Space Physiology

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SPACE PHYSIOLOGY

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To Sarah

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Foreword

Human space exploration to destinations beyond the moon was first envisioned during the Apollo era. Over the course of a decade the world followed the transition from suborbital missions to witnessing humans walking on the surface of the moon. The rate of technological advancement to enable the lunar missions exceeded anything previously seen in history and would be difficult to achieve even with today's resources. While the dream of sending humans to Mars after the Apollo program was not fulfilled, the experience of the Shuttle, Skylab, NASA-MIR, and International Space Station programs was critical in following the roadmap to Mars first proposed so many years ago. The initial steps on the path to Mars have been from robotic explorers. These planetary rovers have played a critical role in exploring the surface of Mars, helping to provide insight into the central question of the origins, complexity, and possible diversity of life within our solar system. Ultimately, though, joint human–robotic missions will be required to answer one of the major scientific questions of this millennium: Does life exist elsewhere in outer space?

As government agencies have acquired more experience and technical capability to support long-duration spaceflight in low earth orbit, there has been the exciting emergence of privately funded spacecraft with the potential to make low earth orbit accessible to members of the public. This capability marks an important transition in human spaceflight. With increased accessibility to low earth orbit, government agencies may now shift their focus to extending the capability for human space exploration. Developing the technical capability to send humans farther into space and support them on longer duration missions will provide numerous challenges that will be the ultimate test of the technical capabilities of the world's space-faring nations. The recent NASA vision for space exploration has clearly focused attention on the path to the Moon and Mars. It will be exciting to follow the development of the Crew Exploration Vehicle, the next generation planetary spacesuit, and habitats required to support these missions.

Developing the technical capabilities for planetary exploration is only one part of the equation for human missions. Understanding the long-term physiological adaptation of humans living for months in microgravitational and partial gravitational environments will be critical in minimizing the health consequences of these missions and safely returning the exploration crews to Earth. The transition from the force of gravity on Earth to 0 *G* while traveling to a planetary destination will be followed by a period of living with a different planetary gravitational force (in the case of Mars, approximately one-third of the Earth's gravity). This process will be reversed when

the crew returns to Earth. These transitions will cause significant adaptive changes in a number of physiological systems that may make it more difficult for the crew to function normally after landing on the planetary surface or back on the Earth.

This book provides an excellent overview of the significant biomedical issues associated with sending humans to explore other planets. The chapters discuss all of the relevant physiological changes associated with astronauts adapting to living in 0 *G*, and recommendations have been made to minimize the deleterious aspects of these changes and optimize the capability of astronauts to quickly transition to performing work after arriving at their destination. Although these recommendations may change as new knowledge and technical capabilities emerge in the future, they focus our current efforts to provide the appropriate support for crews on long-duration missions.

The *Spirit* rover on the surface of Mars took the first picture of the Earth as seen from another planet. The image of the Earth appears as a pale, likely blue, dot on the Martian horizon, making one wonder about the profound behavioral challenges associated with human planetary exploration. The psychosocial issues of long-duration flight are an integral component of this text, and the critical behavioral issues are discussed in detail.

As we plan for human space exploration beyond low earth orbit, my dream can be summarized in the simple statement: "by the fiftieth." In other words, it is a dream to have humans walking again on the surface of the Moon, and possibly on the surface of Mars, by the fiftieth anniversary of the *Apollo 11* lunar landing in 2019. Let us all strive to make this dream reality.

Dave Williams
NASA Johnson Space Center
Houston, Texas

Preface

The possibility of sending people to Mars no longer resides solely in the realm of science fiction. Advances in propulsion, power systems, and materials make a Mars mission an extremely challenging, but potentially achievable, goal. One critical part of a Mars mission, or of any long-duration spaceflight, is keeping the crew healthy and safe. This book outlines the issues that must be addressed to make long-duration space travel successful and provides suggestions on the approaches to use.

Mars has long held a special fascination. At the turn of the twentieth century, many thought Mars harbored an old and dying civilization. They speculated that the Martians had resorted to building canals to irrigate their planet and stay alive. This notion, based on astronomer Percival Lowell's belief that he observed canals on Mars, was eventually thoroughly discredited. But there may have been a grain of truth in it. Mars may once have harbored life, although of a very simple kind. Knowledge about where life can exist on Earth has greatly expanded our willingness to believe that life may exist elsewhere in the universe. On Earth, life has been found in rocks a kilometer below the surface, in hot springs, in salt flats, and in the cooling systems of nuclear power plants. The fact that life can arise and survive in so many hostile environments makes it possible to consider that life may exist, or have once existed, on Mars. This makes Mars exploration compelling. Finding life on another planet could show that life on Earth is not unique and that life may exist in many places throughout the universe.

