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2009. ISBN 978-1-60741-641-8

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NUTRITIONAL BIOCHEMISTRY OF SPACE FLIGHT

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Nova Science Publishers, Inc.
New York

Library of Congress Cataloging-in-Publication Data

Nutritional biochemistry of space flight / Scott M. Smith ... [et al.].
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-60741-641-8 (hardcover)
1. Astronauts--Nutrition. I. Smith, Scott M., 1963-
[DNLM: 1. Nutritional Requirements. 2. Space Flight. QU 145 N9764 2009]
TX361.S63N88 2009
613.202'462945--dc22 2009017392

Published by Nova Science Publishers, Inc. † New York

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PREFACE

This book is the result of a confluence of many activities that have occurred in the last several years. In late 2005, the National Aeronautics and Space Administration created the Human Research Program (HRP), based at the Johnson Space Center in Houston. The HRP held a series of workshops in 2006 to review the state of knowledge of each of the life science disciplines, of which Nutrition was one. In late 2007 and early 2008, HRP sought to document this evidence base, in a unpublished report to the Institute of Medicine. This "Evidence Book" was the largest contributor to this text, but many other efforts, large and small, made some contribution. The HRP Program Reviews in 2006 were preceded by workshops to define nutritional requirements for space flight (in 1991, 1995, and 1999), "tiger teams" to evaluate specific nutritional issues (extravehicular activity, supplement requirements; both in 2000), and extramural reviews of clinical assessment protocols (in 2003) and to define requirements and "operating bands" (in 2005), all of which contributed significantly. Beyond the management reviews and workshops, the authors' efforts to extend the medical and scientific knowledge base of food and nutrition issues for space travelers over the years has also contributed extensively.

It is our hope that this volume reflects a comprehensive review of what has been done in the initial decades of human space flight with regard to human nutrition, and a look at what needs to be known before we take the next steps of exploration.

ACKNOWLEDGMENTS

We gratefully acknowledge the expert work by Dr. Jane M. Krauhs in technical editing of this volume.

I. INTRODUCTION

The importance of nutrition in exploration has been documented repeatedly throughout history. For example, during the roughly 400 years between Christopher Columbus' voyage in 1492 and the invention of the steam engine, scurvy (vitamin C deficiency) resulted in the deaths of more sailors (> 2 million) than all other causes of death combined [66]. Since nutrients are required for the structure and function of every cell and every body system, defining the nutrient requirements for space flight and ensuring provision and intake of those nutrients are primary issues for crew health and mission success.

Unique aspects of nutrition during space travel include its role in and how it is affected by physiological adaptation to weightlessness and psychological adaptation to extreme and remote environments, and the ability of nutrition and nutrients to serve as countermeasures to ameliorate the negative effects of space flight on the human body. Key areas of clinical concern for long-duration space flight include loss of body mass (and associated inadequate food intake), bone and muscle loss, increased radiation exposure, nutrient supply during extravehicular activity, and general depletion of body nutrient stores because of inadequate food supply, inadequate food intake, increased metabolism, and/or irreversible loss of nutrients. Other body systems (such as the cardiovascular and neurovestibular systems) are also affected by space flight and may affect nutrition of space travelers, or may be a target in developing nutritional means to mitigate the effects of space flight on those systems.

The authors' aims with this book are to review the existing knowledge about human nutrition for space flight, and to point out gaps in this knowledge that need to be filled before we can have confidence that the risk of an inadequate food system or inadequate nutrition to support humans on expeditions to the Moon and Mars is as low as possible. Much of the existing knowledge is extrapolated from results of studies, known as ground-based analog studies, conducted in laboratories on Earth by exposing human subjects to one or more environmental conditions similar to those produced by space flight. Since the 1940s [138], the physiological responses of humans to bed rest have been studied [502], albeit, at first, with the goal of improving the health of patients and not space travelers. Bed rest studies have provided much of the data available from ground-based analogs of space flight. The other main source of knowledge is data from space flights: short-duration Space Shuttle missions, and longer missions on the Russian space station Mir and the International Space Station. Historical data from the Apollo missions, which had durations of 5 to almost 13 days, and the Skylab 28-, 59-, and 84-day flights are also reviewed.

II. SPACE PROGRAMS AND SPACE FOOD SYSTEMS

Before food was first consumed in the space environment, it was assumed by some that the greatest challenge of providing food in space might well be that a human would be unable to swallow and thus would be unable to eat in weightlessness. This was quickly disproved by Soviet cosmonaut Gherman Titov, who in August 1961 became the first human to consume food in space. U.S. astronaut John Glenn followed closely when, as the first American to consume food in space, he ate applesauce on the third manned Mercury mission in February 1962 [455, 504]. This began what to this day is an ongoing odyssey of space food development.

A. MERCURY (1961 TO 1963), GEMINI (1965 TO 1966), AND APOLLO (1968 TO 1972)

Early U.S. space food was highly engineered to minimize mass and volume and to prevent any possibility of food contaminating the small cabins of the earliest National Aeronautics and Space Administration (NASA) spacecraft. It consisted primarily of puréed foods in squeeze tubes, small cubed food items coated with an edible film to prevent crumbs from escaping, and freeze-dried, powdered food items. It was agreed by most that this early space food was unappetizing (Figure 1) [504].

As the NASA manned space program progressed in the 1960s toward the first Moon landing in 1969, so did the food system. The food system for the Gemini program included formulations and packaging that were designed specifically for the program [340]. Restrictions in weight and volume led to an emphasis on concentrated foods. Safety of the food system was strongly emphasized, and the testing procedures developed for Gemini signaled the beginning of the Hazard Analysis Critical Control Point (HACCP) program, which is now common practice for food safety around the world [250].

Apollo food systems introduced utensils to space food dining with the addition of the spoonbowl package. This allowed rehydrated food items to be consumed from the package with a spoon. During the Apollo program, U.S. space food systems began using thermostabilized (heat-treated) canned and pouched products. Irradiated food products also appeared for the first time during Apollo [62, 596]. Even this early in human space flight, the real challenge for space food became apparent: how to provide sufficient variety and sufficient quality to get the crewmembers to actually eat the food. Regardless of the nutritional content of the food, if it was not consumed, the crewmembers' health was at risk.

Crewmembers were returning from space flights with decreased body weight, indicating that their food consumption was inadequate [597].

Figure 1. Food kit used by Mercury astronauts. Some packets contained dehydrated food that needed water; other foods were ready to eat. A 12-inch ruler is shown for scale. Included are packets of mushroom soup, orange-grapefruit juice, cocoa beverage, pineapple juice, chicken with gravy, pears, strawberries, beef and vegetables, and other assorted foods. Photo credit: NASA.

B. SKYLAB (1973 TO 1974)

The Skylab space station (Figure 2) of the mid-1970s featured the most sophisticated food system that NASA has ever flown in space [252]. Frozen and refrigerated food items were included as part of the standard menu for the first, and to date the only, time in U.S. space food history [296]. The Skylab astronauts also had a dining table for meal consumption. Because of these advances or because of their participation in metabolic studies, or a combination of the two, the Skylab crews achieved the highest percentage of their planned energy consumption (based on World Health Organization requirements) of any U.S. crews to date.

Figure 2. An overhead view of the Skylab space station cluster in Earth orbit as photographed from the Skylab 4 Command and Service Modules (CSM) during the final fly-around by the CSM before it returned home. The space station is seen against a cloud-covered Earth. Photo credit: NASA.

C. Apollo-Soyuz Test Project (July 15 to July 24, 1975)

The Apollo-Soyuz Test Project (ASTP) was the first space flight to be conducted jointly by the 2 leading nations in space exploration, the United States and Russia. The primary purpose of the mission was to test systems for rendezvous and docking of spacecraft, as might occur in international space rescue missions (Figure 3).

The U.S. vehicle was the Apollo spacecraft, so Apollo-type food and packaging was used.

Previous food systems had been produced by outside contractors, but the ASTP food was produced by NASA at the Johnson Space Center. The facilities and processes used for the production of the ASTP food became the foundation of the facilities currently used to produce the Space Shuttle and International Space Station food systems.

Figure 3. An artist's concept illustrating an Apollo-type spacecraft (on left) about to dock with a Soviet Soyuz-type spacecraft. An agreement between the United States and the Union of Soviet Socialist Republics provided for the docking in space of the Soyuz and Apollo spacecraft in Earth orbit in 1975. The joint venture was known as the Apollo-Soyuz Test Project, or in Russia as the Soyuz-Apollo Test Project. Photo credit: NASA.

Figure 4. A close-up view of cheddar cheese spread, one of the items of food selected for the Apollo-Soyuz Test Project mission flown in the summer of 1975. This food item was also carried on the Apollo missions. Photo credit: NASA.

