APPENDIX C

BONE AND CONNECTIVE TISSUE DISCIPLINE - SUPPORTING MATERIAL

Supplementary reports

C-1. Diet and Acid-Base Balance by Martin J. Fettman

C-2. Role of vitamin D and Parathyroid Hormone in Microgravity-Induced Bone Loss by Michael Holick

Report C-1
Diet and Acid-Base Balance
by Martin J. Fettman

Many factors in space flight may affect calcium metabolism and bone turnover, beyond the effects of microgravity ant changes in physical loading forces. Prior physical fitness may influence remodeling forces. Caloric balance influences the amount of energy available for anabolic processes, including bone matrix synthesis. Nitrogen balance reflects the quantity of amino acids retained which may be used for bone matrix synthesis. Finally, dietary calcium balance will affect the bone mineral density. It is important to note that "balance" is used to describe diet-related factors, rather than "intake". Many processes may affect "nutrient partitioning" so that alterations in balance diverge from those of dietary intake. In space flight, one example is that of dietary protein, nitrogen balance, and differential protein synthesis. Even during periods of decreased overall nitrogen balance, inflammatory cytokine release and hepatic acute phase protein synthesis may be increased, reflecting partitioning of amino acid metabolism (Stein et al, 1993; Stein and Schluter, 1994). Likewise, it is possible to modify mineral distribution through changes in dietary electrolyte composition and influences of acid-base metabolism.

Both respiratory acidosis (increased pCO_2) and metabolic acidosis (decreased HCO_3) have been shown to alter bone surface mineralization through physicochemical effects defined by the solubility product relationship between ionized calcium and phosphate (Bushinsky et al, 1992 Arnett et al, 1994). The precipitation of ionized calcium and phosphate is determined both by their concentrations and that of hydrogen ions ($[Ca^{2+}][P_i]/[H^+] = K$).

This principle has been exploited in veterinary medicine to manage particular animal disorders. For instance, dietary alkalization has been used to improve eggshell quality in poultry (Keshavarz, 1994). Dietary acidification has been used to improve bone calcium mobilization in dairy cows during their "dry" period just prior to parturition (Oetzel et al, 1991). This, in turn, protects against hypocalcemia developing subsequent to the onset of lactation. Likewise, both dietary acidification and alkalization affects the urinary pH and subsequent predisposition to urolithiasis in cats (Thumchai et al, 1996). Dietary acidification prevents struvite stone precipitation, but predisposes to calcium oxalate precipitation.

Metabolic acidosis has also been shown to alter bone remodeling through cellular effects. Decreased bicarbonate concentrations reduce osteoblast activity, and stimulate osteoclast activity, in addition to the physicochemical effects noted above (Krieger et al, 1992; Bushinsky et al, l995). There is controversy in the literature regarding the relative "potency" of respiratory vs. metabolic acidosis in altering bone mineral deposition (Sprague et al, l994; Arnett et al, 1994). Thus, we may have cause for concern about excursions in atmospheric pCO_2 in the Space Station.

Acidosis has also been shown to alter the synthesis, release, and effectiveness of the calciotropic hormones (Ching et al, 1989). Acidosis increases the ionization of calcium, and increased ionized calcium concentrations in turn suppress the release of parathormone (PTH) from the parathyroid glands. On the other hand acidosis promotes the activity of PTH on bone mineral resorption. Acidosis also decreases PTH activity in the kidneys, resulting in decreased calcium reabsorption from the tubular fluid. Finally, acidosis decreases renal la-hydroxylase activity, thereby reducing the production of active calcitriol.

It has been hypothesized that the usual daily load of acid produced through metabolism might have similar effects on calcium metabolism and bone turnover, even in the absence of overt disturbances in acid-base balance. Daily oral intake of $KHCO_3$ (but, not $NaHCO_3$) to neutralize endogenous acid production significantly improves calcium balance, reduces bone resorption, and increases bone formation in healthy adult males (Lemann et al, l989) and in post-menopausal females (Sebastian et al, 1994). In addition, it is possible that in space flight, during periods of negative caloric and/or nitrogen balance, increased endogenous acid generated by accelerated rates of catabolism may also contribute to negative calcium balance.

Increased dietary sodium intake increases the filtered renal load of sodium for excretion. This, in turn, decreases renal tubular calcium reabsorption and increases urinary calcium excretion. Some have suggested that the sodium effect may be dependent on physical fitness and activity level (Navidi et al, 1995). Dietary sodium restriction has been shown to improve calcium balance in rats (Navidi et al, 1995) and in humans (Arnaud et al, 1996). but its effects on bone mineral density have not been confirmed.

Dietary sodium restriction may have other advantageous effects as well. In rats, sodium restriction increases renin-angiotensin-aldosterone responsiveness to subsequent salt repletion and volume expansion (Wilke et al, 1995). This may be useful for preconditioning astronauts prior to administration of volume expansion countermeasures for orthostasis.

Dietary alkalinization with potassium citrate, coupled with sodium restriction, has been shown to decrease the risk for urinary calcium oxalate precipitation (Goldfarb, l988). Thus, an additional benefit of dietary modification as described above might be reduced risk for urolithiasis.

Dietary alkalinization and potassium supplementation have been shown to increase nitrogen balance in some diseases (Gourgeon-Reybourn et al, 1991; Papadoyannakis et al, 1984). In additional benefit of dietary modification as described above might be moderation of reduced or negative nitrogen balance observed during some phases of space flight (Stein et al, 1993). This might also improve calcium balance as affected by endogenous acid produced through catabolism.

Quantitative dietary intake data for astronauts are limited, but indicate significant balances which may affect calcium metabolism and bone turnover. Caloric intake in 13 astronauts (8.76 +/- 2.26 Mj/day) appears to be significantly less than estimated energy expenditure (11.70$^{+}_{-}$ 1.89 Mj/day) (Lane et al, 1997). This would be expected to adversely affect anabolic processes integral to bone remodeling, as well as net acid excretion and calcium balance. Sodium intake in 21 astronauts was 4116.6 ± 883.1 mg/day (Lane, l996), well above that recommended to moderate urinary calcium excretion. This amount might also adversely affect humoral vascular responsiveness to salt and water loading in astronauts prior to return to Earth. Calcium intake (855.4 $^{+}_{-}$ 220.0 mg/day) was very close to the recommended daily intake, and should not require major modification. It might be useful to calculate dietary cation-anion balance for comparison to urinary pH and titratable acid excretion in order to determine potential effects of supplemental dietary alkalinization on net acid excretion and calcium balance. While changes in blood gas parameters have not been observed in limited studies to date (Whitson, 1996), increased urinary calcium and sulfate losses (Whitson et al, 1993) may reflect increases in net acid excretion which could be moderated by dietary alkalinization.

Remaining questions include the following:

1. Are there thresholds for the dietary effects described above?

2. What are the changes in acid-base metabolism in microgravity? This should include not only overt changes in blood gas parameters, but also changes in urinary net acid elimination.

3. Is a lower sodium diet practicable for space flight This would include formulation of lower sodium foods, as well as concomitant modifications to maintain palatability and intake.

4. Is dietary buffer supplementation possible? This would require knowledge of the typical dietary cation-anion balance (potential dietary acidity) and effects modifications on palatability and intake.