Travel to Mars, however, takes a long time. Although there are many possible mission designs and scenarios, the most common ones project a total trip time of 2.5–3 years. With current technology, the Mars trip needs to take place when the orbits of Earth and Mars are in the proper arrangement to allow for a low energy transfer between orbits. At these times, getting to Mars takes approximately 6 months. To make the return voyage, however, the Mars crew would need to wait until Mars and Earth were back in the right alignment to make a low energy return trip. This would mean a stay on the Martian surface of around a year and a half. The trip back would require approximately another 6 months. Overall, a mission to Mars would be more like the 3-year voyages of Ferdinand Magellan and Captain Cook than the 2-week missions to the Moon during the Apollo program.

A mission of this variety and length presents a series of medical and physiological obstacles. On the trips to and from Mars, the crew would have to deal with the effects of weightlessness on the human body, such as bone loss and muscle atrophy. The crew would need to do spacewalks during the journey, and once on Mars, they

would need to work outside in spacesuits. This could expose the crew to the risk of decompression sickness and would require that they be in good physical condition. A variety of different medical and surgical problems could arise at any point. The isolated crew would need superior psychological functioning and support to maintain a high level of individual and team performance. A variety of other problems, such as changes in the balance, cardiovascular, and immunological systems also would need to be understood and addressed.

This book is designed to enable space crews to live and work effectively in space and to provide guidance for the wide community of scientists, physicians, and engineers who support space crews. The objective of this book is to provide a practical handbook and reference to enable flight surgeons, astronauts, and their support teams to make informed decisions about medical care and physiological maintenance. The 12 chapters cover the main medical and physiological issues of spaceflight. Within each chapter, the book provides relevant background material on the area, followed by a summary of space flight experience. The chapters examine both the physiological effects of spaceflight and their clinical treatments. The chapters close with a series of recommendations based on current knowledge. The overall focus of this book is on practical problems and their solutions, and it is not designed to be a comprehensive review of all the physiology in a particular area.

One feature of the book is that each chapter provides specific recommendations. This approach has drawbacks. Sometimes recommendations will be based on incomplete knowledge, so they may suggest that more is known about a particular topic than is actually the case. Other times, the recommendation may choose a side on a controversial issue where the facts may not be completely clear. Also, recommendations may have to change over time as new knowledge becomes available. Nevertheless, this approach does require that conclusions be drawn from the physiological and medical data currently available. This often can be more useful than a simple presentation of the facts. The reader should be aware, however, that the recommendations represent just one perspective. Others may view the same data and arrive at different conclusions.

A human mission to Mars would be extremely difficult. The technological issues are daunting. Inadequate attention to the physiological and medical aspects could cause it to fail. On the other hand, it is possible. The aim of this book is to help surmount the physiological and medical problems so that a mission to Mars could succeed.

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Hanover, New Hampshire

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I was fortunate to have advice and assistance from several knowledgeable and helpful people in preparing this book. Discussions with my crewmate Jim Pawelczyk shaped the book at the outset of the project. A review by my crewmate Dave Williams provided a needed and valuable check at the end.

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SPACE PHYSIOLOGY

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Bone Loss: Managing Calcium and Bone Loss in Space

Introduction

November 11, 1982: aboard the *Salyut 7* space station, Valentin Lebedev finds his crewmate Anatoli Berezovoy writhing in pain. The pain is on the left side of his abdomen. Both the crew and mission control are concerned, but fortunately the symptoms resolve on their own, and the mission moves forward [1]. In retrospect, the leading possible cause of the pain was a kidney stone. Although the details are not known, one explanation is that unloading of the skeleton led to calcium leaving the bones. This calcium entered the urine, increasing the risk of kidney stone formation during the flight. Berezovoy's symptoms started when the stone, which had been growing in the kidney, broke loose and traveled down a ureter. The case highlights one of the major physiological changes facing crews in weightlessness: bone and calcium loss.

Low light levels, high ambient CO_2 concentrations, and minimal skeletal loading—all known consequences of long-duration spaceflight—can have a profound effect on the skeleton. Within a few days of entering weightlessness, urinary calcium excretion increases by 60–70%. Data from the Skylab program in the early 1970s showed that approximately 0.3% of total body calcium is lost per month while in space [2, 3]. This loss is not distributed equally throughout the skeleton. Data compiled from the Mir program show that the hip may lose greater than 1.5% of bone mass per month [4, 5]. The upper extremities show minimal or no bone loss, and bone mass in the skull may actually increase. All the data to date collected in space have been done in the setting of an active exercise countermeasure program.