D. SPACE SHUTTLE (1981 TO THE PRESENT)

Next for NASA was the Shuttle program. As a work vehicle that was designed for short-duration missions, the Shuttle had no space and no power to support refrigerators or freezers for food, and thus NASA reverted to an all-shelf-stable food system [63]. A meal tray was developed as a replacement for a dining table, which had exceeded space limitations. The Shuttle food system originally had rigid plastic packages for rehydratable foods and for beverage items. As the program evolved and crew size and mission duration increased, these rigid packages had to be replaced with more flexible versions that could be compressed to take up less space in the trash.

Figure 5. On April 12, 1981, just seconds after 7 a.m., the launch of the first Space Shuttle, Columbia, carried astronauts John Young and Robert Crippen into an Earth-orbital mission lasting 54 hours. Photo credit: NASA.

In the Shuttle food program, commercially available food items constitute a very large percentage of the menu items. Some items are used exactly as they are marketed commercially (cookies, crackers, nuts, powdered beverages), while others, such as frozen vegetables, are further processed into freeze-dried items for space. The use of commercial items provides significant cost savings over developing unique foods for space flight. It also provides more familiar food items to the crewmembers. However, the use of commercial food items has the significant disadvantage that a company can change the content of a product or discontinue it altogether. Another disadvantage is that many commercial products have more fat and sodium than desired to meet nutritional recommendations.

The use of fuel cells by the Shuttle to create electricity produces a significant quantity of water as a by-product of this process. Thus, freeze-dried foods and powdered beverages constitute a high percentage of the Shuttle menu. This is not the case, however, on the International Space Station, where solar arrays provide power and water has to be transported to orbit.

The Shuttle menu has provided more food choices to the crewmembers than any previous U.S. space food system. After a food preference survey of the astronaut corps was conducted, the first Shuttle menus were designed by a dietitian from the list of available foods and standardized for each crew. Crewmembers quickly expressed their displeasure with this process, and early in the program, the standardized menu was replaced with a personal preference menu, developed for individual crewmembers using their inputs and analyzed by the dietitian for nutritional compliance. Experience has shown that very few adjustments to the menus selected by the crew are required to meet most of the nutritional requirements. The medical requirements for astronauts are such that they must eat healthy, nutritious diets on Earth to maintain their health status for space flight. Thus, when crewmembers select menus, they are generally within the nutritional guidelines.

The Shuttle menus do tend to have more sodium and iron than required. This can be partially attributed to the use of many high-sodium commercial products and to the use of commercial bread and cereal products, which are enriched with iron. The requirement for an all-shelf-stable food system also increases sodium content, since sodium is often used in shelf-stable products to improve flavor and help with preservation.

Although the Shuttle food system presents many improvements to the crew, including personal preference menus, hot and cold water for rehydration, and a more reliable oven for heating food, the average actual intake of food on Shuttle missions is often inadequate. Inadequate intake on Shuttle missions cannot be attributed to the food system alone, however. The short duration of Shuttle missions and the heavy work load often give crewmembers insufficient time to eat meals. In addition, space adaptation syndrome reduces food consumption in the first few days of Shuttle flights.

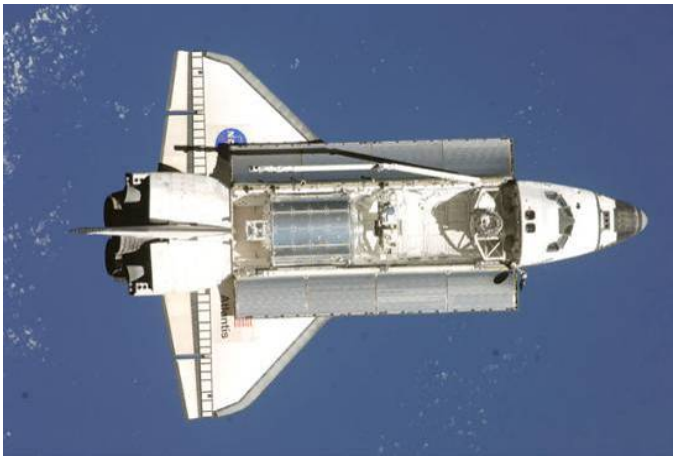

Figure 6. View of the Space Shuttle Orbiter Atlantis on approach to the International Space Station (ISS) during the STS-122 mission. Visible in the payload bay are the European Laboratory / Columbus module, the Integrated Cargo Carrier-Lite, the Orbiter Boom Sensor System, and the Shuttle Remote Manipulator System. Photo credit: NASA.

E. SHUTTLE-MIR PROGRAM (1995 TO 1998)

In Phase 1 of the International Space Station (ISS) program, U.S. astronauts lived for long durations on the Russian space station Mir with cosmonauts. Under an agreement with the Russian Space Agency (RSA), both Shuttle foods and Russian space foods were used by both astronauts and cosmonauts. This early agreement with the RSA was the basis for the current ISS menu, which is designed to be 50% U.S. and 50% Russian space food. As astronauts began to stay for long periods aboard Mir, it quickly became obvious that on long-duration missions, the importance of food to crewmembers was magnified many times over its importance on the short-duration Shuttle missions. The psychological contributions of food to the crew's mental attitude became readily apparent. Crew debriefs from Mir missions began to reveal that the thermostabilized items had far better long-term acceptability than their freeze-dried counterparts. These debriefs also revealed that increasing the variety of foods available to the crewmembers was important for long stays, to prevent menu fatigue.

F. INTERNATIONAL SPACE STATION (NOVEMBER 2000 TO THE PRESENT)

In the initial phases of design for the International Space Station (ISS) (Figure 7, Figure 8), refrigerators and freezers for food were expected to be part of the U.S. habitation module. Preliminary work was done to design a packaging system for the frozen and refrigerated foods, as well as to develop a preliminary food list. However, because of cost and power constraints, the habitation module was deleted from the final ISS configuration. The ISS program had already set aside funding for the development of frozen and refrigerated food items, and NASA food specialists convinced the ISS program to redirect this funding to the development of new shelf-stable food items to add to the Shuttle food list. The duration of the ISS missions was planned to be 4 months, and to support missions of this length, more variety was needed than was available in the food system at that time.

Thus, in 1998 NASA food scientists began the first real product development of custom space food items that had occurred since the Skylab program, 25 years earlier. The product development was focused mainly on thermostabilized food items, because the lack of water generation aboard the ISS reduced the weight advantage of freeze-dried food items and thermostabilized foods had greater long-term acceptability [64]. The products could be formulated to contain a more moderate amount of sodium and fat than commercially available thermostabilized products. Since 1998, about 55 new food items, most of them thermostabilized, have been formulated by food scientists in the Space Food Systems Laboratory at Johnson Space Center and added to the ISS food list.

Although the product development resulted from ISS needs, Shuttle crews are also able to take advantage of the longer list of available foods. The additional variety available in the ISS menu as a result of this product development proved to be even more important when the Columbia accident in February 2003 forced the ISS program to extend mission durations aboard the ISS from 4 months to 6 months.

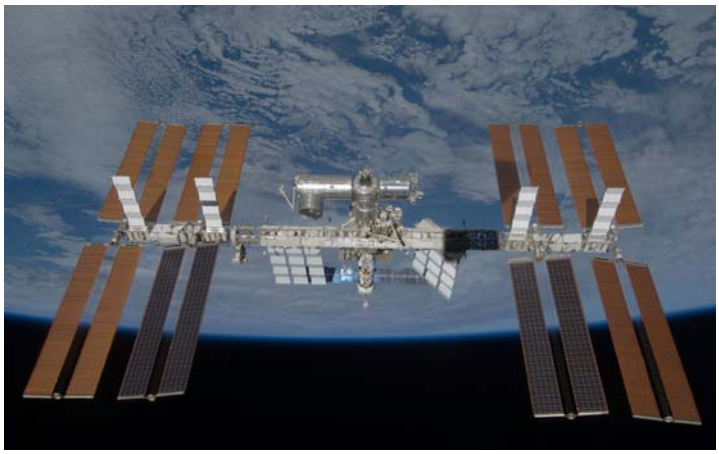

Figure 7. The International Space Station is seen from Space Shuttle Discovery on March 25, 2009. Photo credit: NASA.

The U.S. food list currently consists of about 185 foods and beverages from which the Shuttle and ISS crewmembers can build their menus. As mentioned previously, the crews on the ISS select foods from a menu that is composed equally of U.S. space food and Russian space food. The Russian food list adds about 100 items to the total ISS food selection. The ISS crewmembers sample and score each of the U.S. and Russian food items available to them. Their menus are prepared using the food items to which they gave the highest scores.

Figure 8. Astronaut Peggy A. Whitson, Expedition 16 commander, prepares a meal at the galley in the Zvezda Service Module of the International Space Station. Cosmonaut Yuri I. Malenchenko, flight engineer representing Russia's Federal Space Agency, is visible in the background. Photo credit: NASA.

Crewmembers' flight menus are supplemented with a small quantity of "bonus food" each month. The bonus foods are chosen by the crew and can be additional menu food items, but often are commercially available items, such as candies, cookies, and crackers, that are not part of the standard ISS menu. Bonus food items must have certain levels of microbiological quality and shelf life.