Report C-2
Role of vitamin D and Parathyroid Hormone in Microgravity-Induced Bone Loss
by Michael Holick

Introduction

Vitamin D and parathyroid hormone play important roles in bone metabolism. Therefore, any alteration in vitamin D and parathyroid hormone can potentially alter calcium metabolism, and have significant physiologic and pathologic consequences. Vitamin D must be metabolized in the liver to 25-hydroxy vitamin D (25-OH-D) which, in turn is metabolized in the kidney to 1,25-dihydroxyvitamin D ($1,25(0H)_2D_3$). It is now recognized that $I,25(OH)_2D_3$ is the biologically active form of vitamin D which is critically important for regulating the efficiency of intestinal calcium absorption. Monocytic precursor cells in the bone marrow possess receptors for ($1,25(0H)_2D_3$) (VDR) and are induced to mature, into osteoclasts by ($1,25(0H)_2D_3$). There is evidence to suggest that mature osteoclasts loose their VDR, and therefore, are no longer responsive to $1,25(0H)_2D$ although recent evidence suggest that this may not necessarily be true. Mature osteoblasts also possess VDR and respond to $1,25(0H)_2D$ by increasing the production of osteocalcin, osteopontin, and alkaline phosphatase. $1,25(0H)_2D_3$ also regulates phosphorus metabolism by increasing intestinal phosphorus absorption especially in the lower small intestine.

Parathyroid hormone has a multitude of physiologic activities on both calcium and phosphorus metabolism. Parathyroid hormone enhances the tubular reabsorption of calcium in the proximal and distal convoluted tubules in the kidney. It also causes a phosphaturic effect. In the bone, monocytic precursor cells have receptors for PTH. PTH induces these cells to become mature osteoclasts. Once mature, the osteoclasts loose their receptor for PTH, and therefore, are no longer responsive to this hormone. Osteoblasts have receptors for PTH and there is strong evidence that PTH has an anabolic effect on bone especially on trabecular bone. PTH also can enhance intestinal calcium absorption indirectly and alter bone metabolism indirectly by its action on stimulating the renal production of $1,25(0H)_2D$.

Effect of Bed Rest Microgravity on the Vitamin D and PTH Axis.

A review of the literature from bed rest studies and from microgravity studies have suggested that once the bone is unloaded, there is an increase in the mobilization of calcium stores. This mobilization causes a slight rise in serum ionized calcium concentrations which, in turn, decreases the synthesis and secretion of PTH. The decrease in blood levels of PTH has a variety of physiologic effects. Most importantly, a decrease in the serum levels of PTH causes an increase loss of calcium into the urine. This can potentially increase the risk of developing kidney stones. The decrease in PTH may also decrease osteoblastic activity and therefore, bone formation. Since PTH also regulates phosphorus metabolism in the kidney; it is possible that the depressed production of PTH could lead to a small increase in fasting blood levels of serum phosphorus. PTH also indirectly regulates intestinal calcium absorption by regulating the renal production of $1,25(0H)_2D$. Therefore, when the blood levels of PTH are suppressed, there is a decrease in the metabolism of 25-0H-D to $1,25(0H)_2D$. This results in a decrease in intestinal calcium absorption

Therefore, a vicious cycle is established when the skeleton is unloaded, i.e., the body appears to depend on the bone for its major source of calcium since there is a significant decrease in intestinal calcium absorption presumably because of the decrease synthesis of $1,25(0H)_2D$. Therefore, when considering the calcium intake for astronauts, this issue needs to be carefully considered. Although it is reasonable for astronauts have an adequate amount of calcium in their diet, i.e., 800 to 1000 mg, it is probably not appropriate to substantially increase this level much beyond this. The reason for this that since the efficiency of intestinal calcium absorption is relatively low, the increase of calcium that remains in the intestine and ultimately evacuated in the stool could potentially alter gastrointestinal motility and cause constipation. It is unclear at this time whether the use of $1,25(0H)_2D_3$ to enhance the efficiency of intestinal calcium absorption would be wise. The reason for this is that $1,25(0H)_2D_3$, will definitely enhance intestinal calcium absorption. However, if bone formation is significantly decreased and cannot use this calcium, the increased absorption of calcium into the blood can ultimately increase calcium and the risk of kidney stones, hypercalcemia and soft tissue calcifications.

How Much Vitamin D is Required and what Should the Source of Vitamin D for Astronauts?

Most vitamin D for humans comes from exposure to sunlight. However, on the Shuttle and in the Space Station, the astronauts will not be exposed to any sunlight that could produce vitamin in their skin. Although the RDA for vitamin D in adults is 200 lU/day, there is evidence from our submarine study that suggests that in the absence of any exposure to sunlight, the RDA should be closer to 600 IU/day. Thus, a multivitamin that contains 400 to 600 of vitamin D should be adequate to maintain vitamin D stores in astronauts especially when on long duration flights.

An alternative method to provide, in a passive manner, vitamin D to astronauts is to incorporate into the lighting system a source of simulated sunlight that contains a small amount of ultraviolet B radiation. For example, a simulated sunlight source could be provided in a small area that is used as an active area. There is mounting evidence that exposure to ultraviolet radiation may have some beneficial effects for the body that not only includes the production of vitamin D, but also the feeling of well being due to the production of b-endorphins.

Conclusion

There is no question that microgravity-induce bone loss continues to be a significant physiologic adaptation that can have detrimental short-term and potentially long-term effects on astronauts. Therefore, there continues to be a need to better understand the mechanisms involved in microgravity-induced loss ant to develop counter measures to prevent it. From a hormonal point of view, there is strong evidence to suggest that the mobilization of calcium from the skeleton alters the PTH vitamin D axis. This ultimately results in a decrease in intestinal calcium absorption and the continual removal of calcium from the bone to satisfy the body's calcium requirement for its metabolic functions. It is important that the astronauts have an adequate dietary source of calcium probably in the range of 800 to 1000 mg/day along with an adequate source of vitamin D that approaches 600 IU/day. Consideration should be given to the incorporation of a simulated sunlight source for long-duration space flight as a mechanism to passively provide astronauts with their vitamin D requirement. The solar simulated light source may also provide them with other benefits as well including a feeling of well being.

There are a variety of other hormones that certainly can impact on both calcium and bone metabolism. Most notably, glucocorticoids can significantly alter calcium and bone metabolism. There is strong evidence to suggest that serum cortisol levels are increased in astronauts especially during the early part of their flight. Whether this is due to the stress of the flight or other causes is unclear at this time. There may be other hormonal factors such as IGF and its binding proteins that could be altered in microgravity and this requires further investigation.

C-3 - Additional Material

Excerpts of recommendations from other countermeasures groups

1. Musculoskeletal Adaptations to Weightlessness and Development of Effective Countermeasures. Med. Sci. Sports Exerc., Vol. 10, pp. 1247-1253, 1996.

2. Medical Policies and Requirements Document. Prepared by Medical Policy Board, Revision Three, August 30, 1996.

3. Human Research Facility: Science and Technical Requirements Document, January 19, 1996.

4. ACSM Position Stand on Osteoporosis and Exercise. Med. Sci. Sports Exerc., Vol. 27, No. pp i-vii, 1995.

5. Scientific Prerequisites for the Human Exploration of Space. National Academy Press, Washington, D.C. l993.

6. Musculoskeletal Discipline Science Plan, Space Physiology and Countermeasures Program, Life Sciences Division, NASA, Washington, DC, 1991.

7. Final Report Phase III: Research Opportunities in Bone Demineralization, NASA Contractor Report 3795, April 1984.

Musculoskeletal Adaptations to Weightlessness and Development of Effective Countermeasures

Med. Sci. Sports Exerc., Vol. 10, pp. 1247-1253, 1996

Kenneth M. Baldwin (Co-chair), Timothy P. White (Co-chair), Sara B. Arnaud, V. Reggie Edgerton, William J. Kraemer, Rodger Kram, Diane Raab-Cullen, and Christine M. Snow.