Although bone is lost at a rapid rate, recovery is slow. Recent data from the Mir program in one individual showed that while 12% of bone was lost during 4.5 months in space, recovery of 6% took 1 year [6]. Follow up of the Skylab crew members 5 years after their 1- to 3-month flights suggested that not all the bone lost on the mission had been recovered [7]. In patients who recover completely or partially after spinal cord injury (where bone is lost in a similar way to spaceflight), bone is still not recovered completely after 1 year [8]. The quality of the recovered bone in these instances is not known.

These data indicate that bone loss and the accompanying risk of kidney stone formation present a significant problem for long-duration space missions and must be adequately monitored and controlled. This chapter reviews the basic physiology of bone, presents the effects of weightlessness on bone, and discusses of some potential countermeasures. The chapter concludes with recommendations based on current knowledge.

Calcium and Bone Physiology Relevant to Spaceflight

Bone serves two important functions. One is to provide the rigid structure needed for movement and activity. The other is to serve as a reservoir for calcium within the body. Three basic cell types (the osteoblast, osteoclast, and osteocyte) function within a complex regulatory network to maintain bone integrity, respond to changing skeletal loading conditions, and provide a stable level of blood calcium.

Certain aspects of calcium metabolism are particularly relevant to spaceflight. The changes that occur in response to alterations in dietary intake, lighting, ambient CO_2 concentrations, and loading are especially important for understanding the interventions needed for preserving bone during a long duration spaceflight.

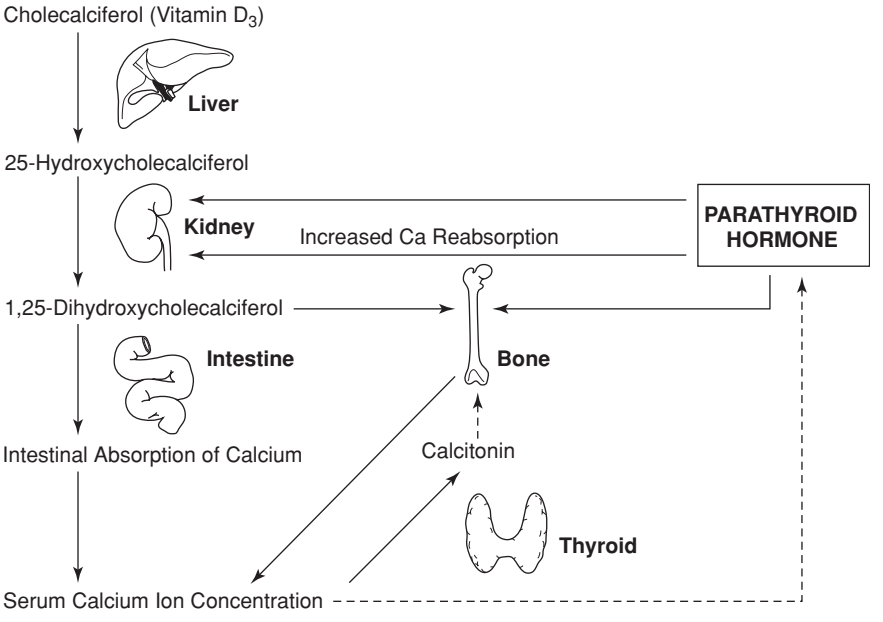

Figure 1-1. A schematic diagram of the overall regulation of calcium homeostasis by the major calcium regulatory hormones. Parathyroid hormone stimulates 1,25-dihydroxyvitamin D3 production, increases renal calcium absorption, and promotes bone resorption. These actions are suppressed when the calcium level increases. Figure reprinted from Breslau [122], with permission of Oxford University Press.

Response to a Decrease in Dietary Calcium

The recommended daily intake of calcium is 1000 mg a day [9]. If calcium intake drops below 400 mg/day, calcium deficiency results [10]. With calcium deficiency, serum calcium levels can fall and cause parathyroid hormone levels to increase. Parathyroid hormone in turn works at a variety of sites to increase calcium absorption, reduce calcium excretion, and restore blood calcium levels to the range needed for proper physiological functioning (figure 1-1).

One important action of parathyroid hormone is to increase bone resorption. Parathyroid hormone works at the osteoblast, which in turn signals the osteoclasts to increase bone resorption. Parathyroid hormone also increases the conversion of 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3. 1,25-dihydroxyvitamin D_3 in turn acts on both the intestine and the kidney. In the intestine, 1,25-dihydroxyvitamin D_3 increases dietary calcium absorption, and in the kidney calcium excretion is reduced. These changes are outlined in figure 1-1. Through a combination of these effects blood calcium levels are well maintained—but at the expense of the skeleton. A persistent low calcium intake will lead to bone loss, which underscores the importance of adequate calcium in the diet.

