge*
- *Egress lighting*
- *Emergency smoke and evacuation systems*
- *Operator Consoles*
- *Medical Monitoring Equipment*
- *All other systems whose continuing function is necessary for safe operation of the lab during an emergency period*

Table 12-09. Items to be connected to the emergency power.

4.4 Construction Materials

The laboratory building should be constructed in accordance with the applicable national and local building codes and regulations. The laboratory walls should be designed and constructed of materials that are flame resistant and provide a "safe haven" for the research subject and support personnel in the event of a fire in and adjacent area. The general philosophy of all interior building design should embrace the idea of eliminating building materials that are responsible for rapid flame spread and heavy smoke generation.

Use of the building to house an operating low-g centrifuge must also be considered during the design and construction of the laboratory. At a minimum the wall and ceiling strength of the centrifuge laboratory shall be impact-resistant for a load of 0.56 kg/cm^2 (8 psi) and should be able to withstand a minimum of 48-km/h (30-mph) circular winds.

4.5 Fire Detection, Alarm, and Suppression Systems

All laboratories and associated workspace should have ionization smoke detectors and heat-sensitive detection systems in addition to standard sprinkler systems with a slower detection quality. Sprinkler system should be designed in accordance with the local fire codes and regulations. All automatic fire suppression systems should be connected to the building central alarm system. Hand held portable fire extinguishers should be located in halls and main exit ways as well as within individual laboratory units. The type of fire extinguisher used is left to the discretion of the local safety authority although it is recommended that a clean fire-extinguishing agent (CO_2) is preferred. A supervised fire alarm or signaling system should be installed throughout the laboratories in accordance with local codes and standards. It should have all manual pull stations, sprinkler alarms and detection systems (heat, fire, and smoke) connected to it.

4.6 Lighting

The suggested minimum light level for a centrifuge laboratory is 50 foot-candles on the work task.

5 TEST SUBJECT SAFETY

The test subject is exposed to a number of hazardous situations and environments during the course of a centrifuge operation. Ingress and egress operations are often opportunities for falling or impact injuries, and centrifugation can produce vestibular disturbances, inducing nausea, or inadequate perfusion of the brain resulting in syncope or *G-induced loss of consciousness* (G-LOC). Scales are often developed for the test subject to report his "general health" or "motion sickness level" at fixed times during the centrifuge run or upon change in status. Usually test subjects are required to pass a general physical examination such as a modified U.S. Air Force Class-3 physical exam before being exposed to centrifugation. Special research requirements may necessitate additional qualification tests such as spinal X-ray or Magnetic Resonance Imaging examinations. In addition, test subjects may be exposed to other requirements of the centrifugation or other protocols that may interact and must be considered in establishing the centrifugation requirements.

Medical monitoring during artificial gravity studies and management of emergencies situations are detailed in Chapter 11, Sections 3 and 4.

The probability that a subject- or operator-induced accident will occur can be minimized by recognizing some principles of human behavior that may result in human errors being committed during operations and maintenance activities. Failure to consider the principles listed in Table 12-10 can lead to people making errors, misusing equipment, and making unsafe judgments.

- *Equipment designs that exceed the physical or psychological limits of the subject's capability can create situations where the likelihood of accidents is high*
- *Any design that makes subjects and/or operators work harder because of physical requirements of the work situation is likely to promote fatigue and increase the probability of error*
- *Supplying inadequate facilities, incorrect information, or poor tools (lack of proper training, inaccurate drawings and procedures) for use in the facilities can promote subject and operator errors in performing tasks*
- *When designs result in making tasks unpleasant or complex to perform, subjects and/or operators may not devote sufficient time and/or attention to achieve satisfactory performance. Human interfaces should be user-friendly and tested in the planned or anticipated user configuration*
- *Along with designing hardware, proper training, and good communication, with specific identification of potentially hazardous tasks related to use of the hardware, can provide a good foundation, so that subjects and operators will perform tasks less frequently if they are aware the task is hazardous*
- *If equipment is insufficient or inadequate, there is a high probability that subjects and operators will attempt to modify it or improvise a better solution at the last minute. Making changes immediately before operating and making numerous changes that are not proven or documented can promote a high risk that errors will occur*
- *Procedures should be definitive, unambiguous, easy to follow, comprehensive, and accurate*
- *Equipment should be designed to encourages safe use and minimize opportunities for subjects and/or operators to be exposed to hazards*

Table 12-10. Principles of human behavior that may result in human errors being committed during operations and maintenance of a centrifuge.

The designer should remember that most safety problems result from equipment not being designed with full consideration of safety factors and/or people using it improperly. The designer must, therefore, anticipate how equipment might be misused and design it so that misuse is less likely and error effects are not catastrophic.

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Chapter 13

RECOMMENDED RESEARCH

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In this final chapter, we address the next steps in artificial gravity research, both short- and long-term, required to understand the fundamentals and validate the operational aspects of using artificial gravity as an effective countermeasure for long-duration space travel. Our recommendations are based on both the summaries presented in the preceding chapters as well as from the outputs generated by the ESA Topical Team on Artificial Gravity. This group of experts worked together to assess the current state of knowledge on this important topic and to then examine ongoing research efforts. A gap analysis was performed, the results of which led to many of the research recommendations presented in the following sections.

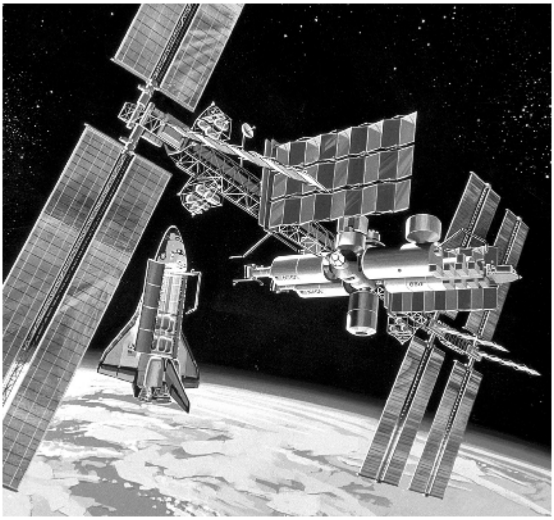

Figure 13-01. Artist view of the ISS after completion. Courtesy of NASA.