ABSTRACT

A Research Roundtable, organized by ACSM with sponsorship from NASA, met in November 1995 to define research strategies for effective exercise countermeasures to weightlessness. Exercise was considered both independently of, and in conjunction with, other therapeutic modalities (e.g., pharmacological, nutritional, hormonal and growth-related factors) that could prevent or minimize the structural and functional deficits involving skeletal muscle and bone in response to chronic exposure to weightlessness, as well as return to earth baseline function if a degree of loss is inevitable. Musculoskeletal deficits and countermeasures are described with respect to: 1) muscle and connective tissue atrophy and localized bone loss; 2) reductions in motor performance; 3) potential proneness to injury of hard and soft tissues; and 4) probable interaction between muscle atrophy and cardiovascular alterations that contribute to the postural hypotension observed immediately upon return from space flight. In spite of a variety of countermeasure protocols utilized previously involving largely endurance types of exercise, there is presently no activity-specific countermeasure(s) that adequately prevent or reduce musculoskeletal deficiencies. It seems apparent that countermeasure exercises that have a great resistance element, as compared to endurance activities, may prove beneficial to the musculoskeletal system. Many questions remain for scientific investigation to identify efficacious countermeasure protocols, which will be imperative with the emerging era of long-term space flight.

INTRODUCTION

For several decades both human beings and laboratory animals have been exposed to the environment of weightlessness associated with space flight. During this time, a large body of evidence has been gathered to clearly show that exposure to such an environment of varying duration--days to weeks to months--results in structural and functional deficits in the musculoskeletal system.

These deficits could affect muscular function during space flight, particularly in activities requiring high precision and muscular force--such as is the case during extravehicular activity. However, the decrements become more significantly expressed as astronauts return to a partial-G or 1 G environment. These deficits could have catastrophic consequences, for example if the need arose for emergency egress upon return to a 1G environment. The deficits also affect motor abilities requiring even modest amounts of strength, endurance, and coordination, such as required for locomotion. If the deficits in bone mass and strength are not restored after return to 1 G, then they may also have long-range consequences by increasing the risk of fracture with aging.

A Research Roundtable was organized by the American College of Sports Medicine (ACSM) with sponsorship from the National Aeronautics and Space Administration (NASA). The Roundtable met at the National Center of ACSM on November 7 and 8, 1995. The goal of this Roundtable was to define research strategies for exercise, both independently of and in conjunction with other therapeutic modalities (e.g., pharmacological, nutritional, hormonal and growth-related factors) that could prevent or minimize the structural and functional deficits involving the skeletal muscle and bone in response to chronic exposure to weightlessness, as well as return to earth baseline function if some degree of loss is inevitable.

BACKGROUND

The driving force behind a Roundtable specifically focusing on the integrative theme of weightlessness, exercise, and the musculoskeletal system stems from an evolving data base derived from both biological and biomedical ground-based and space-related research. These data strongly suggest that in spite of a variety of countermeasure protocols being utilized that involve largely aerobic types of exercise (in which exercise is performed with a bias to many muscular contractions against relatively low loads), there is presently no activity-specific countermeasure that adequately prevents or reduces identified deficiencies in the musculoskeletal system.

The musculoskeletal deficits include, but are not limited to, the following: 1) muscle and connective tissue atrophy and localized bone loss; 2) reductions in motor performance; 3) potential proneness to injury involving both hard and soft tissues; and 4) probable interaction between muscle atrophy processes and cardiovascular alterations that collectively contribute to the postural hypotension observed upon immediate return from space flight.

Because NASA is entering into a new era of long-term space flight, the deficits in musculoskeletal structure and function that were tolerable to some degree with shorter flights, become intolerable with flights that extend months or years. It seems apparent that countermeasure exercises that have a greater resistance element when compared to endurance activities, may prove beneficial to the structure and function of skeletal muscle and bone.

The Roundtable was structured to involve leading researchers in the related fields of muscle and bone biology, biomechanics, exercise physiology, and clinical medicine. These individuals reviewed and discussed currently available information on what is known and unknown concerning musculoskeletal plasticity and function in response to interventions such as: 1) different types of physical activity of varying intensity, duration, and frequency; 2) exposure to space flight of varying duration; and 3) ground-based models designed to simulate weightlessness such as immobilization, water immersion, bed rest, and limb suspension. The review of information included analyses of both human and animal models.

As a result of these deliberations, the Roundtable participants identified a number of key observations that were coupled to a series of recommendations, both general and specific. The recommendations are intended to guide future research on musculoskeletal structure and function in the context of states of unloading, and for the development of effective countermeasures. These recommendations are aimed at both basic and directed research involving both humans and research animals, with the ultimate objective of preserving the functional integrity of not only the musculoskeletal system, but other physiological systems also heavily impacted by chronic exposure to states of weightlessness.

Moreover, the Roundtable participants were cognizant of the fact that information gained from such a research focus would have a tremendous impact on aging and a variety of health problems associated with physical inactivity, debilitating diseases and injury, and rehabilitation.

OBSERVATIONS AND RECOMMENDATIONS

I. OVERVIEW OF ISSUES CONCERNING FUTURE RESEARCH DIRECTIONS

I-A. Observations:

1) Based on the data analyzed by the Roundtable participants, it is apparent that exercise protocols of the endurance type (i.e., cycling, simulated running, rowing, etc.) that are currently used in space flight missions of varying duration to counteract a variety of cardiovascular deficits (and likely other systems as well), are insufficient for the musculoskeletal system and do not fully maintain normal motor control of posture and locomotion, muscle and bone mass, and regulatory processes that prevent postural hypotension. These deficits both individually and collectively could potentially impair the performance of a variety of tasks carried out during space flight (e.g., extravehicular activity) and upon landing in either 1 G or partial G environments.

2) Available information further suggests that a single uniform exercise protocol is likely to be insufficient to fully maintain the structural and functional integrity of those systems impacting motor activity, musculoskeletal function, and circulatory homeostasis.

I-A Recommendations:

1) A broad-based research plan must evolve with an overall strategy of designing a battery of exercise countermeasures aimed at preserving integrated physiological processes necessary for maintaining total body homeostasis during both space flight and upon return to a partial-G or 1 G environment. While the Roundtable participants focused more specifically on the musculoskeletal system, it recognized the importance of the interactions with other systems as well, e.g., the cardiovascular system and particularly its peripheral vascular control.

2) A minimum of four types of activity paradigms should be developed and configured for the space environment that will likely be experienced on either the shuttle and/or space station. These paradigms are defined herein relative to the desired performance outcomes. a) Routine motor skills (tasks) suitable for maintaining posture and basic locomotor function. Motor control tasks should be designed for both the upper

(trunk) and lower body. Preferably this activity paradigm should be developed in conjunction with equipment or devices that could restore partial gravity forces on the body. b) Heavy resistance paradigms, involving isometric, concentric, and eccentric muscular actions, should be designed to optimally load the lower extremity and trunk musculature to maintain a positive protein balance in these muscle groups. c) Activities that generate either a high impact or produce sufficient strain on bone to maintain its structure and mineral density also need to be developed. Where possible, activities that create simultaneous maintenance of the above properties of both bone and muscle should be prioritized. d) An element of aerobic activity should be included in the training regimens with the primary objective of maintaining cardiovascular function and homeostasis, e.g., plasma volume. In all preventive and therapeutic activity paradigms, attention should be paid to the incidence of, and proneness for, injury to soft and hard tissues, and short- and long-term consequences of such injury should be determined.

3) Because time available for the astronaut corps that is dedicated to exercise is such a premium, it is apparent that in order to seek more economical exercise counter measure strategies, research should be undertaken to explore other interventions (pharmacological, hormonal, and growth factors) that could independently or in conjunction with exercise stimuli maintain musculoskeletal structure and function.

4) Future research should incorporate both basic (mechanistic) and directed research programs that utilize both animal and human models in addition to the experimental resources that will be available on the space station. Experiments should be designed around acceptable models of unloading such as bed rest and unilateral lower extremity suspension for humans and the hindlimb suspension model for animals (rodents).

