Bone and Connective Tissue Discipline Report on Countermeasures

I. Nature of the Problem

Bone mass, mineral metabolism and connective tissue changes occur in humans during space flight. Physiologic changes occur as early as one week and continue for more than a year in microgravity. These changes may limit long duration spaceflight if the changes harm space faring individuals either during long duration stays in space, on immediate return to earth or other planetary bodies, or become a "career" hazard which could accelerate the "aging" process. NASA must establish a program to minimize or prevent the changes and/or establish proven rehabilitation programs to restore the human space traveler to their preflight physiologic state. The well documented alterations or deficits reported in humans are listed as follows along with potential problems that may occur to the individuals involved:

1. Bone/mineral loss occurs when body mass is lost. Maintaining body mass appears to be important in maintaining overall bone mass. However, site-specific bone changes are observed even when body mass is maintained.

Concerns include osteoporotic fractures and: decreased bone strength, decreased muscle and strength performance, decreased ability to maintain upright balance with falls resulting in bone fractures.

2. Urinary calcium increases rapidly to approximately 100% above preflight levels, plateauing after 30 days of flight and remaining above the preflight baseline for the duration of the flight..

Concerns include increased risk of kidney stones.

3. Progressive fecal calcium loss may occur; indications of such a change were reported during the Skylab IV mission, indicating that at least over 84 days of spaceflight either gastrointestinal (GI) calcium absorption is continuing to decline, calcium secretion into the GI tract is increasing, or both.

Concerns include decreased GI absorption of other minerals and nutrients related to the changes in calcium metabolism.

4. Calcium balance reaches a nadir of ~200 mg/d within 2 months of continuous spaceflight.

Concerns include bone loss and depletion of calcium which is critical for many physiological functions. If GI absorption of calcium is suppressed and renal excretion of calcium continues to be elevated during spaceflight, then calcium and bone loss over long duration spaceflights could be mission limiting.

5. Elevation in serum calcium occurs during space flight, although the values are within the normal clinical range.

Concerns include the risk of hypercalcemia during periods of dehydration or illness and the resultant potential for metastatic calcification, and brain and heart dysfunction.

6. Decreased levels of systemic calciotropic hormones may occur.

Concerns include decreased absorption of calcium from the gut, increased calcium excretion through the kidney, and a skeletal system that is metabolically sluggish possibly causing delayed readaptation postflight and depletion of calcium stores inflight.

7. DEXA scans show bone loss in the lower spine and hip, averaging about 1.2% loss per month of space flight at these sites. Similar losses in the posterior elements of the vertebrae were shown using CT technology. Muscle atrophy may occur at the sites of bone loss. No changes have been reported in the arms and upper torso.

Concerns include potential balance and locomotion problems with fractures of weight-bearing bones upon entry into a higher gravity environment.

8. Height increases during space flight which may be related to either an increase in the size of the intervertebral discs or a decrease in the curvature of the spine.

Concerns include physical changes to the intervertebral discs which may increase the risk of rupture, back pain and neurologic complications. These changes might be potential recovery risks both for the short term, i.e. immediate on return to a planetary body or long term i.e. increased “aging”.

9. Inflight exercise may help ameliorate specific bone loss, e.g. the calcaneus, but has not successfully prevented bone loss or prevent the urinary calcium increases.

Concerns include the lack of effectiveness of the type and amount of activity currently prescribed; in fact, strenuous exercise which does not properly load the musculoskeletal system could even exaggerate bone loss unless dietary intake is adequate.

10. The time course for recovery of bone mass to preflight levels is still not known although preliminary data suggest that recovery takes up to 2 years. Serum and urinary calcium appear to normalize rapidly following space flight.

Concerns include the possibility that trabeculae once lost may not be replaceable leading to accelerated “aging” and decreased bone strength. Also, multiple missions might compound the bone loss.

II. Countermeasures to the Problem.

Successful countermeasures for maintaining calcium/bone/connective tissue homeostasis during long-duration space flight are dependent upon an appropriate diet and an inflight exercise regime that maintains muscle and bone mass. Nutritional requirements have not been established for microgravity environments. It is possible that substantial changes in dietary intakes are required in space compared to earth. Additionally current Mir exercise programs have been unsuccessful in inhibiting the flight related bone loss.

Many factors associated with space flight, in addition to microgravity and/or changes in physical loading forces, may affect skeletal adaptation and calcium homeostasis. Prior physical fitness and the predominate type of exercise performed may influence initial bone mass and 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 by the body, which may be used for bone matrix synthesis. Finally dietary calcium, other necessary minerals, and adequate vitamin D will affect bone mineral deposition in new bone and the rate of resorption in older bone. Therefore diet is a critical component of bone/mineral metabolism/connective tissue responses. Unless adequate diets can be provided to maintain body mass and to minimize mineral excretion, whole body mineral loss will be exaggerated due to diet. Increases in dietary calcium during space flight above a yet unknown quantity are probably not necessary and may be contraindicated if increased urinary and blood calcium occur. Microgravity-induced 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 and to develop either countermeasures to prevent it or successful rehabilitation programs.