1 INTRODUCTION

Maintaining an Earth-normal physiological baseline requires gravity. The previous chapters have amply emphasized the importance of gravity to almost every body system. However, we do not yet fully understand how these different systems rely on gravity as a controlling or enabling stimulus.

Going into space, coupled with essential ground research, has made it possible to begin to answer these questions.

Gravity pulls in one direction only, i.e., downward, towards the center of the Earth. As mobile bipeds, humans have the choice of orienting themselves relative to the force of gravity in every conceivable direction, mostly in intermittent patterns. They also reduce its effects on the body during night sleep or in continuous bed rest when they are supine, and enhance it as with various activities.

Several aspects associated with how we sense and use the force of Earth's gravity are apparently involved in maintaining normal health and fitness. These include the pull of gravity in the +Gz (head-to-foot) direction, exertion against gravity forces during normal activity, the element of "change" provided by postural and other movement and orientation, and directional cues about our spatial orientation relative to the gravitational vertical. Without regular exposure to these +Gz forces, as during spaceflight (Clément 2005) or bed rest (Sandler and Vernikos 1986), important cardiovascular, musculo-skeletal and neural, primarily vestibular-mediated functions, are compromised.

Past studies and research approaches have focused on varying the characteristics of the gravitational stimulus, i.e., its direction or intensity. Resulting changes in physiological functions were logically attributed to the role of the stimulus. An overlooked aspect is, like other sensory stimuli, that the sensitivity to gravity, and consequently the response to changes in gravity, also changes with the physiological status of the organism, its age, gender, time of day, fitness, health, and genetics. Until we know more about gravity dose-response relationships in healthy ambulatory persons, we will continue to make assumptions that space deconditioned individuals respond in exactly the same way.

The study of the effects of accelerations smaller and greater than 1 g might prove to be of great interest in medical research, both at the molecular, cellular, and clinical levels. Ground-based experiments have demonstrated that paraplegics with some residual muscular function in their legs were able to ambulate when the acceleration along the body longitudinal axis was equivalent to lunar gravity. Artificial gravity generated by short-radius centrifuges may have clinical applications for the treatment of a number of problems. These include osteoporosis in the sedentary elderly; heterotopic ossification, which is the formation of lamellar bone where bone does not usually form in soft tissues, in young paralyzed individuals; bone fractures resulting from sports injuries that require prolonged bed rest; articular deterioration aggravated by weight bearing; and potentially certain forms of pulmonary edema (Cardus 1994).

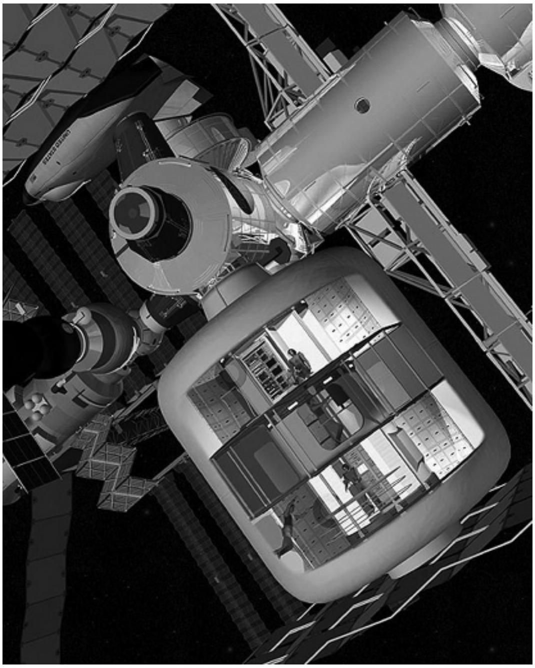

Figure 13-02. "TransHab" was an inflatable 8-m diameter ISS module that could be converted into crew quarters for future manned missions to the Moon and Mars. Photo courtesy of NASA.

2 POTENTIALS TOOLS FOR INVESTIGATION

As discussed in the previous chapters, key research questions need to be addressed before artificial gravity can be prescribed to humans en route to Mars or for any long-duration space mission. These questions include: How much artificial gravity, i.e., at what duration and level, is needed to prevent this deconditioning? Is 1 g a necessity or is a fraction of this level sufficient? If intermittent artificial gravity is enough, how many centrifugation exposures and at what g level per day are required? More importantly, from a medical standpoint, what is the tolerance of the human body to repeated centrifugation?

Although a definite answer to these questions will only come from validation studies performed in space, some important preliminary screening and evaluation studies can be carried out via ground-based studies on Earth. In fact, the difficulty and expense of spaceflight experiments or feasibility demonstrations mandate the appropriate use of ground facilities to design and test artificial gravity concepts.

Analog environments to simulate the effects of weightlessness on long-duration physiological deconditioning have been studied for many years. The most widely used human model is continuous bed rest, with the head tilted down by six degrees. Bed rest is known to result in muscle atrophy, bone loss, redistribution of body fluids and body mass, and decreases in plasma volume and red blood cells (Sandler and Vernikos 1986).

After bed rest, subjects manifest orthostatic intolerance similar to that typically demonstrated by returning astronauts. Although the physiological consequences of bed rest are in most respects quite similar to those of weightlessness, there are a few notable differences. For example, while diuresis is common during the early days of bed rest, it has not been clearly demonstrated in space (Norsk 2001). In addition, bed rest does not produce the full range of vestibular disorders characteristic of space travel. It is likely that postural disturbances seen after bed rest are more attributable to muscle disuse than vestibular deconditioning.

When we sleep, we spend at least a third of the day experiencing gravity along different axes (Gx and Gy), rather than along the longitudinal (Gz) axis, without experiencing the physiological effects of weightlessness or continuous bed rest. Cleary, a period of continuous 6-8 hours per day of Gx and Gy stimulation is sufficient to protect from deconditioning. During continuous bed rest, Vernikos and colleagues at NASA Ames have demonstrated the potential protection afforded by 2-4 hours of daily standing or walking (Gz) in preventing orthostatic intolerance, plasma loss or calcium loss, but not in maintaining aerobic capability (Vernikos *et al.* 1996). Bed rest therefore offers the possibility to investigate the minimum gravity load required along the Gx, Gy, and Gz axes as a countermeasure for some of the effects seen in space.