VI. OBSERVATIONS AND RECOMMENDATIONS ON BONE

VI-A Observation:

When the skeleton is unloaded as in space flight, bone mass is lost in weightlessness. This bone loss is more localized than originally predicted and shows individual variation, ranging from none to 10.1% of preflight values in the spine, 1.3 to 11.4% in the femoral neck, and 0.4 to 9.5% in the tibia bone of Cosmonauts after long-duration flights. The bone loss associated with microgravity can be accelerated by age-related bone loss and changes in reproductive hormone levels and there is no evidence that the bone loss is recoverable. Potential consequences of significant bone loss include fractures on re-entry - particularly in a situation of emergency egress - and accelerated osteoporosis.

VI-A Recommendations:

l) Determine site specific rates and magnitudes of bone loss at 0 G and differences according to gender, age, endocrine, and nutritional status.

2) Determine whether individual variations in rates of bone loss are dependent upon factors such as gender, age, hormonal status, pre-flight bone status - that could be used to identify individuals at risk for excessive bone loss at 0 G and consequent risk for fracture.

3) Assess the efficacy of pre-flight training protocols to mitigate, skeletal loss during space flight. For example, determine if bone mass values that are substantially above the

mean prior to liftoff may allow the astronaut to withstand bone loss and not be at risk for fractures. These protocols should be developed in a gender-specific manner.

4) Establish time and degree of bone restoration upon return to 1 G and determine its relationship to flight duration, exercise done in space, age, and gender.

5) Relate density variations to typical loading patterns to assess fracture risk prior to, during, and postflight.

VI-B Observation:

The endocrine system has profound effects on bone metabolism and there is evidence that space travel alters hormone secretion. Low levels of reproductive hormones (i.e., estrogen and testosterone) and high levels of corticosteroids result in bone loss, whereas increased levels of insulin-like growth factors are associated with higher bone and lean mass.

VI-B Recommendations

1) Define the endocrine profile in long duration space flight for men and women. Identify these changes as central or peripheral processes.

2) Investigate the interaction between reproductive hormones and reduced mechanical forces on bone loss in 0 G.

3) Determine the effect of weight-bearing exercise, which promotes muscle strength and power development, on insulin-like growth factors and bone mass. Evaluate the responses according to gender.

4) Evaluate the efficacy of anti-resorptive agents (e.g., bisphosphonates) on reduction in loading related, hormonal and age-related bone loss in space according to gender.

VI-C Observation:

The structural capacity of whole bones depend on bone geometry (cross-sectional area and moments of inertia) and material properties (strength and modulus) of both cortical and trabecular bone. While age-related and hypo-gravitational changes in the material properties of diaphyseal cortical bone appear to be compensated for by geometric increases in moment of inertia, material properties of trabecular bone are strong, power law functions of density. Trabecular density in turn is strongly associated with measures of trabecular morphology such as average trabecular width, spacing and connectivity. Issues of bone "quality" that may be related to weightlessness are now focusing on mineralization, collagen content, and damage accumulation, and there is some evidence that these factors may be influenced by space flight.

VI-C Recommendations:

1) Develop noninvasive techniques to estimate trabecular bone strength; for example using pQCT (peripheral quantitative computed tomography), DEXA (dual energy x-ray absorptiometry), ultrasound, and MRTA (mechanical response tissue analyzer) technologies.

2) Use these techniques to track the strength of bone systematically from pre- flight, in-flight, post-flight and long-term recovery upon return to normal weight bearing.

3) Determine differences in morphology and material properties of bones remodeled in space compared with those remodeled on Earth.

VI-D Observation:

The current exercise modalities typically used during space flight are inadequate to maintain bone mass. Weight bearing activities performed at I G that incorporate impact loading and which increase muscle mass, power and strength (i.e., gymnastics, wrestling) also increase bone mass. In 1 G environments, running or hopping in place provide substantially higher impact loads (and thus bone strain) than do activities such as cycling, walking or resistance training exercises. In external loading animal models, thresholds for bone maintenance and increase have been shown for loading variables such as strain magnitude, strain rate, frequency (Hz), strain distribution, and number of loading repetitions.

VI-D Recommendations:

1) Characterize actual bone strains at clinically relevant sites in humans during specific movement patterns (including cycling, treadmill walking and running, jumping in place, and resistance training exercises), and determine the relationship of strain to age, size, and gender.

2) Determine mechanical loading thresholds for bone mass maintenance in adults and determine whether these protocols are specific to age, bone size or gender.

3) Determine exercise prescriptions and other mechanical interventions that are sufficient to maintain bone mass during weightlessness, and determine whether these protocols are specific to age, bone size or gender.

4) Determine the molecular and cellular signals associated with bone loss due to decreased loading as observed in disuse and weightlessness, and determine how these signals compare with signals for bone hypertrophy.

5) Determine to what extent the bone loss that occurs during 0 G exposure is due to the lack of mechanical load, and to what extent systemic change (e.g., fluid shifts, hormone expression) can modulate the response to unloading.

VI-E Observation:

Nutrition is important for bone health, independent of its influence on body weight. Specific nutrients, such as calcium and phosphorus, are essential components of bone crystals. In addition, there are other nutrients -- such as vitamin D, magnesium, and protein -- that are known to impact bone mass.

VI-E Recommendations:

1) Define the protein, mineral and energy requirements for bone maintenance.

2) Determine to what extent astronauts in space have adequate energy, vitamin, ant mineral intake and absorption, and to what extent exercise regimens alter these needs and intakes.

VI-F Observations:

1) Experimental models for the musculoskeletal system are classically human adults who volunteer for bed rest of varying periods of time, and for upright models in which some muscles of one leg are unloaded. These models appear to be valid for space flight, but direct comparisons of many measurements from ground-based studies with those made during space-flight are lacking.

2) Small animal models currently in use for space flight experiments have generated a great deal of information on responses to 0 G and bone-muscle unloading. However, little information has been obtained on mature animal models.

VI-F Recommendations:

I) Make direct comparisons of measurements from ground-based studies with those made during space-flight.

2) Compare the responses to unloading in mature animals to those of younger animals of the same species in both ground based and in-flight experiments. Incorporate the differences in maturity for bone and muscle into experimental design (i.e. 95% of the skeleton in the male rat is acquired by 6 months of age, yet muscle experiments typically consider 4-month-old rats to be mature).

SUMMARY AND CONCLUSIONS:

Research aimed at understanding the adaptive processes of human beings in response to the environment of weightlessness is both complex and difficult to perform. This is due to the inherent problems associated with using humans as research subjects, because they must adhere to a variety of operational medical procedures, and perform a wide variety of duties during a given mission. These factors often ultimately compromise the variables being investigated thus making the interpretation of the experiments difficult. Furthermore, the availability of the microgravity environment of space travel often precludes an ideal experimental design, particularly in controlling the important variable of duration and transient high G forces on ascent and descent.

Therefore, it is essential that future research focus both on human and animal subjects that can be configured into ground-based models simulating chronic states of weightlessness in order to examine both the mechanistic and applied components of the scientific issues raised in this report.

It seems highly unlikely that a single exercise paradigm will evolve that effectively ameliorates the important structural and functional deficits occurring in bone, muscle, and connective tissue identified in this report. Thus, it is imperative that a systematic and highly integrated research strategy evolve to ensure the likelihood that a multifaceted exercise prescription is established to maintain the functional integrity of the various components of the musculoskeletal system when they are challenged by the debilitating environment of weightlessness.