Food is transported to the ISS via Shuttle and Progress flights. The Progress is the unmanned Russian resupply vehicle. On each Shuttle and Progress flight, a small quantity of fresh food is stowed for transfer to the ISS crew. This typically consists of fresh fruit (apples, oranges) and fresh vegetables (carrot sticks, onions, and garlic). These fresh items must be consumed fairly quickly by the crew, since they cannot be refrigerated.

Although on the early ISS flights crewmembers selected their own menus and all attempts were made to satisfy crew preferences for both the U.S. and Russian foods, launch logistics often created situations where the menu planned for a given crewmember was not available. Also, foods are typically consumed on a first-in, first-eaten basis, and if food remains after a previous crewmember has left, that is consumed first. In 2007, at crew request, the U.S. switched to providing a standardized menu for all crewmembers. Each crewmember was allowed to select not only a monthly bonus container, but also a "preference" container, with items from the standard food list that could help offset items on the standard menu that were less desired by that crewmember.

Because of the length of the ISS missions, crewmembers typically settle into a more normal eating pattern than is possible on a hectic Shuttle flight. For this reason, food consumption rates are much higher on the ISS, but still not up to the level observed during the Skylab program. A recurring comment is that greater variety is beneficial to food intake. One of the ways this continues to improve is through the development and provision of foods from the other partners in the ISS program. The Canadian, European, and Japanese Space Agencies are all developing foods, either for inclusion in the crews' "bonus" food containers or for eventual inclusion in the standard food list.

III. NUTRITIONAL REQUIREMENTS

NASA's first space flight-specific nutrient requirements were established for the long-duration missions of the 1990s. Nutrient requirements for other programs (Shuttle and earlier) had been based on Earth-based requirements of the day [14].

Nutritional requirements for space crews on long-duration missions (> 30 days of flight) were initially defined in 1991, for planned Space Station Freedom missions of up to 120 days [457]. In 1992, plans for this U.S. space station were abandoned, and collaboration with the Russian space program was reinvigorated with flights on Shuttle, Mir, and ultimately the International Space Station. An updated set of requirements was developed for the Mir flights in collaboration with Russian partners in 1995 [458].

The nutrient requirements for ISS missions of up to 360 d [350, 458] are shown in Table 1. With a few exceptions (most notably vitamin D insufficiency, and iron and sodium excess), the actual menus meet these requirements [612]. As discussed below, vitamin D supplements are provided to mitigate the dietary insufficiency.

In 1999, all ISS International Partners—the Canadian Space Agency, the European Space Agency, the Japanese Space Agency (NASDA, later JAXA), the Russian Space Agency, and the U.S. space agency, NASA—held discussions to review ISS nutrient requirements. Additional reviews have been conducted since then, but a formal, signed agreement for updated nutritional requirements has yet to be established.

Table 1. Planned (menu) and required nutrient intake on International Space Station missions.[1]

	Menu Content[2]	ISS Nutrient Requirements [458]	NASA Exploration Mission Requirements [460]
Energy, kcal/d	2877 ± 167[3]	Based on WHO [736]	Based on DRI [279]
Energy, % WHO	99 ± 13		
Total carbohydrate, % of kcal	50 ± 3	50–55	50–55
Total protein, g/d	126 ± 10		0.8 g/kg BW, NTE 35% of calories
Total protein, % of kcal	17 ± 1	12–15	
Animal protein, g/d	72 ± 7	60%	2/3
Vegetable protein, g/d	33 ± 3	40%	1/3
Total fat, % of kcal	31 ± 1	30–35	25–35

Table 1. (Continued)

	Menu Content[2]	ISS Nutrient Requirements [458]	NASA Exploration Mission Requirements [460]
Total dietary fiber, g/d	33 ± 4	10–25	10–14 g/1000 kcal
Retinol equivalents, µg/d	1420 ± 205	1000	700–900
Vitamin D, µg/d (IU)	4.2 ± 1.0	10 (400 IU)	25 (1000 IU)
Vitamin E (total α-tocopherol equivalents), mg/d	12.1 ± 1.9	20	15
Vitamin K (phylloquinone), µg/d	105 ± 19	80	90 (women) 120 (men)
Vitamin C (ascorbic acid), mg/d	191 ± 39	100	90
Thiamin, mg/d	2.0 ± 0.1	1.5	1.1 (women) 1.2 (men)
Riboflavin, mg/d	2.2 ± 0.2	2.0	1.3
Niacin, mg/d	29.8 ± 1.9	20 mg niacin equivalents	16
Pantothenic acid, mg/d	5.1 ± 0.8	5.0	
Vitamin B_6, mg/d	2.3 ± 0.2	2.0	1.7
Total folate, µg/d	434 ± 53	400	400
Vitamin B_{12} (cobalamin), µg/d	4.6 ± 0.7	2.0	2.4
Biotin, µg/d			30
Pantothenic acid, mg/d			30
Calcium, mg/d	1020 ± 109	1000–1200	1200–2000
Phosphorus, mg/d	1856 ± 165	1000–1200 (NTE 1.5 × Ca)	700 (NTE 1.5 × calcium)
Phosphorus:calcium ratio	1.83 ±0.17	< 1.5	< 1.5
Magnesium, mg/d	424 ± 40	350	320 (women) 420 (men)
Iron, mg/d	22.7 ± 4.5	10	8–10
Copper, mg/d	3.6 ± 0.9	1.5–3.0	0.5–9.0
Zinc, mg/d	22.1 ± 6.2	15	11
Manganese, mg/d	5.7 ± 0.7	2–5	1.8 (women) 2.3 (men)
Selenium, µg/d	146 ± 16	70	55–400
Iodine, mg/d	1.0 ± 2.8	0.15	0.15
Fluoride, mg/d			3 (women) 4 (men)
Chromium, µg/d			35
Sodium, mg/d	5625 ± 531	< 3500	1500–2300
Potassium, mg/d	3995 ± 360	3500	4700
Water, g/d	2155 ± 206	1 mL/kcal, > 2 liters per day	1.0–1.5 mL/kcal, NLT 2000 mL/d

BW, body weight; DRI, dietary reference intake; NLT, not less than; NTE, not to exceed; WHO, World Health Organization.

[1]Table adapted from Smith and Zwart [612] and [460].

[2]Menu data are derived from either proximate analysis of space foods (macronutrients, most minerals) or estimations (animal protein, vegetable protein, all vitamins, selenium) from similar items in the Nutrition Data System for Research (NDS-R) database, versions 4.03/31, 4.05/33, 4.06/34, 5.0/35, 2005, and 2006, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, USA [562].

[3]All data are mean ± SD, and represent the average from menus of 19 ISS astronauts.

For some missions, detailed dietary intakes were recorded by crews during flight, typically in conjunction with life sciences research. These data are compiled in Table 2.

Table 2. In-flight dietary intake of Apollo, Skylab, and Shuttle crewmembers.

	Apollo	Skylab	Shuttle
Number of subjects	33	9	32
Energy, kcal/d	1880 ± 415 [1]	2897 ± 447	2090 ± 440
Energy, % WHO	64.2 ± 13.6	99.1 ± 8.2	74.2 ± 16.0
Protein intake, g/d	76.1 ± 18.7	111.0 ± 18.4	78.0 ± 18.8
Protein intake, % of kcal	16.3 ± 2.1	15.7 ± 2.1	14.9 ± 2.4
Carbohydrate intake, g/d	268.9 ± 49.1	413.3 ± 59.3	304.0 ± 67.3
Carbohydrate intake, % of kcal	58.1 ± 7.1	57.5 ± 9.1	58.4 ± 5.0
Fat intake, g/d	61.4 ± 21.4	83.2 ± 13.8	64.0 ± 17.8
Fat intake, % of kcal	28.9 ± 5.5	26.8 ± 8.6	27.2 ± 4.4
Calcium, mg/d	774 ± 212	894 ± 142	826 ± 207
Phosphorus, mg/d	1122 ± 325	1760 ± 267	1216 ± 289
Magnesium, mg/d		310 ± 58	294 ± 74
Iron, mg/d			15.0 ± 3.9
Zinc, mg/d			12.0 ± 2.9
Sodium, mg/d	3666 ± 890	5185 ± 948	3984 ± 853
Potassium, mg/d	2039 ± 673	3854 ± 567	2391 ± 565
Water, g/d	1647 ± 188 [2]	2829 ± 529	2223 ± 669

[1] All data are mean ± SD. Empty cells (Apollo magnesium, Apollo and Skylab iron and zinc) show where data were not available.

[2] $n = 3$ for water intake during Apollo missions.

Adequate intake and recommended dietary allowance (RDA) of many nutrients, as defined by the Institute of Medicine [276-280], are given in this book for comparison with space flight nutritional requirements [458-460]. The RDA (a recommendation issued by the U.S. government) is calculated from the estimated average requirement (EAR), which is based on scientific evidence. Adequate intake is an estimate that is used when not enough evidence exists about a nutrient to calculate an EAR.