Another technique used to simulate the deconditioning effects of spaceflight is dry immersion (see Figure 1-13). This treatment produces rapid fluid shifts, manifested by a pronounced involuntary diuresis, with loss of electrolytes and decrease in plasma volume. Although, a decline in orthostatic intolerance is typical after dry immersion, the magnitude of the change varies from subject-to-subject, in particular between athletes and non-athletes. There are also problems associated with hygiene and precise thermal control when using this method (Nicogossian 1994).

Short- and long-radius centrifuges, as well as slow rotating rooms, all have their roles in ground-based studies. For in-flight studies, however, a centrifuge should be small enough to fit into a Shuttle middeck or in one of the ISS modules. Human-rated centrifuges have already flown on board the Spacelab module during the IML-1 (see Figure 3-15) and Neurolab (see Figure 3-16) missions. Studies have shown that these centrifuges could be easily accommodated within an ISS module. However, given the small sizes of the modules, these centrifuges present the disadvantage of having the subject's body placed across the axis of rotation, thus generating +Gz force at the head and –Gz forces at the feet.

An additional ISS module with a larger diameter, such as the de-scoped TransHab (Figure 13-02) is the only possibility for having a human-rated centrifuge in the short term. Later flight accommodations could consider the *Crew Exploration Vehicle*, or a lunar or Mars habitat centrifuge.

Eventually, the effects of continuous artificial gravity could be studied by experimenting with spinning vehicles in space (Table 13-01).

- *Ground studies in long radius centrifuges*
  - *To determine the tolerance to acceleration*
- *Ground studies in short-radius centrifuges*
  - *To determine the artificial gravity prescription to counteract the physiological effects of bed rest*
- *Ground studies in slowly rotating rooms*
  - *To determine the adaptation and re-adaptation requirements*
  - *To determine the human factors constraints*
- *Short-radius centrifuges on board the ISS*
  - *To evaluate intermittent centrifugation*
  - *To validate ground-based findings*
- *Spinning the space vehicle*
  - *To evaluate continuous centrifugation*
  - *To determine min. radius and max. rotation rate requirements*
  - *To evaluate perceptual effects*
  - *To validate human factors constraints*
  - *To validate ground-based findings*
- *Short-radius centrifuges on Moon or Mars habitat*
  - *To test protocols and operations necessary to protect crews during long stay on the lunar or Martian surface, if needed*

Table 13-01. This table presents a practical research program for evaluating and validating the effectiveness of artificial gravity during spaceflight.

3 ANIMAL MODELS

There is no question that human subjects must be used for research addressing artificial gravity prescription development and testing. Human studies are essential to consider the unique aspects of the upright biped, especially with respect to cardiovascular implications of gravity gradient. Furthermore, human factors issues, essential to the success of artificial gravity in flight, can only be evaluated with human subjects.

Nevertheless, this research needs to be supplemented where appropriate, by animal experiments. As mentioned above, our limited experience with artificial gravity research in space is associated mostly with animal studies. Animal centrifuge facilities have flown on several space life sciences missions, and a dedicated centrifugation module was in preparation for the ISS until it was recently cancelled, unfortunately.

Animal studies would provide a useful adjunct to the human studies for the following principal reasons. First, animal tests will reduce the total number of human subjects required, thereby making schedule and cost targets achievable. Both cost per subject and schedule-associated costs are far lower using animals as compared to humans. Furthermore, the large sample size that is made possible by using animals to test artificial gravity regimens yields results with less statistical scatter (lower error), and thus improve the basis for drawing definitive conclusions regarding success or failure of the test conditions. Modeling on the basis of a well-defined set of animal responses allows extrapolation from a limited data set derived from human subjects. Finally, tests with animals can include invasive telemetry, hazardous procedures, and post-mortem tissue analysis to support the definition of artificial gravity prescriptions.

3.1 Non-Human Primates

Primate models used in spaceflight experiments have included rhesus monkeys, squirrel monkeys, capuchins, chimpanzees, cynomologous monkeys, and pig-tailed macaques. Many of these flights were of short duration, ranging from 5 to 14 days (see Clément and Slenzka 2006 for review).

The rhesus monkey provides a biomedical model with close phylogenetic ties to humans. Rhesus monkeys have been the subjects of studies on the effects of exposure to microgravity on thermoregulation, immune responses, musculo-skeletal system, cardiovascular system, fluid balance, sleep, circadian timing, metabolism, neurovestibular/neurosensory, and psychomotor responses. In ground-based studies, rhesus monkeys have served as subjects in bed rest and dry immersion experiments as well as in continuous and intermittent centrifugation experiments. The systems examined in many of these studies have paralleled those examined during spaceflight.

The rhesus monkey confers many advantages as a research subject in the field of artificial gravity. First and foremost, the rhesus monkey is the most widely accepted biomedical primate model for the human. Secondly, the rhesus has a bipedal upright posture, and thus experiences the ambient gravitational force environment along the same body axes as the human. Third, the reproductive cycling of the female rhesus is menstrual, similar to humans. Fourth, the cognitive abilities of the rhesus monkey allow the use of psychomotor testing to discern the effects of artificial gravity on neurovestibular physiology, performance, and behavior. Finally, the larger size of the rhesus also allows for collection of larger tissue samples and provides the ability for simultaneous measurement of multiple physiological and behavioral factors.

3.2 Rats

Rats are the most commonly used biomedical research model and thus a great deal is known about their normal physiology, including the characteristics of well-established strains. The relative uniformity of specific strains also presents fewer of the confounding factors that are typical of human studies and thus these studies are likely to be both easier to interpret and to repeat. Rats offer a number of other advantages as a model system for countermeasure development. Rats, unlike primates, do not require special isolation or quarantine procedures. With modest caging and care requirements, higher numbers of subjects can be accommodated to increase the statistical power of analyses. Rats readily adjust to centrifugation and because they can be used in hind limb immobilization and tail suspension studies, they can also serve as models for deconditioning. Previous centrifugation and suspension studies provide a baseline against which artificial gravity protocols can be evaluated. Similarly, rats can be used in exercise studies of metered activity using running wheels or treadmills.

Figure 13-03. The short-radius centrifuge of the Neuroscience Laboratory at NASA Johnson Space Center. Subjects are lying on a linear track that allows a variable radius of rotation. Eye movements and perceptual effects are recorded by a video camera and psychophysics methods. Photo courtesy of NASA.