MEDICAL POLICIES AND REQUIREMENTS DOCUMENT

Prepared by Medical Policy
Board

Revision Three, August 30, 1996

7.0 Rationale for Selection of Monitoring and Countermeasure Modalities

Exposure to microgravity and the space environment has important medical and health implications, including bone loss (matrix and mineral), increased cancer risk, neurovestibular changes, orthostatic hypotension, etc. Because of mission costs and the risks inherent in human space flight, as well as other factors, it is imperative that crew members function at peak performance levels at all times. Clearly, based on these factors, certain minimal requirements for crew performance exist. Crew members must remain physically and mentally healthy and physiologically capable of performing all mission tasks. The flight deck crew (for U.S. Shuttle missions) must be able to maintain orthostasis and perform the critical operations required to fly the Shuttle, while sitting upright, during entry. All crew members must be capable of egressing the spacecraft unaided in an emergency. In addition, astronauts must have some degree of career longevity, with recovery, rehabilitation and repair capabilities available upon their return from space flight. For these reasons, we must be able to provide preventive measures, monitor the health of the crew both on the ground and inflight (human performance and environmental effects are evaluated periodically by monitoring both the sustained physiological changes during space flight and the spacecraft environment), provide appropriate medical care when needed, and prescribe effective countermeasures to prevent or ameliorate the debilitating effects of exposure to microgravity.

7.1 Baselining Current Knowledge and Available Countermeasures

To date, life sciences research has yielded countermeasures addressing some of the health issues listed above. Tables 1-8 and Charts 1-4 (found in Appendix 3) contain a basic outline of the current status of our knowledge of physiological changes, inflight and postflight, and available countermeasures, for those body systems of primary concern for health maintenance (i.e., those systems for which adaptation to microgravity does not necessarily present a risk to the person while in space, but can be debilitating upon return to Earth: the cardiovascular, muscular, skeletal, and neurosensory/neuromotor systems. The responses of the remainder of the body systems are not yet fully understood and research is not yet complete. A summary of prioritized research questions can be found at Appendix 4.

7.2 Developing and Applying New Countermeasures

The NASA MPB is ultimately responsible for approving what countermeasures are actually applied. This is done via the creation of Level 1 Policy Statements. Level 2 documents regarding the interpretation and application of the MPB policies, as well as Level 3 documents discussing, in detail, implementation methodologies, protocols, flight rules, etc., are the responsibility of the AMB at JSC. Appendix 5 provides a summary of what countermeasures are currently accepted and approved by the MPB and also displays those countermeasures which are under consideration but have not yet been fully validated from a scientific and clinical standpoint.

7.3 Selecting Countermeasure Protocols

1) General concepts - Planned health monitoring modalities and responses to countermeasures will be conducted at regular intervals (no more than three times), in conjunction with the physical health evaluations prior to the first mission, to establish a baseline normative data base against which postflight recovery will be implemented. During subsequent missions, depending on the clinical judgment of the crew surgeon, only select protocols might be implemented if adequate baseline data already exists. In the postflight phase, guided by clinical manifestations and physical evaluations, only those protocols will be implemented which are required for diagnostic purposes or to guide the rehabilitation process and the return to flight duties. Hydration with an orally consumed isotonic solution, during LBNP and exercise protocols, is required to minimize orthostatic responses and reduce the risks of renal calculi.

9.0 Definition of Terms

The following definitions are provided to clarify the context within which they were developed. The adoption of clearly enunciated principles minimizes chances for misinterpretation of the requirements contained within this document.

4. <u>Countermeasures</u> - application of procedures and/or therapeutic means to prevent or minimize adverse health and medical events. These can be divided into the following categories:

4a. <u>Primary Prevention</u> - eliminating the adverse or harmful agent or preventing it from reaching the astronaut. Examples include: 1) the Crew Health Stabilization Program and immunizations, which protect against infections; 2) preflight medical exams to identify and correct risks; and 3) providing a gravitational substitute effect on orbit, preventing microgravity from degrading the health of the astronaut.

4b. <u>Secondary Prevention</u> - mitigating the effect of adverse or harmful agents or enhancing the astronauts ability to ward off the harmful effects of these agents. Examples include: cabin air and water purification, exercise to counteract the microgravity effect, and fluid loading and antigravity suits to minimize orthostatic intolerance. Astronaut selection standards might also be considered a form of secondary prevention.

4c. <u>Tertiary Prevention</u> - to minimize the effect of adverse or harmful agents on the crew once maladaptation, disease, or injury has been identified. The postflight rehabilitation program is a good example of such restoration, hopefully leading to treatment and issuance of waiver for continued flight duties with periodic observation.

Appendix 3

Monitoring and Countermeasures Tables and Charts

<u>BONE AND CALCIUM STATUS</u> (Table 5)

Physiological Parameters--Hypercalcemia, hypercalciuria, altered GI absorption, skeletal architecture, altered hormone levels, back pain.

BONE AND CALCIUM COUNTERMEASURES UNDER CONSIDERATION

Hypercalcemia--fluid, diet (currently accepted practices [needs adjustments based on absorption and metabolic research information overview]) both inflight and postflight
Hypercalciuria--fluid, diet (currently accepted practices [needs adjustments based on absorption and metabolic research information overview]) both inflight and postflight
Skeletal architecture--exercise (intensive resistive exercise[requires further research into protocols and type of hardware]) inflight, rehab postflight
Back pain--posture control (intensive resistive exercise[requires further research into protocols and type of hardware]) inflight, rehab postflight

NUTRITION

Monitoring

1. Pre/postflight
    a. Weight (body mass)
    b. Selected hematologic and clinical chemistry studies

2. Inflight
    a. Body mass measurement weekly
    b. Questionnaire

Inflight diet

1. Adequate calories based on individually calculated needs
2. Adequate variety and selection of foods
3. Vitamins
4. Fiber

1. Balanced Diet a. calories b. fat c. protein d. carbohydrates e. fiber	1. General metabolism 2. Food Stuff absorption and utilization

SKELETAL SYSTEM (BONE AND CALCIUM (Chart 3)

Monitoring (Long Duration Missions)

1. Baseline monitoring:
    a. Two imaging studies (two years apart) to establish fast or slow type of bone loss.
2. Preflight monitoring:
    a. Imaging to evaluate skeletal status (if indicated).
    b. Renal stone risk profile
3. Inflight monitoring:
    a. Non-invasive bone density measurement (ultrasound of skull and trochanter).

  - b. Body mass measurement

4. Postflight monitoring:
   - a. Imaging ASAP and as clinically indicated for follow-up.

Countermeasures

1. Rehabilitation (postflight)

NUTRITION

Monitoring (Short- and Long-Duration Missions)

1. Pre/Postflight monitoring:
   - a. Weight (body mass)
   - b. Selected hematologic and clinical chemistry studies
2. Inflight monitoring:
   - a. Body mass measurement weekly
   - b. Questionnaire

Inflight Diet

1. Adequate calories based on individually calculated needs
2. Adequate variety and selection of foods
3. Vitamins
4. Fiber

Appendix 4

Research Questions

A. Health Maintenance

Skeletal System (Bone and Calcium

1. Appropriate exercise countermeasures for bone preservation
2. Use of medications as a countermeasure for hypercalciuria and bone loss
3. Hormonal status and space loss interactions
4. Bone/skeletal architecture
5. Mineral absorption (oral) and general metabolism

Nutrition

1. How are nutrients absorbed and metabolized?
2. What is the optimal diet composition to maintain muscle and bone mass?
3. What are the optimal vitamins and trace elements in the prevention of the adverse effects of microgravity?