IV. SOURCES OF NUTRITION DATA AND GAPS IN NUTRITION KNOWLEDGE

In addition to establishing requirements for nutrient intake of astronauts, NASA requires crewmembers to participate in evaluations of their health; these are called Medical Requirements. One such evaluation is the "Clinical Nutritional Assessment" [459], in which all U.S. crewmembers on ISS missions are required to participate. The findings from this assessment are included in the sections on findings from space flight and ground-based research, to provide background information about the changes seen in flights of 4 to 6 months (during which time resupply by at least one Progress vehicle occurred).

In many cases in this book, we have extrapolated from ground-based space analog studies—studies performed in a laboratory on Earth under conditions that simulate some of the conditions found during space flight. In others we have only the ground-based nutrition literature for support, knowing nothing of the effects of space travel. We have pointed out the areas where we are at highest risk of being wrong, with little or no evidence base to support nutritional requirements and recommendations for space flight.

In 2006, the NASA Human Research Program created the Human Health and Countermeasures Element Small Assessment Team, a group of individuals representing the Human Adaptation and Countermeasures Division, the Space Medicine Division, and the Astronaut Office. The review and final report of the team listed 15 specific gaps in knowledge about the risk of inadequate nutrition during long-term space travel. Five of these pertained to specific nutrients and will be discussed under those nutrients, but the other 10 are more general and are listed here:

1. Are nutrients in food stable during space flight?
2. How do nutritional status and nutrition requirements change during space flight?
3. Do countermeasures to other physiological effects of space flight affect nutrition?
4. What impact does flight have on oxidative damage to nutrients?
5. How much energy and how much of which nutrients are required for crewmembers to perform extravehicular activity? What is the best system for delivering these nutrients?
6. Can nutritional countermeasures mitigate muscle loss?
7. What are the risks of the release of minerals and metals from bone?
8. Can the risk that a crewmember will develop a renal stone be decreased using nutritional countermeasures?
9. What nutritional countermeasures can mitigate bone loss?

10. Can generally good nutrition or particular nutrients mitigate the risks that oxygen and radiation pose to health?

V. FOOD, ENERGY, AND MACRONUTRIENTS

In this section, the longest in this book, we review available information about individual nutrients and human requirements for them, and the evidence base of existing ground-based and space flight research and clinical findings.

A. FOOD AND ENERGY

1. Background

Ensuring that the spacecraft food systems provide palatable, safe, and nutritious foods is obviously critical for any space mission. The longer space station missions have included semi-closed food systems, with periodic resupply and transient exposure to unique and fresh foods [62, 242, 353, 504]. Exploration missions will have a more closed food system (because of the difficulty of resupply and shelf-life requirements). The food system on these missions is likely to be supplemented with food grown on a planetary surface or even potentially on the spacecraft [62, 353, 504].

From the early days of the space program [250, 251, 321, 322, 340, 596], development of foods for space flight has proven a significant challenge, yet the design criteria have changed little since then: minimal crumbling, ease of preparation and consumption in microgravity, minimal trash volume, and high palatability. With one exception, the food systems used in every space program to date have been entirely shelf-stable, and they are composed primarily of rehydratable or thermostabilized (heat-treated) food items [62, 353]. Although these foods are known to have lower hedonistic value (palatability) than fresh or frozen foods, ground-based studies have clearly shown that the Shuttle food system can adequately support most nutritional requirements [214]. Skylab is the only U.S. program that has included frozen foods [62, 353].

Energy itself is not readily stored in the body, but the substrates for energy are. Energy in the form of heat is obtained by oxidizing carbohydrates, fats, proteins, and alcohol; this energy is also known as the heat of combustion. Fat provides the most energy of these sources, at about 9 kcal/g. Carbohydrates and proteins provide about 4 kcal/g, and alcohol about 7 kcal/g. Because the body can adapt to different energy sources, large variations in intake of macronutrients (carbohydrates, fats, proteins) are generally well tolerated. Adipose tissue is the only viable long-term source of stored energy. Carbohydrate stored as glycogen in liver and muscle provides a transient (hours) source of carbohydrate. Protein can be broken

down to release amino acids, but this is done at the expense of muscle tissue.

The small amount of starvation data available suggest that for every 500 kcal consumed per day, about 1% of body mass can be conserved every 12 days. It would not be acceptable, however, to use these numbers for a long-term (> 21 days) prediction of body mass loss or conserved body mass loss because after 21 days of starvation the basal metabolic rate of the body decreases [74, 492]. This can be and has been accounted for using a mathematical model to predict body mass loss given changes in basal metabolic rate [492], with results estimating that survival on 1000 kcal/d could exceed 3 years (compared with only 6 months without accounting for decreased metabolic rate).

2. Findings from Space Flight and Ground-Based Research

Despite indications that energy requirements are similar before and during flight [348, 736], energy intake during flight is commonly lower than the estimated requirements for individual crewmembers [14, 242, 243, 292, 348, 365, 526, 527, 604, 609, 610, 626] (Figure 9). From the Apollo program through the more recent flights, crewmember dietary intakes during flight have averaged about 70% of predicted requirements [610].

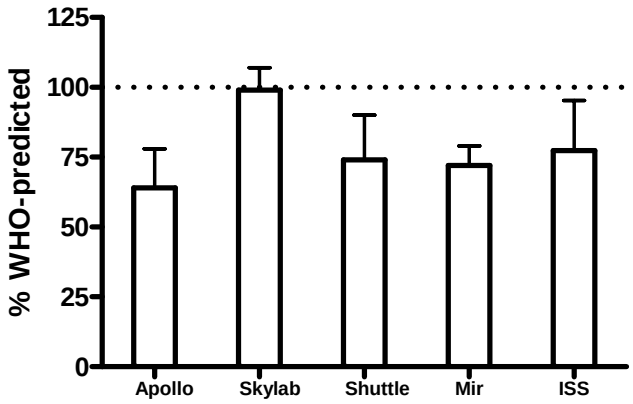

Figure 9. In-flight dietary intake of crewmembers in different space programs. Data are expressed as percentage of energy requirements predicted by the World Health Organization (WHO) [736]. Apollo n = 33, Skylab n = 9, Shuttle n = 32, Mir n = 7, ISS n = 23. Apollo and Skylab data are from Bourland et al. [62]. Figure is adapted from Smith and Lane [611], with additional data from Smith et al., 2005 and Smith and Zwart, 2008 [610, 612].

Exceptions to the average inadequate intakes do exist. A number of ISS crewmembers have been able to consume recommended dietary intake requirements and maintain body mass [610]. In some cases, such as during Skylab [361, 524] and European flights to the Mir space station [146], metabolic experiments have required crewmember subjects to consume a eucaloric diet, with the goal of weight maintenance. These crewmembers ate essentially 100% of their recommended energy requirements. It is difficult to determine if the intakes on Skylab were related more to the requirement to consume the food or to the fact that the food was more palatable because of the additional variety available with frozen foods; however, increased palatability is generally beneficial.

Anecdotal reports from crewmembers on long-duration missions indicate that crewmembers who had lost a significant amount of body mass on orbit had a rebound gain in body mass after landing, but in general, the data do not support this finding (Figure 10).

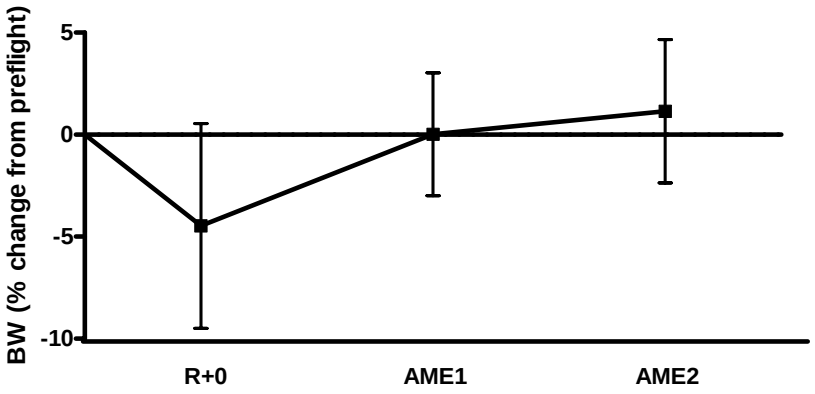

Figure 10. Postflight body weight (BW) of Mir and ISS crewmembers (n = 20). Data are expressed as mean ± SD of the percent change from preflight body weight. R+0 = landing day, AME1 = first annual medical exam after return from the mission, and AME2 = second exam.

The cause of reduced dietary intake during flight is unknown, but many potential explanations have been proposed [292, 350, 596]. A common cause of reduced dietary intake during the first days of a mission [246] is space motion sickness [246, 341, 467, 535, 569]. The effects of space motion sickness typically pass after the first several days of flight, but the decreased dietary intake can extend beyond the first week [350].

Anecdotal reports of appetite vary significantly, as indicated in a Russian study in which 40% of Mir crewmembers reported decreased appetite, 40% reported no change, and 20% reported increased appetite [2].