Response to Low Light Levels

Vitamin D plays an important role in the mineralization of the skeleton [11]. Pre-vitamin D_3 is formed in the skin by the action of ultraviolet light on 7-dehydrocholesterol. Pre-vitamin D_3 is then converted to vitamin D_3. Vitamin D_3 and vitamin D_2 (the usual form of vitamin D in dietary supplements) are jointly referred to as vitamin D. Vitamin D is further metabolized to 25-hydroxyvitamin D in the liver, and 1,25- dihydroxyvitamin D in the kidney. 1,25-dihydroxyvitamin D is the most active form of vitamin D, and it stimulates intestinal calcium absorption and bone calcium mobilization.

Without sunlight or ultraviolet light exposure (such as in spacecraft or submarines), vitamin D deficiency will occur if dietary intake is inadequate. Vitamin D deficiency can lead to poor mineralization of bone (osteomalacia), diminished calcium absorption in the intestine, decreased serum ionized calcium levels, and an increase in parathyroid hormone. The combination of these effects will weaken bone.

Response to High Ambient Carbon Dioxide Levels

Carbon dioxide levels on Earth are 0.03% of the atmosphere, but on a space station or in a submarine CO_2 levels can rise to 0.7–1%. The increased carbon dioxide levels affect acid-base balance and can have secondary effects on bone. Bone plays a role in neutralizing excess acid. The carbonates and phosphates in bone serve as buffers for acid. At the cellular level, acidosis has been shown to increase bone resorption [12]. Providing base in the form of potassium citrate can decrease bone resorption in postmenopausal women [13]. Presumably the mechanism is that the citrate helps to neutralize endogenous acid, eliminating the need for skeletal buffering.

Chronic exposure to high ambient CO_2 levels produces a compensated respiratory acidosis and contributes to the acid load that the body must neutralize. The magnitude of this effect is not clear. Drummer et al. [14] examined calcium balance in four subjects exposed to 0.7% and 1.2% carbon dioxide atmospheres. At the higher carbon dioxide level, markers of bone resorption were increased, consistent with the idea that bone calcium is being used to help neutralize the acid load. A study done on submarines, however, showed no increase in urinary hydroxyproline (a marker of bone resorption) while the crew was exposed to carbon dioxide levels of 0.8–1.0% [15]. In-vitro studies show that a respiratory acidosis has a much less profound effect on bone than does metabolic acidosis [16]. Overall, the net effect of high ambient CO_2 levels on bone is not clearly established and seems significantly less important than the effects of a metabolic acidosis. Nevertheless, the increased acid load in respiratory acidosis may decrease urinary pH and decrease urinary citrate. Both of these factors would increase the risk of kidney stones because a high urinary pH and high urinary citrate concentration help to prevent stone formation [17].

Bone Remodeling and Genetic Factors

Bone is constantly remodeled. Osteoclasts remove bone, creating a resorption area that is subsequently filled in by osteoblasts. The constant bone turnover and continual remodeling is thought to be essential for maintaining the strength and integrity

of bone. Without it, the continual impacts on the skeleton could lead to the accumulation of microfractures throughout the bone, progressively producing mechanically weaker bones. Different physical and dietary factors can tip the balance in this complex interplay and enhance either the formation or loss of bone.

The baseline level of bone remodeling and the changes in remodeling that occur in response to various stimuli (such as spaceflight) can be profoundly affected by genetics. For example, Boyden et al. [18] identified a group of people with a high bone mass who all shared a mutation in the *LRP5* gene. Judex et al. [19] showed that in rats the bone response to various anabolic and catabolic stimuli is strongly influenced by the genome.

Factors that favor bone formation

Mechanical loading. How bone senses and responds to loading is not fully understood. According to Frost [20], bone has a "mechanostat" that senses strain and maintains bone mass at an appropriate level to keep the strain within range. In this concept, when the strain within a bone exceeds a setpoint, modeling of the bone is initiated to reduce the strain back to that setpoint.

Even though the mechanism for sensing strain may not be firmly established, bone clearly changes in response to the loads placed upon it. Cross-sectional studies in athletes show that, on average, weight lifters have a greater bone mass than swimmers [21]. Gymnasts have a high bone mass, which may be attributable to the significant impact loads that their skeletons experience [22, 23]. The playing arm of tennis players has a higher bone mass than the nonplaying arm [24]. In addition, there is evidence that peak loads, rather than the frequency of loading, is important [23]. This suggests that short periods of high-impact loading may be as effective as frequent low-level loading for maintaining bone.