B. Medical Care

Appendix 5

Categorization of Countermeasures

Operational and Research Status

SKELETAL SYSTEM (BONE AND CALCIUM)

Operational

To Be Further Refined (Research)

1. Exercise (loading)
2. Medications
3. Diet

NUTRITION

1. Balanced diet
    a. calories
    b. fat
    c. protein
    d. carbohydrates
    e. fiber

1. General metabolism
2. Food stuff absorption and utilization

HUMAN RESEARCH FACILITY
SCIENCE AND TECHNICAL REQUIREMENTS DOCUMENT

JANUARY 29, 1996

3.0 SCIENCE REQUIREMENTS

The science requirements for the HRF have been derived from the science needs of the communities listed in Subsection 3.1 and the Discipline Science Plans listed in Appendix A. There are several research objectives that are common to all disciplines and are therefore of high priority. The common objectives include

- Determine the rate, extent, and time course of the effects of exposure to microgravity on all human physiologic systems (and determine if these effects are reversible after return to Earth)
- Understand the underlying mechanisms responsible for the physiological adaptation to space flight, including any variations between gender and age groups.
- Identify the potential risks of microgravity exposure to humans for both health and performance in space and on the ground and develop effective countermeasures.
- Use microgravity and other unique characteristics of the space environment to enhance our understanding of fundamental biological processes on Earth.

3.1 DISCIPLINES ENCOMPASSED
3.1.3 Muscle, Skeletal and Connective Tissue

I. BACKGROUND

Long-term exposure to microgravity will most assuredly cause significant loss of muscle and bone unless effective countermeasures can be developed. The severity and significance of these changes are unknown at this time. The limited data obtained from the U.S. (Skylab era - 28, 56, and 84 days) and the Soviet/Russian flight experience (Soyuz/Mir flights to 15 months) do not adequately address these problems. The International Space Station (ISS) will provide flight opportunities to study the magnitudes, time courses, and mechanisms of changes in muscle, skeletal, and connective tissues and the implications for their combined system performance capabilities during long-duration flights and subsequent readaptation to l-g.

Musculoskeletal integrity is vital to successful human performance during space flight and upon return to a l-gravity (l-g) environment. Effective countermeasures to the changes in the musculoskeletal system that occur during prolonged space flight have not been employed to date. Thus, the determination of appropriate countermeasures is an important scientific objective in its own right. Musculoskeletal changes also affect the control of movement in fine motor tasks, control of posture, strenuous physical work (IVA and EVA), and responses that involve visual feedback, and perceptions of movements to be executed. Insight gained from changes to the musculoskeletal system in space may also have direct relevance to changes seen in l-g as a consequence of aging, and recovery from trauma and surgery.

3.1.3.2 Connective Tissue (CT including soft CT and bone)

II. SCIENCE OBJECTIVES

1. To determine the time of adaptation of bones and tendons that have different functions and loading histories in microgravity (and upon return to 1-g).
2. To determine the in-vivo biochemical assessments of bone turnover, electrolytes, and hormones that reflect changes in connective tissue metabolism in a microgravity environment.
3. To determine the dose-response relationship between loads of different characteristics and bone mass.
4. To develop appropriate countermeasures to maintain connective tissue structure and bone mass during prolonged exposure to microgravity.

III. FUNCTIONAL REQUIREMENTS

l. Capability to accurately quantitate the loss in bone and tendon quality and mass that occurs during space flight (e.g., ultrasound, bone densitometry).
2. Capability to monitor blood and urine concentrations of proven biochemical markers of bone turnover and the electrolyte and hormonal changes that substantiate these changes.
3. Capability to collect, store, and prepare tissues inflight and return to Earth (e.g., freezer, N2, chemical fixing, centrifuge)
4. Capability to generate and measure different loading profiles to the axial and peripheral skeleton during spaceflight at rest and during exercise (e.g. LEAP, dynamometer, treadmill, bicycle).

3.1.4.3 Endocrinology and Renal Function

I. BACKGROUND

Exposure to microgravity profoundly affects fluid homeostasis. The headward shift of fluids observed in either real or simulated microgravity results in decreased volume of body fluid compartments and an apparent shift of fluid from the extracellular to intracellular compartment. Reduced fluid volume probably contributes to cardiovascular deconditioning during space flight and orthostatic intolerance after landing. The development of successful countermeasures to these, and perhaps other undesirable effects, will be based on the understanding of the sequence of physiologic events during adaptation to weightlessness and readaptation to Earth's gravity.

The physiological changes associated with space flight contribute to an altered urinary chemical environment. Inflight changes previously observed include decreased urine volume and increases in urinary calcium, phosphate, potassium and sodium excretion, all of which could potentially exaggerate the risk of renal stone formation. The formation of a renal stone could have severe health consequences for the crew member.

Description of the response of the endocrine system to space flight has come from comprehensive measurement of hormones in the blood and urine of crew before and after flight as well as during flight. However, little information has been obtained from flight or ground based investigations regarding reproductive function. In short Shuttle missions, as in 7 day bedrest studies, female reproductive hormones and their cycles do not appear to be greatly affected. The effect of more prolonged exposure is completely unknown. Therefore, for prolonged missions, reproductive regulation and function need to be addressed.

II. SCIENCE OBJECTIVES

1. Describe and understand the effects of exposure to microgravity on endocrine function. Specifically, the impacts on hormonal regulation of fluid homeostasis (including drinking behavior) and calcium bone balance are essential.
2. Determine the effects of space flight on renal function, specifically as it relates to regulation of body fluid volume.
3. Quantitate the pre-, in-, and postflight risk of renal stone formation associated with spaceflight.
4. Determine the influence of environmental factors (diet, fluid, exercise, and medication use) on the risk of renal stone formation.
5. Define and evaluate countermeasure(s) to minimize the risk of inflight renal stone formation.
6. Assess the consequences of short and long term exposure to space flight on female reproductive endocrine cycle.

III. FUNCTIONAL REQUIREMENTS

1. Capability to measure fluid compartments and renal function during space flight.
2. Capability to accurately quantitate the urinary risk factors associated with renal stone formation.
3. Capability to collect, preserve/store, and analyze blood inflight for measurement of endocrine and biochemical profiles.
4. Capability to collect, measure, aliquot, preserve/store, and analyze urine inflight. This capability should include both male and female urine collection devices.
5. Capability to monitor diet, fluid intake, exercise, and medication use by crew members during flight.

ACSM Position Stand on Osteoporosis and Exercise

Med. Sci. Sports Exerc., Vol. 27, No. 4. pp i-vii, 1995

Summary

American College of Sport Medicine Position Stand on Osteoporosis and Exercise. Osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk. Both men and women are at risk for osteoporotic fractures. However, as osteoporosis is more common in females and more exercise-related research has been directed at reducing the risk of osteoporotic fractures in women, this Position Stand applies specifically to women. Factors that influence fracture risk include skeletal fragility, frequency and severity of falls, and tissue mass surrounding the skeleton. Prevention of osteoporotic fractures, therefore, is focused on the preservation or enhancement of the material and structural properties of bone, the prevention of falls, and the overall improvement of lean tissue mass. The load-bearing capacity of bone reflects both its material properties, such as density and modulus, and the spatial distribution of bone tissue. These features of bone strength are all developed and maintained in part by forces applied to bone during daily activities and exercise. Functional loading through physical activity exerts a positive influence on bone mass in humans. The extent of this influence and the type of programs that induce the most effective osteogenic stimulus are still uncertain. While it is well-established that a marked decrease in physical activity, as in bedrest for example, results in profound decline in bone mass, improvements in bone mass resulting from physical activity are less conclusive. Results vary according to age, hormonal status, nutrition, and exercise prescription. An apparent positive effect of activity on bone is more marked in cross-sectional studies than in prospective studies. Whether this is an example of selection bias or differences in the intensity and duration of the training programs is uncertain at this time. It has long been recognized that changes in bone mass occur more rapidly with unloading than with increased loading. Habitual inactivity results in a downward spiral in all physiologic functions. As women age, the loss of strength, flexibility, and cardiovascular fitness leads to a further decrease in activity. Eventually older individuals may find it possible to continue the types of activities that provide an adequate load-bearing stimulus to maintain bone mass. Fortunately, it appears that strength and overall fitness can improved at any age through a carefully planned exercise program. Unless the ability of the underlying physiologic systems essential for load-bearing activity are restored, it may be difficult for many older women to maintain a level of activity essential for protecting the skeleton from further bone loss. For the very elderly or those experiencing problems with balance and gait, activities that might increase the risk of falling should be avoided. There is no evidence at the present time that exercise alone or exercise plus added calcium intake can prevent the rapid decrease in the immediate postmenopausal years. Nevertheless, all healthy women should be encouraged to exercise regardless of whether the activity has a marked osteogenic component in order to gain the benefits that accrue from regular exercise. Based on current research, it is the position of the American College of Sports Medicine that: 1. Weight-bearing physical activity is essential for the normal development and maintenance of a healthy skeleton. Activities that focus on increase muscle strength may

also be beneficial, particularly for nonweight-bearing bones. 2. Sedentary women may increase bone mass slightly by becoming more active but the primary benefit of the increased may be avoiding the further loss of bone that occurs with inactivity. 3. Exercises cannot be recommended as a substitute of hormone replacement therapy at the time of menopause. 4. The optimal program for older women would include activities that improve strength, flexibility, and coordination that may indirectly, but effectively, decrease the incidence of osteoporotic fractures by lessening the likelihood of falling.