Food palatability is occasionally reported as a cause of reduced in-flight intake, and many anecdotal reports exist of changes in taste and aroma of food during flight [35, 488, 569]. One hypothesis is that fluid shifts and congestion associated with the first days of microgravity can alter taste and odor perception. Other possibilities exist as well, including effects of atmospheric contaminants, stress, radiation, and psychological factors [488]. Experimental research has not been able to clearly document changes in taste or olfaction during space flight or head-down-tilt bed rest [75, 488, 715].

When tongue taste perception was measured before, during, and after a 30-day –6° head-down bed rest period, subjects reported decreased appetite and lack of taste early in the bed rest phase [75, 338]. By day 13 of the bed rest phase, for all tastes (sweet, salt, acidic, bitter), the threshold for taste sensitivity had increased. In contrast, a more recent study found no changes in odor and taste perception after 14 days of head-down bed rest [537], suggesting that multiple factors are likely involved in this process.

Flight-related changes in gastrointestinal function may also occur. Fluid shifts, in combination with reduced fluid intake, would tend to decrease gastrointestinal motility. Gastrointestinal transit time has not been systematically studied during flight, but during 10 days of –6° head-down bed rest, mouth-to-cecum transit time was significantly longer than during ambulatory control periods [344]. However, because the Skylab astronauts and others

were able to maintain a eucaloric diet in space, hypotheses regarding inability to consume the requisite amount of food because of stomach fullness or other factors are not likely to fully explain decreased dietary intake during flight. Russian studies of gastrointestinal function during actual and simulated space flight, in humans and in animal models, have previously been reviewed [593].

The obvious and immediate reason for concern about reduced dietary intake is the risk of body mass loss, and more specifically, loss of lean and bone tissue. Body mass losses of 1% to 5% of preflight body mass have been a typical finding in the history of space flight, although some crewmembers have been able to maintain body mass [610]. In-flight and postflight losses of body mass are compiled in Figure 11, Figure 12, and Figure 13. Documented weight losses have occurred on short- and long-duration flights in both the U.S. and Russian space programs [292, 340, 343, 387]. Indeed, all crewmembers on Gemini, Apollo, Skylab, and Apollo-Soyuz Test Project missions lost body mass [369]; thus, ingestion of the prescribed energy intake on the U.S. Skylab missions did not ensure maintenance of body mass [524]. In one study of 13 male Shuttle crewmembers, body mass losses ranged from 0 to 3.9 kg [348]. Body mass loss has been observed to reach 10% to 15% of preflight body mass [603]. Crewmembers on the ISS have shown similar patterns of mass loss during and after flight.

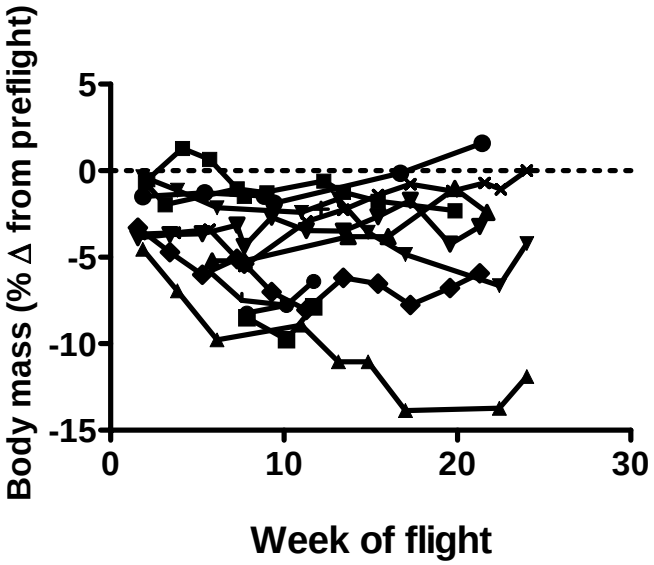

Figure 11. In-flight body mass measurement data from ISS crewmembers. Data are expressed as percent change from preflight values. Data collection was scheduled every 2 weeks, but complete data for all crewmembers were not always available. Each line represents data for 1 crewmember.

Data relating reduced dietary intake to loss of body mass were collected from 2 ground-based studies in which subjects were semi-starved. In the first study [74], subjects who consumed 580 kcal/d lost 7% of their body mass in 12 days and subjects who consumed 1010 kcal/d lost 11% of their body mass in 24 days. In the other study, starved subjects lost 9% of their body mass after 11 days, 15% by day 18, and 18% by day 43 [158].

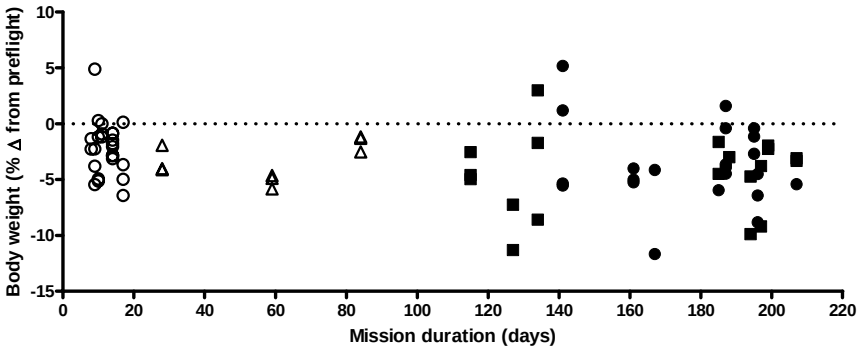

Figure 12. Changes in body weight on the day of landing. Data are expressed as percent change from preflight values. Each symbol represents 1 crewmember from a Shuttle (open circles), Skylab (open triangles), Mir (filled squares), or ISS (filled circles) mission. Duration data have been adjusted slightly to ensure anonymity. From Lane et al., Food and nutrition for the moon base: what have we learned in 45 years of spaceflight. Nutr Today 2007;42(3):102-10 [353], adapted with permission.

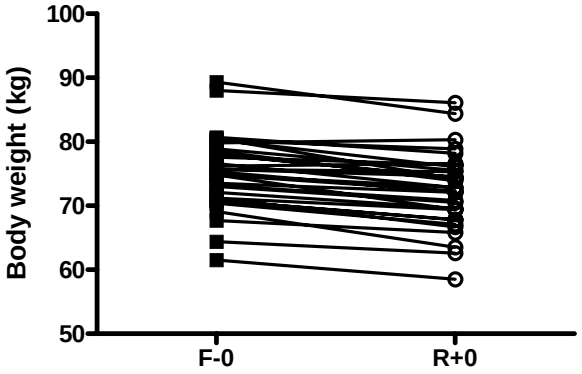

Figure 13. Body weight of Apollo crewmembers (Apollo 7 through 17) before (F–0) and after (R+0) flight. Data are from Johnston et al., 1975 [295].

Only about 1% of the loss of body mass can be explained by loss of body water [365]; most of the observed loss of body mass is accounted for by loss of muscle and fat tissue [291, 349]. The water loss may be confounded by lean tissue loss, as metabolic water loss will be associated with depletion of glycogen stores and protein catabolism, both of which occur with inadequate intake. Inadequate energy intake is associated not only with loss of fat tissue (Figure 14) but also with decreased protein synthesis [627] (in flight), increased protein catabolism [50] (in bed rest), and subsequent loss of lean tissue mass.

Besides the obvious concerns about body mass loss and dehydration [710], existing data suggest that many systems are affected by inadequate nutrient intake, including the muscle, bone, cardiovascular, and immune systems. The German Institute of Aerospace Medicine at the German Aerospace Center conducted a study jointly with the European Space Agency (ESA) to evaluate the impact of hypocaloric nutrition on multiple systems. A crossover design was used, with hypocaloric and eucaloric phases, and bed rest and ambulatory phases. Results for protein metabolism (Figure 15) document the fact that undernutrition exacerbates the negative effects of bed rest.

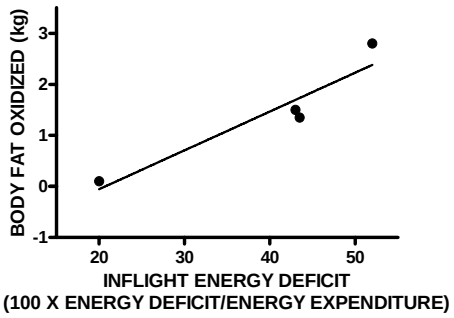

Figure 14. In-flight oxidation of body fat related to in-flight energy deficit. Stein et al., Am J Physiol Regul Integr 1999 [628], adapted with permission.

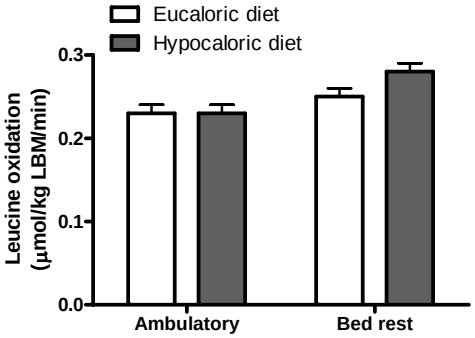

Figure 15. Leucine oxidation (an index of net protein catabolism) in a crossover-design bed rest study to evaluate the impact of hypocaloric nutrition on integrated physiology. There was a significant (P = 0.04) interaction between bed rest and diet. Data are from Biolo et al. [50]. LBM, lean body mass.