From a hormonal perspective there is strong evidence to suggest that the mobilization of calcium from the skeleton alters the PTH-vitamin D axis. This alteration ultimately results in decreased intestinal calcium absorption and the continual removal of calcium from the bone to satisfy the body’s calcium requirements for its metabolic functions. When considering the calcium intake of astronauts, this issue needs to be carefully considered. 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 including a feeling of well being. It is unclear at the present time if the use of the vitamin D hormone (calcitriol) to enhance the efficiency of intestinal calcium absorption would be wise. Although calcitriol will definitely enhance intestinal calcium absorption, any decrease in bone formation would minimize the ability of the bone to use this calcium. If less calcium goes into bone, then the increased absorption of calcium into the blood can increase the risk for kidney stones, hypercalcemia and soft tissue calcifications. Supplementation of the diet with calcitriol to enhance the efficiency of intestinal calcium absorption during inactivity without causing other problems has not been validated.

A variety of other hormones could impact both calcium and bone metabolism. Glucocorticoids can significantly alter calcium and bone metabolism. Strong evidence suggests that 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. There may be other hormonal factors such as IGF and its binding proteins that could be altered in microgravity and this requires further investigation. Other local bone factors which control bone turnover have not yet been studied in humans during space flight and it is unknown if the changes in these factors could cause or contribute to the bone atrophy.

III. Concerns

NASA does not have a required preflight fitness level. "Human exploration in space requires the ability to maintain crew health and performance in spacecraft, during extravehicular activities, on planetary surfaces, and upon return to Earth." (Strategic Considerations for Support of Humans in Space and Moon/Mars Exploration Missions, Vol 1, Page 1, NASA Advisory Council, Aerospace Medicine Advisory Committee, June 1992). If the goal of the human flight program is to assure health, productivity, and safety of the crews both in space and upon return to a gravity environment, it may not require maintaining preflight physical status.

One valid concern is the apparent focus of many recommendations on establishing preflight, and maintaining inflight, an elite physical status. The recommendations have been correctly based on what appears to be effective on Earth, i.e., an increase in bone and connective tissue mass such that one can afford to lose some mass over time. However, these recommendations may be counterproductive for spaceflight. The establishing of an elite physical fitness status may increase the metabolic requirements of an individual and make that individual more susceptible to changes that occur under conditions of decreased biomechanical loading. The unique environment of space requires unique thoughts and countermeasures that may be different from those that would be recommended for individuals remaining on Earth. For example, swimming might provide better preparation than jogging since the muscles used and motions learned will be similar to those used inflight. Yet, jogging or high impact loading at 1G, that is often suggested for preflight training, produces loads that are virtually impossible to reproduce inflight with available exercise equipment. The Russians provide individual trainers for their cosmonauts and recommend swimming for preflight conditioning.

Caloric intake of Shuttle astronauts appears to be significantly less than their estimated energy expenditure. This could adversely affect anabolic processes integral to bone remodeling, as well as net acid excretion and calcium balance. Sodium intake in astronauts has been reported to be 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, on the other hand, appears to be very close to the recommended daily intake, and it 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 the limited studies to date, increased urinary calcium and sulfate losses may reflect increases in net acid excretion which could be moderated by dietary alkalinization.

Few data are available that define the mechanisms associated with the changes in mineral mass/bone loss/calcium homeostasis during spaceflight. Data are required to determine if dietary sodium restriction or dietary alkalinization might be effective. Also, preflight conditioning and changes in skeletal loading levels preflight might be helpful. If diet and preflight conditioning are not effective in minimizing the changes in bone/calcium/connective tissue, then drug therapy might be implemented. However, most drugs that are effective in inhibiting bone resorption are incorporated into the bone mineral and may have long-lasting effects. It may be preferable to maintain musculoskeletal mass and integrity as a system rather than provide countermeasures effective for only muscle or only bone. The musculoskeletal changes must be minimized if crewmembers are to be able to function effectively upon return to Earth or when they land on other planets.

IV. Recommendations

1) NASA needs to review its current dietary protocols, considering diets that minimize calcium and nitrogen loss. Specific recommendations are delineated in Appendix C.

2) Preflight conditioning and appropriate onboard exercises are recommended and would be similar to those recommended in the Skeletal Muscle Discipline section.

3) Drugs should be evaluated if the physiological countermeasures recommended above are ineffective; most available drugs have unwanted side effects and their efficacy against bone loss during space flight is not established. Certain drugs, particularly those known to increase bone formation, e.g. intermittent PTH, and/or inhibitors of bone resorption, e.g. bisphosphonates, could be evaluated for efficacy in preventing space flight induced osteopenia. .

4) NASA should investigate practical strategies for creating artificial gravity as a means to counteract bone loss.

5) Long term goals of NASA, in conjunction with the Exercise Countermeasures Program and Nutrition Program at JSC, need to focus studies toward basic and applied research that identifies the mechanisms of urinary calcium elevation, endocrine changes, bone loss, and connective tissue changes associated with spaceflight and to seek more effective countermeasures for preserving mineral mass, bone strength, and connective

tissue integrity. These studies should consider interactions of physical activity, diet, fluid shifts, pharmacological, and other factors to understand these changes.

V. Overarching issues

Nutrition and exercise that integrates activities supporting cardiovascular, vestibular and neuromotor, and musculoskeletal homeostasis were issues raised by most disciplines. In addition, the countermeasures selected should be based on crew compliance and health issues.