Scientific Prerequisites
for the
Human Exploration of Space

National Academy Press
Washington, D.C. l993

Critical Research Issues

The lack of scientific data in some areas leads to unacceptably high risks to any program of extended space exploration by humans. These critical research issues concern those areas that have the highest probability of being life threatening or seriously debilitating to astronauts and that are thus potential “show stoppers” for human exploration. The areas in which additional scientific information must be obtained prior to extended exploration of space by humans include the:

6. Detrimental effects of reduced gravity and transitions in gravitational force on all body systems (especially the cardiovascular and pulmonary systems) and on bones, muscles, and mineral metabolism, together with possible countermeasures;

Optimal Performance Issues

The second category of research includes issues that, based on current knowledge, do not appear to pose serious detriments to the health and well being of humans in space. They could, however, result in reduced human performance in flight or on planetary surfaces and, thus, in a less than optimal return from the mission. Some of these issues may become critical research issues relative to long-term human space-flight and return to terrestrial gravity following extended flights, or when extraterrestrial habitation is considered.

BONE DEGENERATION AND MUSCLE ATROPHY

Microgravity has major, potentially dangerous effects on human physiology. Extensive research is required to understand the responses of humans to microgravity and to assess their implications for long-duration space flight. Because a small number of astronauts and cosmonauts have survived long-duration missions in low Earth orbit, there is a false perception that there is no need to be concerned about health-related issues when contemplating interplanetary voyages. According to the Committee on Space Biology and Medicine, "Based on what we know today, this assumption of continued success cannot be rigorously defended. The committee continued, "If this country is committed to a future of humans in space, particularly for long periods of time, it is essential that the vast number of uncertainties about the effects of microgravity on humans and other living organisms be recognized and vigorously addressed. Not to do so would be imprudent at best—quite possibly, irresponsible.’’

The bone degradation (osteopenia) and muscle atrophy that occur in a microgravity environment are severe hurdles to an extended human presence in space. The primary risk is to the functioning of the musculoskeletal system upon reexposure to planetary gravity**.** At present, our under standing of the causes of space-induced osteopenia and muscle atrophy is inadequate to devise effective countermeasures to be taken on long-duration space missions. Also lacking are data on the temporal sequence of bone remodeling and muscle atrophy in prolonged exposure to microgravity and the ways in which these processes may depend on other risk factors such as age, gender, race, or nutrition. Without such data, we cannot be confident that a prolonged microgravity mission such as a Mars flight would not lead to irreparable musculoskeletal damage. Such damage could both impair the effectiveness of crew members during their stay on Mars and pose serious problems upon their return to Earth. There is also the possibility that some bone demineralization will occur during prolonged flight in spite of countermeasures. If so, astronauts en route to Mars might be at risk for bone fracture with mild trauma and for the formation of kidney stones.

There is great depth and breadth to current research on osteopenia, muscle atrophy, and their underlying causes, thanks to sponsorship by the National Institutes of Health. These studies have concentrated on the problems of bone metabolism in relation to aging, menopause, endocrine disorders, poor nutrition, immobilization, and extended bed rest. A major effort is now needed to develop parallel studies to acquire basic knowledge about these problems as they occur in microgravity and to begin devising appropriate countermeasures. A critical factor in such studies must be the use of appropriate animal models and the development of computational and experimental methodologies to test and validate mechanisms of bone remodeling and muscle conditioning. In addition, the development of suitable in vitro systems using bone and muscle tissue cultures should be undertaken.

One approach to counteracting the physiological effects of microgravity is to subject organisms in space to artificial gravity. Although such an environment could correct bone degeneration, muscle atrophy, and other changes due to microgravity, it could also exacerbate other effects not now perceived to be major problems. Head movements made in a spinning environment or Coriolis effects can lead to disturbing vestibular sensations and motion sickness. Changes in gravity experienced when moving to different parts of a spinning spacecraft or when changing the spin rate might induce symptoms of disequilibrium.

A comprehensive program is required to (1) determine the gravity threshold required to reverse or prevent the deleterious effects of microgravity and (2) evaluate the effects of centrifugation on behavior and/or sensorimotor function. Part of the required research could be accomplished by using human surrogates, including nonhuman primates, on a dedicated centrifuge in low Earth orbit. Studies of human responses to spinning will require a centrifuge of sufficient dimension to accommodate humans. An alternative strategy would be to investigate the use of rotating tethered spacecraft to provide artificial gravity. It is possible that the detrimental vestibular effects of spinning can be eliminated if the tethers are sufficiently long.

Even assuming an optimistic schedule for lunar operations or space station activation, the relevant life-sciences knowledge developed from them will probably not be available before the beginning of the second decade of the 21st century. This implies a substantial technical risk in any program of Mars exploration that relies on a comprehensive solution to problems of human adaptation to microgravity. The prudent alternative is to carry forward, during conceptual design phases, alternatives providing for artificial gravity (as recommended in a National Research Council report) during the cruise flight phase, and possibly in Mars orbit as well. If satisfactory countermeasures are confidently identified during a vigorous and rigorous 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 design, construction, and operation of rotating spacecraft may pose formidable technical challenges. Nonetheless, all investments in the program will otherwise be hostage to a favorable outcome in the human adaptation issue. In the view of CHEX, the Synthesis Group's report erred ab initio in discarding consideration of artificial-gravity scenarios in its four architectures. Indeed, the provision of artificial gravity may well prove to be an architectural variable of more fundamental importance than the thematic differences between alternative mission emphases presented in the report of the Synthesis Group.

Conclusions

The Committee on Human Exploration finds that a program for the exploration of the Moon and Mars by humans offers both challenges and opportunities for the participation of the scientific community. Foremost is the fact that particular, enabling scientific information is required if a Moon/ Mars program is ever to succeed in one of its prime goals, the expansion of human presence and human activity beyond Earth orbit into the solar system. This will remain the case even if a major Moon/Mars program is not initiated for 5 years or 25 years. The information that the committee deems critical is concerned largely with aspects of space biology and medicine and associated characteristics of the radiation environment. This in itself is not a new finding; recognition of the need for such information has been building over the past 30 years with little progress on solutions. What is required is that NASA (and other agencies involved in implementing a human exploration project) make a long-term commitment to sponsoring a rigorous, efficient, high-quality research program on the ground and in space. The resources required will be significant and challenge NASA to structure, market, implement, and ultimately manage an adequate plan.