Gravity clearly has a role in skeletal loading. Heavier people have a higher bone mass than individuals of normal weight [25, 26]. Patients with spinal cord injuries lose considerable bone mass in the lower extremities, but can maintain bone mass in the lumbar spine, which still experiences gravitational loading in a wheelchair [27, 28]. Part of the loading on the hip and lower extremities during walking or running is the ground reaction force, generated by the gravitational acceleration of the body to the ground during locomotion. These gravitationally induced forces are key components of the loading on the hip and lower extremity [29].

Static loading and ground reaction forces are not the only loading forces lost when gravity is no longer present. Muscle contractions also play a major role in generating forces on the bone in 1 *G* [29, 30], and muscular effort is needed to work against gravity both supine and upright. During rehabilitation after hip replacement, very high hip pressures can be generated with muscular movements while supine [31], indicating that the upright posture is not necessary for creating substantial hip pressures. The absence of gravity could affect loading on the skeleton both through a loss of ground reaction forces and also due to a marked reduction in forces needed to move the weightless limbs.

Hormonal factors. Sex steroids play an important role in bone biology. Low testosterone levels lead to osteoporosis in men, and replacing testosterone can help to

restore bone mass. Also, increasing testosterone levels in men who are not androgen deficient can increase bone mass further, suggesting that testosterone can be used to increase bone formation [32]. Estrogen deficiency is the critical factor in the increased bone turnover and bone loss produced after menopause.

Growth hormone has been shown to increase bone mass [33]. When given to young men, growth hormone increased bone mass, but the results with older individuals have been disappointing [34]. Insulinlike growth factor-1 (IGF-1) has also shown promise as an agent that can increase bone mass [35]. IGF-1 was given to rats that flew for 10 days on the Space Shuttle and increased bone formation in the humerus. Whether the same effect would be seen in humans, however, is not known.

Parathyroid hormone has complex effects on the skeleton. A chronic increase in parathyroid hormone levels, such as occurs with secondary hyperparathyroidism from reduced calcium intake or vitamin D deficiency, will lead to increased bone resorption and a reduction in bone mass. Parathyroid hormone, however, can also have anabolic effects on bone. Cyclic administration of parathyroid hormone can increase bone mass. [36, 37]. Studies of postmenopausal osteoporosis show that the cyclic administration of parathyroid hormone can reduce fractures and improve bone mass [38, 39]. Animal studies have shown an increased risk of osteosarcoma during high-dose parthyroid hormone treatment.

Calcitonin is used to treat postmenopausal osteoporosis. It has not proven to be effective at preventing bone loss in immobilization in either animals [40] or humans [41].

Dietary factors. Calcium and vitamin D are two critical dietary factors for bone formation that have been discussed above. Other dietary factors can also be important. Phytoestrogens are a family of plant compounds that have a variety of estrogenic and antiestrogenic properties. Isoflavones are one class of phytoestrogens that may be effective in preserving bone mass [42]. In one study, postmenopausal women who consumed a diet high in soy protein (which is a good source of isoflavones) showed a significant increase in lumbar spine bone density [43]. Ipriflavone, a synthetic isoflavone, has also shown effectiveness against postmenopausal osteoporosis [44]. Whether isoflavones would be effective in the bone loss caused by immobilization or weightlessness is unknown. The physiology of postmenopausal bone loss differs substantially from that of immobilization or weightlessness.

Vitamin K is another nutritional factor that can affect bone health [45]. Available evidence suggests that vitamin K is important in osteocalcin metabolism, and osteocalcin seems to play an important role in bone formation. Vitamin K_2 may also affect bone through the osteoprotegerin/osteoprotegerin ligand system (discussed later in this chapter). In rat studies, vitamin K_2 prevented bone resorption after ovariectomy, reduced the increase in bone turnover after orchiectomy, ameliorated the increase in bone resorption after sciatic neurectomy, and prevented the decrease in bone formation after glucocorticoid treatment. Clinically, vitamin K sustains lumbar bone mineral density (BMD) and prevents fractures in patients with age-related osteoporosis, although data are limited. There is some evidence that taking vitamin K in space may help to reduce bone turnover [46, 47].

Physical factors. Bone is sensitive to electric fields. The application of low frequency, low intensity electric fields to marrow culture inhibited the recruitment of osteoclasts [48]. Applied electric fields are used in clinical medicine to assist with fracture healing.

Low magnitude (0.25 *G*, producing < 5 microstrain), high frequency (30–90 Hz) mechanical signals (vibration) have been shown to inhibit bone loss and increase bone formation [49, 50]. Vibration has been shown to be effective in increasing bone mass in a rat model of postmenopausal osteoporosis [49]. Rubin et al. [50] mechanically stimulated the hindlimbs of adult sheep every day for a year with 20-minute bursts of very low magnitude, high frequency vibration. This increased trabecular bone density in the proximal femur by 34% compared to controls [50]. Human studies have also shown promise [51, 52].