Rats provide opportunities for more invasive or terminal procedures that would not be possible with human subjects. Rats can be used for studies involving both acute and chronic implantation, including the use of catheters, electrodes, and telemetry. When fully implanted, these sensors also provide the means for a completely hands-off data collection scheme, including monitoring of blood pressure and flow, ECG, and heart rate, as well as temperature and physical activity. Rats easily provide repeated samples of fluids such as blood or urine. Post-mortem tissue sampling is easily accomplished, and at considerably less expense than alternatives like non-human primates. The short gestation time and rapid development of rats makes them ideal for developmental studies. Further, the time scale of some changes, for example muscle wasting in microgravity or hind limb unloading, is more rapid than in humans, thus multiple studies can be accomplished in a much shorter time-frame using rats.

Rats are also relatively well studied in microgravity and share the advantages of other non-human spaceflight subjects in that they do not have conflicting schedules and operational duties to confound experimental findings. Thus rats have been important in contributing to our understanding of spaceflight induced changes in musculo-skeletal, neurovestibular, immune, developmental, cardiovascular and metabolic physiology. Rats flown on the

Russian Bion biosatellite provided the only in-flight evidence for the efficacy of 1-g centrifugation in preventing many of the degenerative changes seen in microgravity (Figure 13-03). Spaceflight validation of artificial gravity as a potential countermeasure was to have soon begun with rodent studies. Both the habitats and a flight centrifuge were recently under development for use with rats and mice on board the ISS (see Figure 3-13). However, this research program has been canceled. With no human-rated centrifuge being flown in the foreseeable future, initial in-flight studies using artificial gravity will necessarily eventually be performed with rodents.

Using rats has its disadvantages, however. Their small body size, relative to rhesus monkeys for example imposes limits on how much instrumentation, including telemetry, can be applied in a given animal. Small body size also means that smaller blood and urine volumes are available, especially in situations requiring repeated sampling. Unlike the rhesus, which sit for most of the time in an upright posture, rats are quadrupedal and thus the acceleration vector in both normal gravity and during centrifugation is from dorsal to ventral rather than from head to foot. Consequently, fluid shifts and muscle loading obviously differ from bipeds. Their weight is also distributed across four limbs rather than being borne on two. Rats also differ from both rhesus and humans in being nocturnal, which reverses the relationship of certain endocrine cycles, notably that of melatonin, to that seen in diurnal species, including rhesus and humans. In addition, rats have poorly consolidated circadian cycles, including sleep and wake. Rats are thus not ideal models for human sleep and circadian rhythm studies. Rats are estrous in their reproductive cycle. Finally, although much is known about the physiology of rats, some responses do not match those of humans, limiting their utility for some studies.

3.3 Mice

Like rats mice are small, easily managed and have short generation times. Being even smaller than rats makes it easy to increase sample sizes and reduces required maintenance, thus making the use of mice more cost-efficient. Generation and maturation times are further reduced from rats and thus mice may be more suitable for some developmental studies. More so than rats, genetically defined strains are seeing increased use in biomedical research with the benefit of reduced variability in studies due to differences between subjects. Numerous genetically manipulated strains with specific properties have been developed making mice uniquely suited for detailed examination of mechanisms and pathways. These include a large number of transgenic, knock-in and knockout strains, including several with deficient vestibular pathways for gravity sensing. Because many mouse and human genes are homologous, mice are well-established models for many physiological mechanisms in humans. For example, the mouse has been especially useful in immunological studies. Mice are good candidates for centrifuge studies and have been used successfully in the past.

However, mice share some of the disadvantages of rats as experimental subjects, with smaller body size further aggravating many of these. Their ability to tolerate implants and telemetry is further reduced, as is the available quantity of tissues and fluid for sampling. Like rats they are nocturnal and possess somewhat poorly consolidated circadian rhythms. Because mice have a more objectionable odor than rats, their acceptance as flight animals is also impaired. Also, because not all of their physiological responses parallel those of humans, mice may not be the best animal models for some studies, and this will need to be evaluated on a case-to-case basis.

4 CRITICAL QUESTIONS

As discussed in Chapter 4, an internal short-radius centrifuge would contribute little to the maintenance of sensory-motor calibration of movement control mechanisms of the body. Therefore, it is not likely that the spatial disorientation, movement disturbances, and the postural control disturbances would be attenuated following landing on Mars[42]. An alternate approach to generating artificial gravity in flight is to rotate the entire space vehicle or a chamber in it. Again, because of the small size of the spacecraft, significant gravity gradient would exist in any such rotating device, but the occupants would at least be able to move about, thus providing a more effective way to challenge the sensory-motor and musculo-skeletal systems.

It is unclear what effect artificial gravity would have on the regulation of body fluid volume and bone mineralization. With blood volume reduced in weightlessness, a centrifuge might produce orthostatic intolerance and syncope. Fluid loading before riding the centrifuge, like that used prior to return from spaceflight, and an anti-g suit might alleviate this problem. Other unknowns include the effects on the circulatory system and hormonal regulation of periodic exposures to artificial gravity, and the accompanying gravity gradient, coupled with exposure to weightless, and whether there are aftereffects. Remodeling of the bones of the feet, ankles, and legs would also occur with intermittent exposure to contact forces on the feet. The potential extent and functional significance of such changes has not yet been explored.

Obviously, research on the effects of centrifugation is required to prioritize and determine the optimal range of parameters, including radius of rotation, rotation rate, gravity level, gravity gradient, as well as frequency and

[42]This would be true unless the subjects are forced to maintain balance on a short-radius centrifuge, via a freely moving backplate, for example. Such balance training combined with the stimulation of the otolith organs when the head is off-center would aid crewmembers in retaining terrestrial internal models of sensory-motor integration (see Chapter 4, Section 5.2).

duration of artificial gravity exposure, on the physiological responses and well-being of the crew. However, once the optimal combination of centrifugation parameters is found, this **artificial gravity prescription** will have operational consequences on the vehicle and mission designs. For example, centrifugation exposure executed in several shorter bouts instead of one longer period is likely to improve both the efficiency and the tolerance of the centrifugation by the crew. But, in turn, such a prescription will impose a burden on crew time and the mission operational constraints. Therefore, both fundamental physiological, medical, and well-being issues as well as operational issues must be addressed.