To enable long-duration human flight to, and operations on, the Moon and Mars, we must obtain critical relevant data. However, we must also consider ab initio that the enabling research has a purpose above and beyond the simplistic, but prime, goal of achieving human presence and implied elementary survival. If a Moon/Mars program is to accomplish more than merely establishing a human presence in space, then achieving the program's yet-to-be-established specific goals and objectives demands that human performance and "pre-presence" preparation be optimized. This imperative places additional weight on the acquisition of scientific data on, for example, the distribution of potential lunar resources, details of the atmosphere of Mars, and information on the physical, chemical, and biological properties of the Martian surface.

Science permeates all aspects of human exploration, no matter which architecture is finally selected and regardless of which set of candidate goals and objectives evolves. The involvement of the scientific community is needed to help set the goals for purely robotic missions, to analyze both scientific and engineering data, to structure appropriate tasks for humans, and to assist in the optimal integration of human and robotic activities. This pervasive requirement for scientific input mandates that the piloted spaceflight community develop a new understanding of and attention to the conduct of space science. It simultaneously requires that the scientific community interact constructively with those charged with implementation of a Moon/Mars program. In fact, success will require a technical and programmatic approach that eliminates the historical dichotomy between the "manned" and "unmanned" spaceflight programs.

MUSCULOSKELETAL DISCIPLINE SCIENCE PLAN, 1991
Space Physiology and Countermeasures Program
Life Sciences Division, NASA, Washington, DC.

Flight research, which also uses both human and animal subjects, primarily addresses the questions of "What happens to the musculoskeletal system during weightlessness?" and "What effects do certain countermeasures have?" These flight data have been obtained from subjects on both U.S. and U.S.S.R. missions. Countermeasures that have been examined on the ground and/or in flight include various types and prescriptions of exercise, electrical stimulation, pharmacology, changes in nutrition, and muscle stretch. Artificial gravity is a potential countermeasure for musculoskeletal effects of space flight.

1.3 GOALS AND OBJECTIVES

1.3.1 Goals

The overall goals of the NASA Musculoskeletal Discipline Research Program are to:

- Ensure adequate physiological and performance countermeasures

The achievement of these goals is predicated on specific objectives concerned with understanding the mechanisms whereby the organism, tissue, cells, organelles, and extracellular matrix of muscle, bone, and connective tissue

- achieve and maintain Earthbound homeostasis

- function in either a microgravity environment or under conditions of non-weightbearing

- undergo adaptive changes in structure and function in response to prolonged exposure to a microgravity environment

- respond to a variety of countermeasures (mechanical, hormonal, pharmacologic) designed to maintain normal structure and function in the face of prolonged exposure to a microgravity environment as undergo readaptation to Earth’s gravity.

1.3.2 Objectives

The specific objectives leading to the attainment of the goals of the research program are to:

- Develop and verify ground-based human and animal models to study musculoskeletal changes.

This plan incorporates recommendations from reports by the Committee on Space Biology and Medicine (Goldberg), the NASA Life Sciences Strategic Planning Study Committee (Robbins), and the Federation of American Societies for Experimental Biology (FASEB) (see List of References).

Current knowledge about physiological changes associated with short-term and long term space flight is summarized in Appendix 1, which is from Space Physiology and Medicine. 2nd edition, by Drs. Nicogossian, Leach Huntoon, and Pool.

Final Report Phase III: Research Opportunities in Bone Demineralization

NASA Contractor Report 3795, April 1984

SUMMARY

Bone demineralization and negative calcium balance have been reported consistently as a physiological response to space flight. Additionally, changes in calcium metabolism have been observed that may be associated with bone loss and a possible increased risk of fracture. The changes include increased fecal loss of calcium and hypercalciuria with a possible change in potential for formation of calcium-containing renal stones. In United States space flights as long as 3 months and Soviet flights as long as 7 months, neither loss of bone mineral nor the resultant hypercalciuria has been associated with impaired functional capacities of astronauts. However, concern for the health, effectiveness, and safety of space crews during and following extended or repeated space flights requires that gaps in knowledge of bone demineralization be identified and priorities for future research efforts be indicated.

The processes underlying bone loss in man during space flight are poorly understood. Histomorphometric studies of bone changes in rats flown aboard Cosmos biosatellites suggest that periosteal bone formation is inhibited and endosteal bone resorption is unchanged in weight-bearing bones in this species. Information concerning bone loss in weightlessness has also been obtained in ground-based studies of suspended rats, immobilized monkeys, and normal human volunteers during bed rest. Comparison of histomorphometric changes in bone of rats during space flight with bone changes in the suspended rat model and with bone changes in a monkey model indicates that some changes are similar for these models despite differences in bone growth and remodeling systems of the two species. Histomorphometric studies of bone changes in man have not been done during space flight or uncomplicated bed rest.

Evidence for loss of bone mineral in man during space flight has been supplied by metabolic balance studies and by non invasive measures of bone density changes. These studies indicate an overall difference between anabolic and catabolic processes but provide little information concerning the changes occurring in bone during weightlessness. Metabolic balance studies in man during bed rest have shown changes in calcium balance generally similar to those of astronauts during space flight. Increased urinary and fecal losses of calcium have been reported in each situation. It has not been determined whether the fecal losses represent increased endogenous losses or decreased intestinal absorption of calcium. Noninvasive measures of bone density indicate that preferential loss of calcium from weight-bearing bone (os calcis) is common to space flight and bed rest.

Studies of changes in levels of calcitropic hormones (parathyroid hormone, vitamin D, and calcitonin) during space flight and bed rest do not consistently indicate changes of a magnitude that would ordinarily be associated with increased mobilization of bone. It is difficult to draw conclusions from these data, because at the time the measurements were made in space flight and in published reports of bed-rest studies, assays for a number of hormones were not well refined. Plasma levels and urinary excretion of cortisol are increased in man during space flight and adrenal glands are enlarged in rats following

flights of the Cosmos biosatellites. However, urinary excretion of cortisol is not increased during bed rest. General systemic effects of endocrine agents cannot readily explain the local and preferential demineralization of weight-bearing bones. However, since physiologic responses during weightlessness differ from those under gravity, it may be possible that responses of bone cells to normal levels of endocrine agents in weightlessness differ from responses on the ground. This may be particularly evident in weight-bearing bones that lack their normal gravity-related stimuli.

Trials of countermeasures to prevent bone demineralization have been conducted in crews during space flight and, more extensively, in ground-based studies of human subjects during bed rest. Exercise during space flight has not completely reversed negative calcium balance or hypercalciuria. However, there is some evidence that use of a treadmill during space flight may have moderated loss of os calcis mineral. In Soviet flights exercise has reportedly been associated with decreased calcium loss. A number of levels of weight-bearing and/or exercise regimens have been tested in ground-based bed-rest studies in the United States in an effort to determine the amount of physical stress necessary to prevent calcium loss. Of all the protocols evaluated, only controlled ambulation on a prescribed course for 4 hours completely alleviated negative calcium balance. Dietary intervention (supplementation of fluoride or supplementation of calcium and phosphorus) did not reverse hypercalciuria or negative calcium balance over a long period of bed rest. A combination of calcium and phosphorus supplements, longitudinal compression and administration of synthetic salmon calcitonin was partially effective for a shorter period; however, administration of synthetic salmon calcitonin or longitudinal compression alone was not effective. Diphosphonates (EHDP or clodronate) administered to normal subjects during bed rest have been the most effective pharmacologic agents tested. How ever, side effects of these particular compounds contraindicate their further use.

The following report comprises an overview of bone demineralization during space flight, observations of the ad hoc Working Group on the NASA Biomedical Research Program in Bone Demineralization and experiments related to bone loss planned for Spacelab flights, and suggestions for further research. The observations of the ad hoc Working Group focused upon the following topics: (1)pathogenesis of bone demineralization, (2) potential for occurrence of renal stones consequent to prolonged hypercalciuria, (3) development of appropriate ground-based and inflight models to study bone demineralization, (4) integration of research efforts, and (5) development of effective countermeasures. Priorities for further research are indicated.

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