Factors that favor bone resorption

Immobilization. Reduced bone loading occurs on Earth though prolonged bed rest, immobilization, or paralysis. Animal models of immobilization show reduced bone formation, increased resorption, and loss of bone down to a plateau [53]. In some animal studies up to 60% of trabecular bone mass is lost before bone mass stabilizes at a lower level. Studies of patients with spinal cord injuries show that approximately 30–50% of lower extremity bone mass can be lost before reaching a plateau [28, 54]. The plateau is reached approximately 16 months after spinal cord injury.

Ischemia-reperfusion. Bone perfusion can have a marked effect on bone turnover. Stress fractures can result from overuse of bone. Although it might be expected that bone loading would increase bone mass, in some settings excessive bone loading can create transient bone ischemia. The subsequent increase in blood flow to the ischemic area once the activity stops can markedly increase bone turnover, with a net loss of bone. The area weakens rather than strengthens due to overuse, and stress fractures can result [55].

Hormones. Chronically increased parathyroid hormone levels increase bone resorption and are a cause of osteoporosis. Low calcium intake and vitamin D levels can increase parathyroid hormone levels. As discussed previously, however, parathyroid hormone can also be anabolic when given intermittently. Excess thyroid hormone is a cause of osteoporosis, but is unlikely to be a factor in spaceflight. Similarly, glucocorticoid excess markedly reduces bone formation and produces osteoporosis but is unlikely to occur in space.

Dietary factors. A high sodium intake increases urinary sodium excretion, which in turn increases urinary calcium excretion. The increased calcium excretion could aggravate ongoing bone loss, and there is some evidence that a high sodium intake can reduce bone mass in the hip [56]. Typically, sodium intake has been high on Space Shuttle flights (> 4 g/day) [57].

A diet high in protein provides an acid load that may increase the need for skeletal buffering and increase bone loss [13].

Cellular control of bone mass

The ability of bone to sense and respond to changing loading conditions is regulated by a complex series of cytokines and receptors on the osteoblast, osteocyte, and osteoclast. Understanding the action of these factors is critical for designing a rational countermeasure program.

Sensing mechanical loads. One critical ability for modifying bone mass to accommodate different loading conditions is the ability to sense and respond to mechanical strain. How the bone converts a change in strain into a biological signal is not understood. Whether it is mechanical strain, piezoelectricity, or intraosseous fluid pressures that form the main stimulus to bone is not known. This has some relevance for countermeasure design because exercise countermeasures can increase stress and strain on bone but cannot reproduce the hydrostatic gradients that existed in the bone on Earth.

Although the exact stimulus may not be known, recent evidence suggests that the response to increased strain may work at the cellular level through osteoprotegerin, which can markedly reduce the activity and activation of osteoclasts [58] (see below).

Regulating bone resorption. The discovery of the cytokine osteoprotegerin (also known as osteoclastogenesis inhibitory factor) and its receptor osteoprotegerin ligand (also known as osteoclast differentiation factor or RANK ligand) has led to a better understanding of how bone resorption is controlled at the cellular level [59, 60]. Fig-

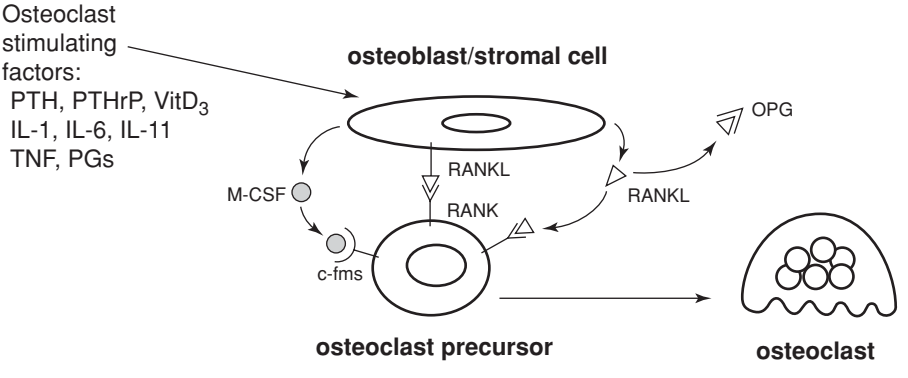

Figure 1-2. Schematic representation of the function of the osteoprotegerin/osteoprotegerin ligand system. Osteoprotegerin ligand (also known as RANKL as shown in the graph) stimulates the production of mature osteoclasts from osteoclast precursors. Osteoprotegerin (OPG) also binds to osteoprotegerin ligand (RANKL) and prevents osteoclast development. Transgenic mice that overexpress osteoprotegerin develop osteopetrosis because they do not form osteoclasts. Many of the factors that stimulate osteoclast formation seem to work through the osteoprotegerin ligand system. Figure reprinted from Boyce et al. [123], with permission of *Laboratory Investigation*.