During the NASA/NSBRI Workshop organized in League City in 1999 by Bill Paloski and Larry Young, participants drafted a set of critical questions to be answered by a broad artificial gravity research program. This list has been updated as follows in light of recent research and further meetings, and the likely uses of artificial gravity for a human Mars mission.

4.1 Physiological Deconditioning

4.1.1 What combination of centrifugation parameters (radius, rotation rate, gravity level, gravity gradient, frequency and duration of exposure) leads to the most effective protection of crews against bone, muscle, cardiovascular, and sensory-motor deconditioning?

4.1.2 Would additional (most likely intermittent) artificial gravity exposure be required on the Lunar or Martian surface?

4.1.3 What are the severities and time responses of the physiological consequences associated with the onset (spin-up) and offset (spin-down) of centrifugation, both en route to and from Mars and on the surface of Mars (or the Moon)? In particular, what are the consequences as related to sensory-motor adaptation, orthostatic hypotension, and fluid shift?

4.1.4 What additional countermeasures are required to supplement artificial gravity exposure to form an integrated countermeasure prescription during a mission to Mars?

4.2 Crew Health and Performance

4.2.1 Is the artificial gravity prescription resulting from 4.1.1 compatible with crew health and performance; in particular as related to disorientation, motion sickness, and mal-coordination caused by cross-coupled angular accelerations or Coriolis forces?

4.2.2 What operational restrictions should be placed on crewmembers during the onset and offset of centrifugation?

4.2.3 Are exercise or other countermeasures (mechanical, pharmacological, procedural) independent of or synergistic with the effects of exposure to the artificial gravity perception resulting from 4.1.1?

4.3 Other Spaceflight Environmental Factors

4.3.1 Is the physiological response to radiation exposure changed by artificial gravity exposure?
4.3.2 Is the physiological response to altered light/dark cycles changed by artificial gravity exposure?
4.3.3 Is the behavioral response to spaceflight changed by artificial gravity exposure?
4.3.4 Does exposure to artificial gravity have secondary effects on wound healing, immune system response or pharmacological response?

4.4 Vehicle and Mission Design

4.4.1 What is the impact of the artificial gravity system (i.e., centrifuge) in terms of weight, size, vibrations, and power requirements on the space vehicle or mission design?
4.4.1 What are the impacts of the artificial gravity prescription in 4.1.1 in terms of duration and frequency on crew time and flight schedule?

5 RECOMMENDATIONS

5.1 Artificial Gravity as a Multipurpose Countermeasure

The search for effective countermeasures to mitigate the effects of spaceflight deconditioning has so far been approached in piece-meal fashion on an individual system-by-system level. Frequently a symptom is targeted without basing the choice of a countermeasure on a full understanding of the mechanisms that induced it in the first place. It has been presumed that a daily bout or two of artificial gravity along the Gz axis would replace the gravitational force that constantly surrounds us and therefore affects all body systems. A few continuous hyper-gravity exposure studies in humans in rotating rooms (see Chapter 3, Section 3.1) have been of limited duration mostly addressing tolerance limits and the appearance of unpleasant side effects. With the exception of the attempts to use centrifuges in the 19th century to treat mental disorders (see Wade 2002) (Figure 13-04), most research on the use of artificial gravity in humans as a countermeasure to space deconditioning has been focused on the cardiovascular system. Animal research on the other hand has provided more information on the effects of hypergravity exposure on other physiological systems, but has predominantly focused on nearly continuous hypergravity exposure, with the apparatus stopped daily for an hour or two for cleaning (Smith 1975).

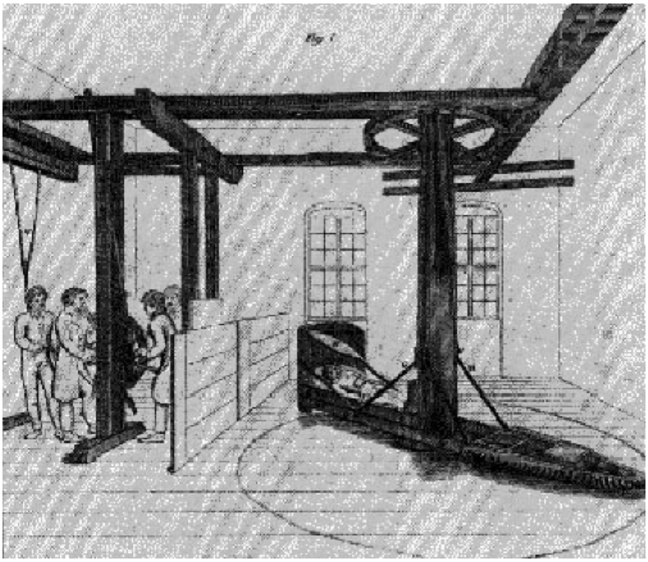

Figure 13-04. Two hundred years ago, Joseph Mason Cox (1763-1818) introduced a novel technique for treating the mentally disturbed: spinning the body round a vertical axis in a centrifuge. The human centrifuge was the realization of a plan for a rotating machine proposed by Erasmus Darwin (1731-1802) that can be seen in Wade (2002).

5.2 Artificial Gravity Prescription

A prescription for artificial gravity as a countermeasure to spaceflight deconditioning must be effective, comprehensive (protect more than one system), efficient (require minimum time), rewarding (in that it is appealing and acceptable to the user or crew) and safe (no adverse side-effects). Unpleasant side effects can be expected, but methods of minimizing these should be developed.

Acceptability of an artificial gravity countermeasure by the crew is a very important criterion as well. However effective, artificial gravity regimens that produce discomfort, are boring, or excessively time-consuming even if accepted, will probably be abandoned on a long-duration flight. This aspect is important to assess before expensive, specialized flight-devices are designed and built.

It has long been presumed that a spinning spacecraft would provide the best artificial gravity solution to providing an Earth-like environment in space (see Chapter 3). However, the feasibility of building such a physiologically effective gravity-providing structure in space with a sufficient radius to minimize or eliminate gravity gradients is not likely. Nor is it unlikely, at the other end of the gravity spectrum, that intermittent therapeutic doses of artificial gravity or hypergravity provided by an on-board acceleration device would not suffice. Ultimately, vehicle design, cost, and environmental considerations must be traded against countermeasure efficacy and reliability requirements before a decision can be made. However, such evaluation cannot be performed until after further physiologic research and vehicle design concept evaluations have been completed.