Undernutrition has also been found to impair cardiovascular performance (orthostatic tolerance) in controlled bed rest settings [176] and after space flight (William Carpentier, personal communication). The mechanism for this energy-cardiovascular connection has been hypothesized to involve multiple functions of many endocrine factors, including insulin, leptin, and growth hormone [57].

Besides undernutrition, another possible explanation for loss of body mass is altered energy expenditure. According to early hypotheses, energy expenditure during flight would be less than on the ground, because of the relative hypokinesia in space [596]. Lower energy expenditure was observed during extravehicular activity (EVA) on the lunar surface than during similar activities at 1 G [712] (Figure 16 and Figure 17). However, studies of Space Shuttle crewmembers during in-flight EVA [349] and non-EVA (that is, intravehicular activity, or IVA) [348] showed that in-flight energy expenditure was unchanged from preflight levels (Figure 18). More recent studies have even shown greater energy expenditure during flight than before flight, most likely as a result of increased exercise [628].

These recent studies involved Shuttle astronauts and indirect calorimetry techniques to determine total energy expenditure (TEE) over several days. The doubly-labeled water (water enriched with deuterium and ^{18}O) technique was used to determine oxygen consumption [564]. The benefits of this technique are that it is noninvasive and it takes into account the

energy cost of all activities for several days. The drawback of the method is that information about the individual components of TEE (such as resting, sleep, and exercise) is not available. The wide range of differences between preflight and in-flight TEE makes it important to have information about the components of TEE. Although it is assumed that moving the body mass around the cabin requires less expenditure of energy during weightlessness than at 1 G, other metabolic activities, such as maintaining resting metabolic rate and responding to stress, may require increased energy expenditure during weightlessness.

In ground-based studies, resting energy expenditure did not change, but TEE was less during bed rest than before bed rest [215]. Because (except during lunar EVA) TEE during flight is unchanged [348] from preflight levels or increased [628], the lower TEE during bed rest may indicate that bed rest is not an appropriate model for studies of energy metabolism during flight. One possible explanation for this difference between bed rest and space flight is the lack of a metabolic response to stress during bed rest [630]. Attempts have been made to improve the utility of bed rest studies by administering a metabolic stressor (such as triiodothyronine or cortisol) to provide a better ground-based model than bed rest alone for the metabolic effects of space flight on energy and fuel metabolism [400].

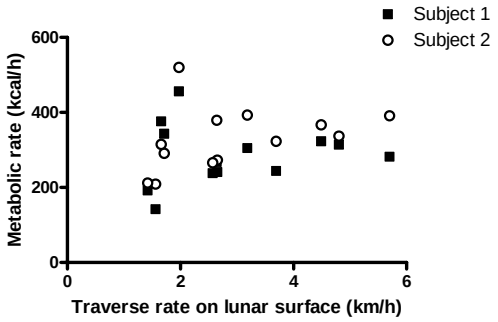

Figure 16. Metabolic rate of Apollo 14 astronauts while they traversed the lunar surface on foot during EVA. Data are from Waligora and Horrigan [712].

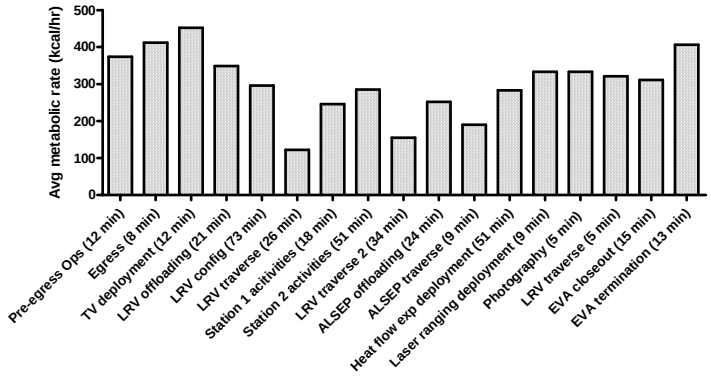

Figure 17. Metabolic expenditures of the first Apollo 15 lunar EVA in chronological order (durations of each activity are noted in parentheses). The average total energy expenditure during the EVA was 1800 kcal. ALSEP = Apollo Lunar Surface Experiments Package, EVA = extravehicular activity, LRV = Lunar Roving Vehicle, TV = television. Data are from Waligora and Horrigan [712].

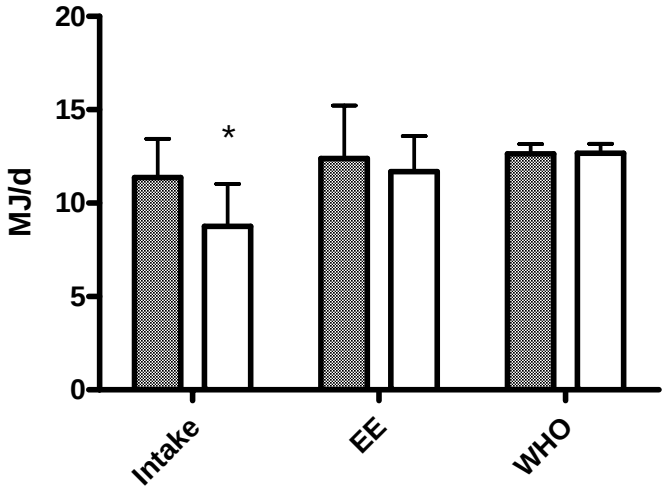

Figure 18. Energy intake, energy expenditure (EE), and WHO-predicted energy requirements (WHO) of Space Shuttle crewmembers before (checked bars) and during (open bars) space flight. Data are from Lane et al., 1997 and Lane et al., 1999 [348, 351].

3. Dietary Intake and Requirements

The estimated energy requirements (EERs) for space missions are based on total energy expenditure (TEE) as calculated from the 2002 Institute of Medicine Dietary Reference Intake reports [279], using an activity factor of 1.25 (active) along with the individual's age, body mass (kg), and height (m) in the following calculations:

EER for men 19 years and older

$$EER = 622 - 9.53 \times Age\ [y] + 1.25 \times (15.9 \times Mass\ [kg] + 539.6 \times Height\ [m])$$

EER for women 19 years and older

$$EER = 354 - 6.91 \times Age\ [y] + 1.25 \times (9.36 \times Mass\ [kg] + 726 \times Height\ [m])$$

For historical reference, the daily energy requirements for male and female astronauts were defined in 1991 [457], and again in 1995 [458], and are as follows:

Missions of 30–120 days: Energy consumption should be sufficient to maintain weight and body composition, with continuous monitoring during space flight. A 70-kg man exercising 1 to 2 hours per day is expected to require about 3,000 calories/day [457].

Missions up to 360 days: Intake of energy should be sufficient to maintain body weight and composition, and the extensive activities planned for International Space Station crew members. Energy requirements will be calculated for each individual by using the World Health Organization [736] equations:

Men

- 18-30 y: 1.7 (15.3W + 679) = calories/day required
- 30-60 y: 1.7 (11.6W + 879) = calories/day required

Women

- 18-30 y: 1.6 (14.7W + 496) = calories/day required

- 30-60 y: 1.6 (8.7W + 829) = calories/day required
- where W = weight in kg

These equations are to be used for moderate levels of activity. The original space flight requirements included an additional 500 calories/d that would be supplied to the diet during the period when end-of-mission countermeasures (such as more intensive exercise) are being conducted.

On the basis of results from previous space missions, it was also recommended that an additional 500 calories/d be supplied to crew members on days of extravehicular activity (EVA); the extra energy should be similar in nutrient composition to the rest of the diet [458].

4. Risks on Exploration Missions

It is imperative that adequate resources be provided to support food consumption on exploration missions. A reliable food system must include a variety of palatable foods and the means to process them (such as rehydration, heating, and cooling). Time (for meal preparation, consumption, and cleanup) is another limited resource that often hinders dietary intake during space flight.

The availability of freezers and refrigerators for food storage and preparation would provide a more palatable food system, which would increase dietary intake as well as provide added psychological support.

Deficiency of dietary energy intake leads to wasting and ultimately tissue breakdown, or even death. The loss of lean body mass during space flight is significant, and is associated with increased proteolysis and catabolism related to metabolic stress [170]. Inadequate energy intake can also have negative effects on bone, exacerbated by exercise [28, 275]. This highlights the interaction between systems, and the fact that exercise regimens must be coordinated with energy provision.