ure 1-2 shows how this system of bone regulatory cytokines works. Osteoprotegerin ligand is the essential cytokine for stimulating the production of osteoclasts and for normal osteoclast differentiation and activation [61]. The effects of this ligand are counterbalanced by osteoprotegerin, which competes with osteoprotegerin ligand for a receptor site on the osteoclast. If osteoprotegerin is given exogenously, this inhibits osteoclast differentiation and markedly reduces bone resporption. Most of the calciotropic cytokines, peptides, and steroid hormones have been shown to regulate the expression of these two factors. These factors seem to serve as the final common effector system to regulate the formation of osteoclasts [61].

Space-related Bone Loss

The most comprehensive study of calcium metabolism in space occurred during the three manned Skylab missions [2]. The three-man crews spent 29 (*Skylab 2*), 59 (*Skylab 3*) or 84 (*Skylab 4*) days in space. Before, during, and after the flight, the crew members all took part in a metabolic balance study on the effects of weightlessness on calcium metabolism. Aspects of calcium metabolism have also been studied on various other spaceflights.

Markers of Bone Resorption and Formation

Calcium excretion rises promptly in space and remains elevated for several months, as shown in Figure 1-3. Whether calcium excretion stays elevated throughout weightlessness exposure or eventually returns to normal is not known. Limited data from a Russian long-duration flight showed no increase in calcium excretion after 218 days in space for 2 people [62]. It is not known whether this indicates that calcium excretion returns to normal eventually in space or that the countermeasure program was effective in minimizing bone loss. Experience from bed-rest studies and from studies on spinal cord injury suggest that the increase in calcium excretion in space should eventually taper off.

Urine samples that had been saved from the Skylab missions were examined recently using newer markers for bone resorption [63]. These data show that *N*-telopeptide, a sensitive marker for bone resorption, was increased throughout the flight. Another study also showed increased bone resorption markers in space. Caillot-Augusseau et al. [64] measured *C*-telopeptide on a 180-day *Mir* flight. *C*-telopeptide remained elevated throughout the flight. Together, these studies demonstrate that the increase in urinary calcium excretion was due to an increase in bone resorption.

Data on bone formation markers are limited. The one subject studied on a 180-day *Mir* flight showed decreased osteocalcin levels, which is a marker for bone formation [64]. Animal studies have shown that bone formation is reduced in weightlessness [65].

Location of Bone Loss

Bone mass and bone mineral content have been measured after spaceflight using a variety of techniques. Figure 1-4 provides a compilation of the data through the Mir