5.3 Developing Gravity Requirements

Gravity, or the lack thereof, is directly or indirectly the root of the spaceflight deconditioning problem. Whether replacing gravity will fully restore Earth-like health in space remains in the realm of conjecture until the question is attacked in a concerted and systematic manner. For instance, we do not know the gravity-use profile of normal healthy men and women. Much can be learned by observing on Earth how, when and how much humans use gravity as a physiological stimulus in the process of normal living.

The U.S. Department of Agriculture develops minimum daily requirements for nutrients by monitoring what a group of people normally eats. Continuous monitoring devices such as activity meters and accelerometers, together with daily logs, can go a long way in developing daily gravity-use profiles. Selectively depriving humans on the ground individually of each of these stimulation parameters may tell us a great deal about daily gravity requirements and patterns.

Few systematic gravity-dose-response studies have been done in animals, but only with continuous exposure to higher gravity levels. This is a good start. Any human studies should initially involve measuring only a few parameters before settling on a particular gravity stimulus level. Gravity, in fact, should be the standard against which other countermeasures are assessed. For instance, current countermeasures like exercise in LBNP or some exercise routines should be compared to artificial gravity once its dose-response is established.

5.4 Effectiveness of a Countermeasure

5.4.1 Measures of Effectiveness

What are the *measures of effectiveness* (MOE) of a countermeasure? What are acceptable limits of loss of tissue or function? Is it based on the average or relative loss from previous studies or missions? Is it relative to the required ability to perform? Stand? Ride a bicycle? Heal? Resist infection? Recover? Recovery rate? Or just how the subjects feel?

Should the objective of a flight countermeasure be to maintain the physiological functions as before flight or to maintain physiological functions required for a minimum safety level without compromising the long-term health of the astronaut?

Lack of agreed-upon MOE is perhaps the most significant deficiency in enabling accurate assessment of a countermeasure and comparing information across simulation studies and flight data. So far, during simulation studies the MOE have been left up to the investigator. Effectiveness has been measured most often by comparing the post-bed-rest results to similar measures taken pre-bed-rest. Alternately, the post-bed-rest results have been compared to synchronous controls housed under the same conditions or occasionally those living at home.

Flight surgeons, astronauts, and mission planners must be involved in establishing the operational requirements for successful countermeasures. Their involvement is important in the development of any effective countermeasures, but is even more so in the case of artificial gravity. Without the requirements, researchers have no accepted standard for assessing the efficacy of a countermeasure. It is therefore essential that these requirements be formulated as a prerequisite to launching any extensive program in countermeasure research.

5.4.2 Countermeasure Evaluation Methods

Methods used to evaluate countermeasures must be continuously reviewed, improved and refined. Although a great deal of progress has been made in establishing a battery of tests to evaluate countermeasures, the list is far too long and cumbersome. The tests may themselves have counteractive properties and lead to erroneous conclusions. They should be restricted in number to those that are most relevant to how the astronaut is expected to feel and perform. Methodologies such as the way plasma volume or aerobic capacity are measured should be standardized, so that data are directly comparable across a spectrum of countermeasures.

5.4.3 Monitoring Technology Requirements

There is great need for fast response, if not real-time, physiological parameter monitoring technology. Instruments should be minimally invasive, enabling more frequent or continuous monitoring. Clearly defined limits of normal responses that are physiologically meaningful and performance-relevant should be incorporated into instrument designs. To allow research to build sequentially on studies, data should be made available to artificial gravity research teams as soon as possible, thus reducing repetition of negative results and delays.

5.4.4. Bed-Rest Study Standardization

Bed-rest studies and procedures need to be standardized. One of the most efficient ways of developing artificial gravity countermeasures is by leveraging existing or modified ground facilities, talent, and experience to conduct a coordinated research program. Tapping into expertise across disciplines and exchanging results freely would enable earlier success.

Standardization across selected institutions enables more of these studies to be done in parallel and expands the information return on investment. Standardization is also very important from an ethics point of view so that all volunteers are informed and exposed to similar controlled conditions regardless of which country or facility the experiment is conducted. Environmental variables that will affect outcome, such as light intensity, light/dark cycles, nutrition, psychological stimulation, and intellectual stimulation, must also be standardized. During the pre-bed rest ambulatory control period or throughout in the case of synchronous controls, age, diet, activity, and fitness levels must be maintained. Adequate time should be allowed during this period for participants to adapt to the artificial gravity protocol so that adaptation transients do not confound the benefits of the artificial gravity treatment. This process of familiarization and adaptation might best be conducted before the subjects are admitted to a facility.

Figure 13-05. View of the centrifuge located in the Flight Acceleration Facility at the NASA Johnson Spacecraft Center in the 1960s, designed for training Apollo astronauts. The 15-m arm could swing the three-man gondola to create gravity forces that astronauts experience during launch and during re-entry. NASA no longer has an in-house centrifuge facility. Astronaut centrifuge training is currently performed at the Brooks AFB in San Antonio, Texas (see Figure 12-01). Photo courtesy of NASA.

6 EXPERIMENTAL APPROACH

A comprehensive program is required to: (a) determine the gravity threshold required to reverse or prevent the detrimental effects of microgravity; and (b) evaluate the effects of centrifugation on various physiological functions. Part of the required research can be accomplished using human surrogates, including nonhuman primates, on a dedicated centrifuge in low Earth orbit. Studies of human responses to centrifugation using centrifuges could to be performed during ambulatory, short- and long-duration bed rest, and in-flight studies.

Limits for and artificial gravity prescription should be tested in Earth-based rotating rooms before attempting to design a flight test. Earth-based tests are encumbered by the constant vertical surface gravity because it dominates the artificial component, prevents testing at sub-normal gravity levels, and changes the orientation of people and actions with respect to the rotation axis. Nevertheless, experimental procedures can be designed to account for these differences. A list of potential facilities for implementing such experiments is given in Chapter 3, Table 3-01.

The following section proposes some guidelines for future experiments aimed at validating the regimes of centrifugation as a countermeasure for space missions.