It is difficult to predict the impact of suboptimal (or lack of) energy intake on otherwise healthy individuals. One issue is that the energy equivalent of the lost mass changes with time, as different body fuels are used at different times during semi-starvation [74, 492]. With partial rations available (1000 calories per day), it is reasonable to expect that a person could survive for more than 4 to 6 months, potentially longer if the metabolic rate were to decrease because of decreased intake. If energy availability were restricted further, survivability would range between this amount of time and the 1 to 2 months possible with no food. These projections obviously include many assumptions, unknowns, and extrapolations. Data from 10 Irish Republican Army hunger strikers, who consumed water ad libitum but no energy, vitamins, or minerals, indicate that an average 25-year-old male could survive no longer than 60 days without energy [331, 384].

Other possible effects of long-term low intake of calories include decreased motor and cognitive function, each of which could impair an astronaut's ability to perform work-related tasks necessary for landing. According to military survival studies, astronauts would be expected to experience decreased endurance early on, and the decrease in strength would parallel the decrease in lean body mass [507]. During total fasting, degradation of coordination, speed, and cognitive function would be evident within the first 2 weeks [507].

The metabolic condition of ketosis, which would be expected to result from starvation,

not only would have metabolic effects (including decreased appetite), but might also affect other aspects of the mission (for example, the life-support systems might not be able to remove the ketones from the air). Ketoacidosis can obviously have negative effects on acid-base balance, which in turn can affect bone, muscle, and other systems.

It is speculated that a crew could survive on a spacecraft or planetary base for 40 to 60 days without food. With limited rations (1000 calories/d), a crew could survive 4 to 6 months (although physical performance capability might be severely degraded). The high-stress environment of a contingency during transit or on a planetary surface would likely exacerbate the basic effects of limited rations, and would shorten projections of survivability estimated from ground-based studies.

Insufficient dietary intake and subsequent loss of body mass are significant not only for crew health but also for medical operations and research studies, in which clear interpretation of essentially all other physiological data is impossible when subjects are malnourished. That is to say that virtually all space flight data collected on Shuttle, Mir, and ISS missions are confounded by inadequate dietary intake. Investigators who have studied bone and muscle, cardiovascular function, immune response, and other systems during space flight cannot say to what degree undernutrition affected their findings.

5. Remaining Questions

Further research is warranted to better understand why astronauts typically do not consume 100% of their recommended daily energy intake. Decreased energy intake has numerous negative implications for the body, and is often associated with decreased intake of other nutrients.

Studies of energy expenditure have been conducted only on short-duration (Shuttle) flights [348, 628]. Whether the same trends continue on longer flights is not known (an ESA-sponsored study of energy expenditure on ISS missions is currently in development). The health implications of decreased energy expenditure need to be determined, and ways to prevent both in-flight loss and postflight gain of body mass need to be evaluated.

At least 2 approaches exist to controlling body mass and composition while studying human adaptation to bed rest: maintaining body mass (as is typically done in the U.S.) or allowing subjects to lose total mass while keeping fat mass constant (and thus losing lean tissue). While this latter approach sounds intriguing, implementing it has proven very difficult, given the difficulties in measuring fat mass and adapting intake in a timely manner. Nonetheless, Biolo and colleagues have recently reported data suggesting that the more the fat mass increases during bed rest, the more lean tissue is lost [51], and that this is confounded by increasing oxidative and inflammatory damage markers [51]. Altered fuel homeostasis has been documented in other bed rest studies [56] and animal studies [635, 636], and remains to be fully elucidated, in bed rest or space flight [636, 745].

B. PROTEIN AND MUSCLE

1. Background

As the major structural component of all cells in the body, protein includes molecules that perform many essential physiological functions, serving as enzymes, hormones, transporters, and other important molecules. The total energy contribution of protein to the average diet is about 15%. The nitrogen in its amino-acid building blocks makes protein, along with nucleic acids, one of the major nitrogen-containing macromolecules. The type of protein, such as animal or vegetable protein, incorporated into the diet may be an important factor to consider in determining protein requirements.

Protein is one of the most important limiting factors when the body is deprived of energy, because essential amino acids are not stored in the body. A complete depletion of energy and protein reserves is said to be the cause of death from starvation. It is estimated that when 33% to 50% of total body protein is lost, death results [589]. Loss of more than 40% to 50% of initial body mass is not compatible with life [194, 507]. In one case report, individuals on a hunger strike lost 30% of their total body mass and 19% of total body protein before they died [331, 384].

2. Findings from Space Flight and Ground-Based Research

Blood concentrations of total protein and albumin were elevated at landing after Skylab missions (Figure 19). Urinary albumin has been shown to be reduced during space flight and bed rest [100-102]. Measurements of urinary albumin excretion, which are typically low in healthy individuals, have not been reported after landing.

Potassium and nitrogen balances became increasingly negative throughout the Skylab flights, but urinary creatinine (a product of muscle protein breakdown) did not change [361, 725] despite losses of leg volume [524, 666]. Nitrogen balance has also been shown to be negative during Shuttle flights [625].

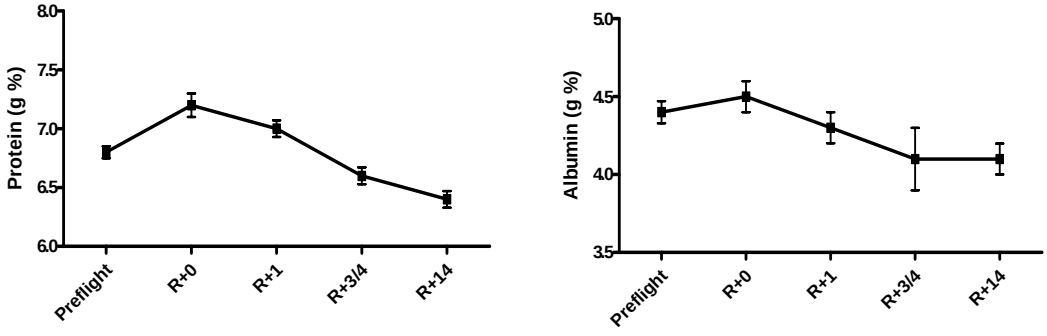

Figure 19. Plasma total protein (left panel) and albumin (right panel) in Skylab crewmembers before and after flight. Data are from Leach and Rambaut [361].

Exposure to microgravity reduces muscle mass, volume, and performance, especially in the legs, on both long [19, 31, 174, 430, 524, 746] and short flights [1, 133, 174, 219, 375, 524]. Muscle biopsy studies demonstrated that the cross-sectional area of type II (fast-twitch) but not type I muscle fibers decreased after landing. Type II is the muscle fiber type that responds to resistive exercise [128].

Disuse atrophy of muscle in space may be related to changes in turnover of protein in the whole body. The results of one ground-based study showed that whole-body protein synthesis decreased about 13% during 2 weeks of bed rest, and that half of that decrease could be accounted for by the leg muscles [168]. This bed rest study did not include exercise, and body mass was maintained during the bed rest period. In the same study, excretion of 4-pyridoxic acid, a vitamin B_6 metabolite, increased during bed rest [106], suggesting that metabolically active muscle tissue was lost.

Turnover studies with stable isotopes indicate that during short-term space flight, whole-body protein turnover increases. Protein synthesis increases, but protein breakdown increases even more [623, 625]. The increase in synthesis is hypothesized by Stein et al. [632] to be related to physiological stress, as indicated by generally (but not consistently) increased urinary cortisol during flight [365, 630, 631]. These findings are similar to those found in catabolic patients, those undergoing metabolic breakdown. Decreased prostaglandin secretion has also been implicated in the loss of muscle tissue during space flight, secondary to decreased mechanical stress on muscle [631].

On long-duration Mir flights, conversely, investigators have noted decreased rates of protein synthesis [628]. Protein synthesis was directly correlated with energy intake (Figure 20), suggesting that the reduced protein synthesis was related to inadequate energy intake [627].

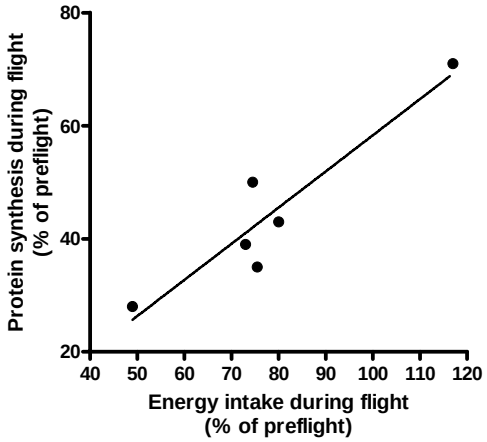

Figure 20. Protein synthesis and energy deficit. Stein et al. , Am J Physiol Endocrinol Metab 1999 [627], adapted with permission.

Evaluation of plasma and urinary amino acids often does not provide a clear picture of muscle metabolism. However, an increase in plasma amino acids was noted in cosmonauts after flight [687, 688]. Limited Shuttle flight data indicate a tendency for plasma branched-chain amino acids to be increased during flight, compared to preflight levels [629]. Data from

short-duration Shuttle flights reveal little or no change in urinary amino acid profiles [626]. Apollo (Figure 21) [366] and Skylab studies did reveal increases in excretion of the amino acid metabolites creatinine, sarcosine, and 3-methylhistidine [362], suggesting that contractile proteins of skeletal muscle are degraded in weightlessness.