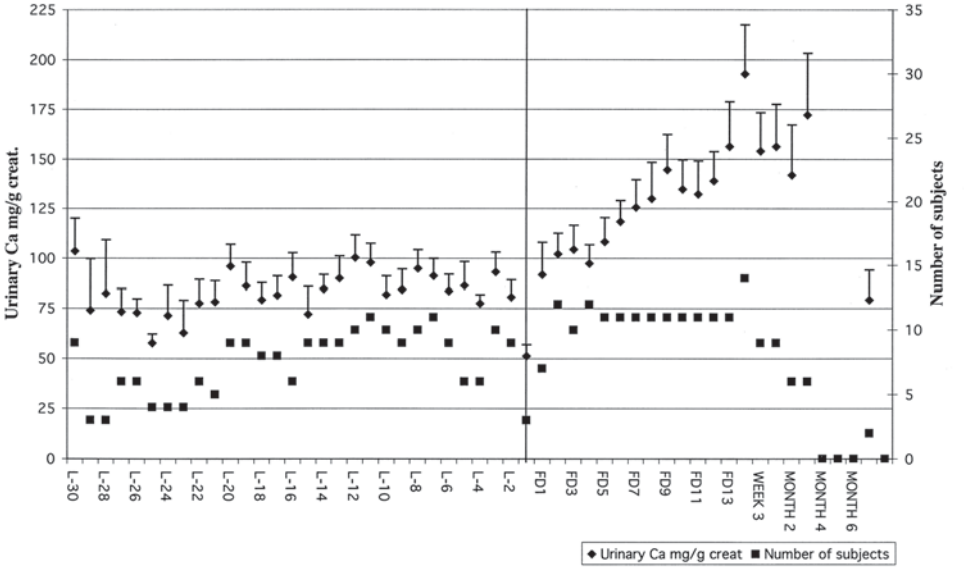

Figure 1-3. Compilation of all available urinary calcium excretion data in space done by the Life Sciences Data Archive at NASA-Johnson Space Center (www.lsda.jsc.nasa.gov). Data include *Gemini*, *Skylab*, *Salyut*, *Mir*, and Shuttle missions. L indicates the number of days before launch (e.g., L-30 is 30 days before launch); FD is flight day. Spaceflight increases calcium excretion markedly within a few days of weightlessness exposure, and calcium excretion stays high throughout the flight. Two data points taken from day 217 of a long-duration *Mir* mission show no increase in urinary calcium excretion. It is not known if this represents individual characteristics of those cosmonauts, a tapering off of a previously elevated urinary calcium level, or an effective countermeasure program.

program on changes in bone mineral after spaceflight. Data from the International Space Station are similar [66]. In weight-bearing areas such as the hip, losses of up to 1.7% per month have been documented in space. The upper extremities are spared, and evidence suggests that the skull may even gain bone mass. Taken together the data suggest the bone loss in space is concentrated in the lower spine and lower extremities, those areas most loaded by gravity on Earth. These data, however, show average results. Some individuals showed substantial reductions, while in others the changes were quite small. These large interindividual differences need to be taken into account by the countermeasure program [67].

Parathyroid Hormone and Vitamin D

Serum calcium was measured during the Skylab program and showed a small increase within the normal range. This increase might be expected to decrease parathyroid hormone, and data collected on parathyroid hormone suggest this is true. Parathyroid hormone levels decreased on the *Spacelab Life Sciences 1* and *2* flights (9 and 14 days, respectively) and on a 180-day *Mir* flight [64]. Reduced parathyroid hormone

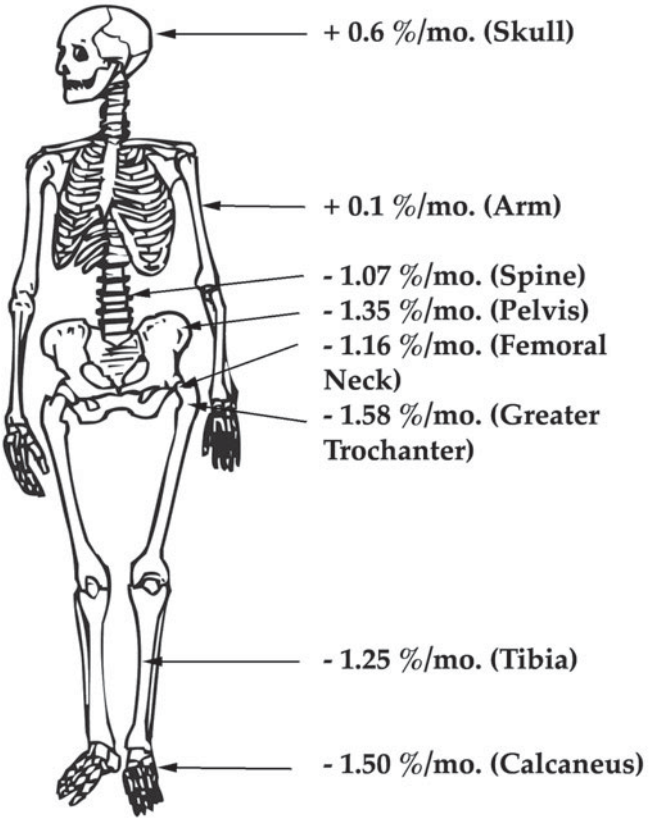

Figure 1-4. Compilation of bone loss rates from data presented in LeBlanc et al. [4] and Oganov and Schneider [83]. Bone loss is concentrated in the lower extremities; the upper extremities are unaffected, and the head may actually gain bone mass.

concentration would also reduce the production of 1,25-dihydroxyvitamin D, with an accompanying reduction in calcium absorption.

Bone Loading during Spaceflight

Astronauts and cosmonauts exercise in space using a treadmill, ergometer, and resistance exercise device. Bungees and expanders are also available. As a result of the coutermeasure program, bone loading is not zero in space, but is instead intermittent. Data collected on ground reaction forces on the foot in weightlessness show that, in general, the impact forces that crew members experience are usually below the level for similar activities on Earth. The treadmill used in space has bungees to keep the crew member in contact with the treadmill surface, but the forces generated are still less than those generated during similar activities on the ground. This indicates that, in general, even when crew members are taking part in the countermeasure program, they are not generating high loads [68–70].