6.1 Ambulatory Studies

6.1.1 Map daily gravity use and develop minimum daily gravity requirements.

6.1.2 Determine the effectiveness of intermittent centrifugation on test subject fitness and physiology.

Research could include, but not be limited to the following topics.

a. Optimize the radius, rotation rate, and gravity level parameters with respect to countermeasure effectiveness, acceptability, and practicality. Include gravity levels both below and above unity.
b. Place the head at different distances from the centrifuge axis of rotation to investigate the effectiveness of intermittent otolith stimulation on long-term vestibular and cardiovascular effects. (Control of head position rather than foot position will allow the study of the influence of the gravity gradient on the artificial gravity effectiveness.) Postures other than supine should also be investigated. The pros and cons of head restraints to reduce motion sickness require further study.
c. Exercise devices and protocols for their use on the centrifuge must be developed, both to enhance the countermeasure effectiveness and to permit deconditioned subjects to tolerate the centrifugation. The importance of the venous blood pump in returning blood to the heart must be considered during high gravity-gradient centrifugation. Active vs. passive centrifugation needs further investigation. The biomechanical consequences of Coriolis effects on limb and head movements during exercise must be studied and steps must be taken to avoid repetitive stress injuries.

d. Subject position, including orientation relative to the radius and spin axis (e.g., supine vs. lying on the side or seated) should be examined.
e. Investigate the limitations on angular accelerations of the centrifuge for normal operations to minimize vestibular disturbances while permitting adequate emergency braking.
f. Visual surroundings during rotation (external, bed fixed, head fixed, or darkness) as they affect motion sickness and their compatibility with work and recreation need to be examined.
h. Evaluate circadian effects as they influence the relationship between time of day and artificial gravity effectiveness, including the evaluation of artificial gravity while sleeping.
i. Determine if gravity gradient enhances the benefit of artificial gravity on cardiovascular training.

6.1.3 Compare the effectiveness of artificial gravity to LBNP and exercise.

6.2 Bed Rest Studies

6.2.1 Use standing as the 1-g standard.

a. Determine at time of day, how often, for how long standing daily in 1 g, both passively and actively or in combinations thereof, (Hargens found LBNP required both to be effective) is needed to prevent the development of deconditioning symptoms. The advantage of this approach is that it eliminates the adverse effects of rotation.
b. Compare the results obtained between men and women.
c. Combine with other countermeasures, e.g., nutrition (does 1 g and protein enhance effectiveness on muscle?).

6.2.2 Use centrifugation to provide a range of from 1-g to hypergravity levels.

a. Once the most effective 1-g modality is defined, use the optimal time and duration to develop a dose-response curve with the artificial gravity system.
b. Determine the gravity dose-response threshold or any change in sensitivity to gravity with bed rest. Include gravity levels both below and above unity.
c. Validate the best option in long-duration bed rest for comprehensive evaluation of long-term effectiveness, acceptability, and practicality.

d. Combine with other countermeasure options to reduce the artificial gravity level required.

6.2.3 Use short-duration (five days) bed rest studies for screening.

Studies have shown that in as little as four to five days of bed rest, plasma volume and aerobic conditioning are significantly decreased, orthostatic intolerance is evident calcium excretion and bone loss markers are increased (Vernikos *et al.* 1996). Based on these parameters, five-day bed rest studies should suffice for the rapid screening of countermeasures such as centrifugation to converge upon appropriate values for intensity, duration and frequency variables. This model allows crossover design studies with repeated measures pre-bed rest in the same subject, as well as a no treatment bed rest exposure. An interval of one month between studies was shown to be adequate for full recovery from this type of bed rest protocol.

6.2.4 Use intermediate-duration (21 days) bed rest studies for comprehensive effectiveness evaluation.

Bed rest studies of the order of 21 days would be required for evaluating countermeasure effectiveness for those systems such as muscle and bone where techniques to detect significant changes within five days are not available. In addition, some studies may require a longer pre-bed-rest equilibration period on diet or for training as subject in the use of some device.

6.2.5 Use long-duration (60 days) bed best studies for countermeasure validation.

After independent review of the results, the most promising countermeasure candidates thus screened should then proceed to comprehensive evaluation in a long-term bed rest study protocol of 60-90 days. These studies should include balance and coordination measures. Pre-bed rest ambulatory periods of 7 to 14 days would provide more functionally relevant outcomes, such as structural and performance changes in bone and muscle. An adequate period of recovery on the order of 14 days should be included followed by long-term follow-up to assure recovery of even the slowest responding systems such as bone density.

6.2.6 Evaluate combinations of centrifugation with other countermeasures.

Recent approaches in testing combinations of countermeasures, such as nutrition and exercise, have yielded interesting results and show great promise. Foot vibration, nutrition, or virtual reality to reinforce directional cues when not rotating, may prevent losses in muscle mass and metabolism while, as on Earth, allow greater effectiveness of an appropriate exercise regime to maintain strength and function. This approach could also be useful in increasing compliance by introducing variety and entertainment or operational training elements.

6.3 In-Flight Studies

As discussed above, the artificial gravity design and prescriptions, once developed during ground-based studies, must be validated and tested in space. Due to the constraints of the terrestrial gravitational field, the applicability of ground-based results will be somewhat uncertain. Thus, the likelihood of successful flight operations will be significantly improved by flight validation. We recommend the following potential venues for flight validation and testing studies in both animals and humans.

6.3.1 Flight Animal Centrifuge and Free Flying Biosatellites

Flight animal centrifuges, such as the ones originally planned in the *Centrifugation Accommodation Module* (CAM) of the ISS, or those previously used in Biosatellites, are near-term venues that could provide invaluable data to calibrate and validate animal studies of intermittent or continuous artificial gravity in deconditioning animals. They could also provide the only accessible continuous partial-gravitational environment that would allow for the early evaluation of the amount of deconditioning expected during long-term exposure to Mars gravity.

6.3.2 Human Short-Radius Centrifuge on board the ISS

This relatively near-term venue could provide an important test-bed to calibrate and validate ground-based findings of human responses to intermittent artificial gravity. Efficacy and practicability of artificial gravity would be compared to other countermeasures.

6.3.3 Spinning Capability of the *Crew Exploration Vehicle* (CEV) or within the CEV

While not likely for the lunar CEV, centrifuge capability will be essential for Mars Transit Vehicles and their precursors, if artificial gravity is included in the transit plan. If the CEV is too small to accommodate an on-board centrifuge, is it possible to generate artificial gravity by connecting modules together using a tether or rigid truss and then spinning the entire complex. Gemini-11 demonstrated this basic concept during a manned space mission in 1966. A recent study described in Chapter 2, Section 4.1 has investigated the requirements for spinning a manned vehicle.

6.3.4 Artificial Gravity Devices and Protocols for Lunar or Martian Surface Operations

A lunar habitat centrifuge will be essential for testing protocols and the operations necessary to protect crews during long stays on the Martian surface.

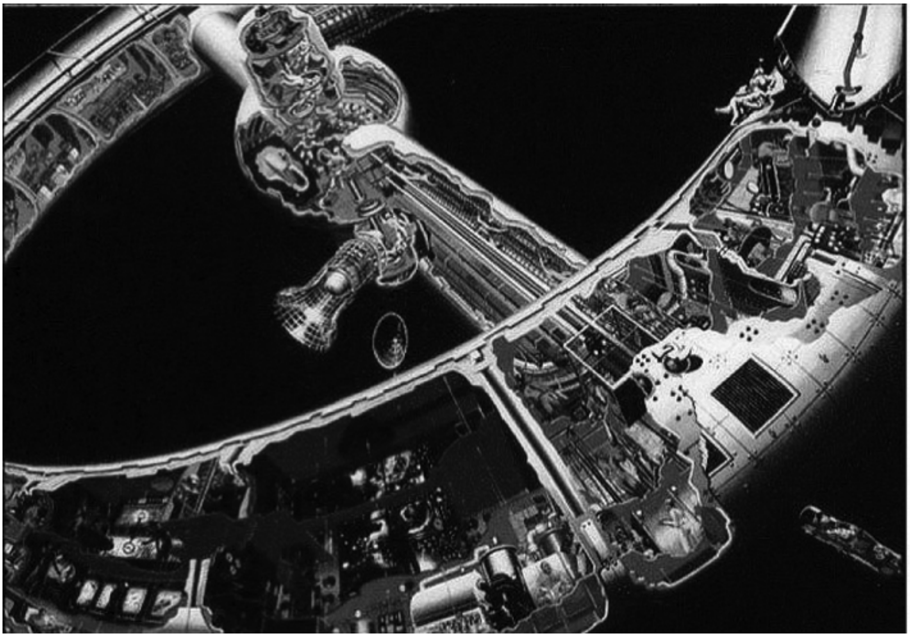

Figure 13-06. Von Braun's original vision for a spinning space station with its crew of fifty was to serve as a major jumping off point for exploring the Solar System. This cutaway drawing appeared in the 30 April 1954 issue of Collier's. It shows only a part of the space station, with sections devote for laboratories, servicing, and living quarters. Photo courtesy of NASA. See also color plate.

7 CONCLUSION

A program for human exploration of the Moon and Mars offers both challenges and opportunities for the participation of the scientific community. Foremost is the fact that specific enabling scientific information is required if a Moon or Mars program is ever to succeed in one of its prime goals, the expansion of human presence and activity beyond Earth orbit and into the solar system. A critical information gap concerns the capability of humans to adapt to long-term exposure to weightlessness or reduced gravity. The relevant life-sciences knowledge developed from studies on board the ISS will probably not be available before a Moon/Mars program is initiated, particularly in light of recent cutbacks in scientific research using the ISS. Therefore, a comprehensive solution to the challenges of human adaptation to microgravity is the development and validation of effective countermeasures.

Because the reduced apparent effectiveness of the force of gravity is the major reason for the changes we see in space or during bed rest, replacing this stimulus in the variety of ways gravity acts on the body should achieve the greatest return. Theoretically, artificial gravity (or hypergravity) in space should be the most comprehensively effective countermeasure.

The best technique for implementing artificial gravity in space can only be determined after weighing a complex set of trades among vehicle design and engineering costs, mission constraints, countermeasure efficacy and reliability requirements, and vehicle environmental impacts. There have been many proposals for orbital habitats that incorporate artificial gravity. Most of the analysis has focused on studies of structure, mass, deployment, axis orientation, dynamic stability, and habitability factors. In contrast, few studies have considered an internal, small-radius centrifuge. The design, construction, and operation of a continuously rotating spacecraft may pose formidable technical challenges. However, intermittent artificial gravity generated by spinning crewmembers periodically in a centrifuge within the habitable environment combined with exercise seems a more realistic and affordable solution.

We recommend that substantial international effort be focused on a cooperative and coordinated program of studies designed to answer the critical questions posed in this chapter. Both human and animal models have their place in the exploration of the proper application of artificial gravity with the goal of a practical and effective flight countermeasure.

Artificial-gravity scenarios should not be a priori discarded in Moon and Mars mission designs. Indeed, the provision of artificial gravity, which would potentially serve to ensure crew health and performance throughout the mission, may well prove to be an architectural variable of fundamental importance. The program recommended in the NASA Task Force on Countermeasure and National Research Council reports (1997) is to carry forward, during conceptual design phases, alternatives that provide artificial gravity during the cruise flight phase, and possibly in Mars orbit as well. If satisfactory countermeasures are confidently identified during a program of orbital life-sciences research, this alternative design path can be abandoned. Conversely, if an effective artificial-gravity system is developed, research on countermeasures will become less urgent.

The most efficient means of developing an effective in-flight artificial gravity countermeasure is by appropriate and timely use of ground facilities. The likelihood of a successful flight validation will be significantly elevated when the ground studies are thoroughly conducted. Several current studies that contribute to increasing our understanding of artificial gravity, in conjunction with exercise, are already underway in the U.S., Russia, Europe, and Japan. This research should be pursued until all critical questions are answered. One major step is to determine the relationship between the artificial gravity dose level, duration, and frequency and the physiological response as determined for the major body functions affected by spaceflight. Once its regime characteristics are defined and a dose-response curve is established, artificial gravity should serve as the gold standard against which all other countermeasure candidates are evaluated, first on Earth and then in space. Furthermore, it is this knowledge that will yield the greatest benefits to human health on Earth.

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