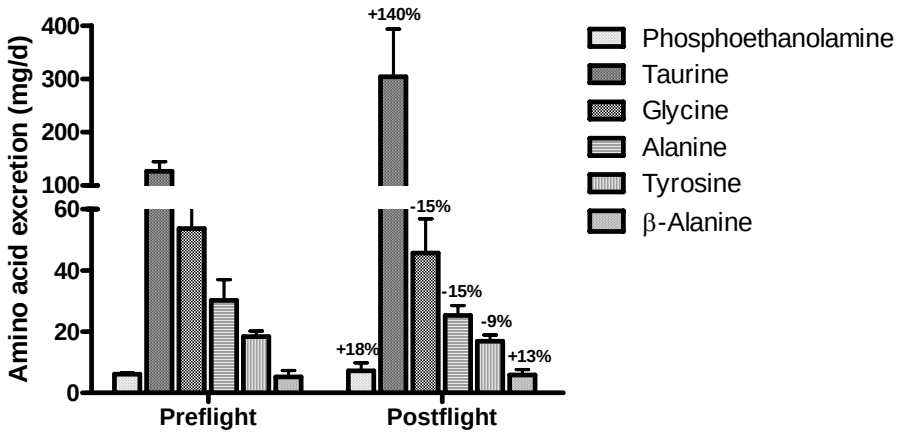

Figure 21. Urinary amino acid excretion by Apollo crewmembers (n = 12) before and after flight. Data are from Leach et al. 1975 [366].

Some data suggest that during the recovery period after short-duration Shuttle flights, protein is a limiting nutrient, and that competition for substrate to replenish plasma proteins and muscle mass strains the system [637]. This has not been tested experimentally, but clearly good nutrition is required for rapid return to optimal health.

3. Muscle – Comparison of Space Flight and Bed Rest

Although, as described above, both space flight and bed rest studies have shown decrements in muscle strength and volume, the mechanisms by which these decrements occur seem to be different in the two types of studies. Differences between flight and ground studies may relate to a number of variables, in addition to potential shortcomings of the analog studies. Dietary intake is one major difference between the two types of studies. On the SLS missions, in-flight intakes of protein and energy were about 20% less than preflight intakes, and crewmembers lost approximately 1 to 1.5% of their body mass [625]. Ground-based studies typically have prescribed and controlled dietary intakes or are designed to maintain body mass. Variability in stress levels might explain some of the variability in the results from this type of study, both flight and ground-based. An increase in stress level is typically associated with the initial days of space flight. In many cases, urinary cortisol levels return to preflight levels after 5 to 9 days, although this phenomenon has yet to be fully characterized or generalized to all crews. Ground-based studies have the potential for stress to increase, but this is not an entirely consistent finding. Some studies have shown no change, or even a downward trend, in cortisol excretion during bed rest [434]. As seen with studies of energy metabolism, administration of exogenous cortisol or thyroid hormone induces metabolic

stress, which produces a more accurate ground-based model of protein metabolism during space flight [175, 400, 495, 496]. Ground-based rodent studies generally show increased proteolysis along with reduced synthesis [31], a pattern similar to that seen in studies of humans during flight, described above.

4. Muscle Loss Countermeasures

A. Mechanical

Exercise is the most common first-pass approach to maintaining muscle mass and strength [1, 33, 34, 136, 677]. The exercise regimens tested as countermeasures to date have not succeeded in maintaining muscle mass or strength (or bone mass) during space flight [677]. On Mir flights, crewmembers differed significantly with respect to in-flight exercise frequency and intensity (related to such factors as mission requirements and personal habits). However, losses of leg muscle volume, detected immediately after flight by magnetic resonance imaging, were almost 20% in all subjects [377]. Similar findings (wide variations in exercise, lack of difference in bone loss) have also been documented for bone loss [603].

Many types of resistive exercise and combination resistive and aerobic exercise protocols have been proposed to aid in the maintenance of both muscle and bone during flight [11, 12, 169, 212, 232, 410, 432, 532, 543, 567, 578, 661], but these have yet to be fully tested on orbit.

Vibration has also received much attention recently in the hope that it can provide a viable musculoskeletal countermeasure [44, 58, 550], but initial reports have found it to be ineffective for muscle [747].

B. Pharmacological

Exogenous testosterone administration during bed rest studies has maintained muscle mass and protein balance, but with no effect on muscle strength [744]. Because of the necessary route of administration (injection) and other issues, this has not been vigorously pursued. Testosterone has also been suggested as a bone loss countermeasure for animal models [734, 735], because a reduction in testosterone concentrations has been observed during flight in humans, animals, and cellular models of space flight [640-647]. A potential confounding factor is the drop in testosterone that has been observed in exercising bed rest subjects (but not controls) [711].

C. Nutritional

Use of protein and amino acid supplementation has long been studied as a potential means to mitigate muscle loss associated with space flight [18, 49, 72, 175, 494, 678], but results have been inconclusive. Oral doses of branched-chain amino acids had little effect on leg-muscle protein kinetics in ambulatory male subjects [167], whereas feeding a bed rest group adequate energy with excess protein reversed nitrogen losses [649]. However, feeding Skylab crewmen energy and protein equivalent to those given to the bed rest group did not prevent negative nitrogen balance and loss of leg muscle strength during flight [430, 666, 725]. In another bed rest study, a leucine-enriched, high-protein diet failed to mitigate muscle loss, and in some sites exacerbated loss [678]. It remains unclear whether nutritional

measures beyond the consumption of adequate energy and protein would be beneficial in reducing muscle atrophy.

5. Protein and Bone

The interrelation of protein and bone health is complex, and often seemingly contradictory. In certain populations (such as growing children), protein is essential for bone growth. However, in some cases, high protein intakes can be detrimental to bone [126], a fact confounded by the type of protein (and amino acids) consumed and by their relation to other dietary factors [127, 523].

High-protein diets lead to hypercalciuria, and increase the risk of fracture and the risk of renal stone formation [127, 249]. In one 5-year study of 120 men, the relative risk of stone formation on a restricted protein (52 g/d) and salt (50 mEq/d) diet was found to be half that of men on a calcium-restricted diet (400 mg/d) [61]. The reason for the decreased risk of renal stones on a low-protein diet is not well understood, but several potential mechanisms have been postulated. It is generally well accepted that high-protein diets induce hypercalciuria, and this can contribute to formation of calcium oxalate or calcium phosphate stones. One hypothesis to explain protein-induced hypercalciuria is related to the "acid-ash" hypothesis that excessive intake of animal protein provides excess sulfur-containing amino acids that are metabolized to sulfuric acid. Since bone is a large reservoir of base, it can be broken down to provide carbonate or phosphate to neutralize fixed acid loads. Furthermore, low urinary pH decreases urinary excretion of citrate, which is a potent inhibitor of stone formation. In addition, dietary animal protein represents a rich source of purines that may raise uric acid excretion, which could increase the risk of forming uric acid stones [750].

Protein-induced hypercalciuria may also be detrimental to bone [497]. Some studies show that high-protein diets increase intestinal absorption of calcium [312], but this has not been widely accepted. The key to understanding the interrelationship of protein and bone may lie in understanding the complexities of these types of studies, which may require a full accounting of many nutrients and environmental factors [355, 356].

Several studies show that animal protein increases acid load more than vegetable protein because of the higher sulfur content per serving of food. Vegetable protein itself does not necessarily have less sulfur per gram of protein, but a larger mass of foods containing vegetable protein would have to be consumed to get the same amount of protein as from foods containing animal protein. It can be assumed that foods containing vegetable protein contain less sulfur than foods containing animal protein. In studies with controlled dietary intakes with varying sulfur content, diets consisting of animal protein yielded greater urinary calcium excretion and lower urinary pH than similar diets consisting mainly of vegetable protein [70]. The results of another study comparing the effects of 2 sources of protein (meat and soy protein), with and without additional supplementation with sulfur amino acids, indicated that dietary meat elicited a greater positive association between protein intake and urinary calcium, sulfur, ammonia, and titratable acids than dietary soy elicited [302]. When the soy diet was supplemented with sulfur amino acids, urinary calcium and acid excretion increased. Conversely, the addition of dietary potassium (as fruit or K^+ supplement) to both diets decreased urinary calcium and acid excretion [302]. Other studies have shown that greater amounts of protein or higher ratios of animal protein to potassium are more

detrimental when bone health is already compromised (such as during bed rest, and potentially during space flight) [756, 757].

Dietary intake of protein, specific types of protein, and patterns of acid and base precursors have recently been associated with the concentrations of urinary markers of bone resorption during bed rest [756, 758, 759]. In one study with male identical twins, the relationships between acid and base precursors in the diet and markers of bone and calcium metabolism during bed rest were investigated [607]. With regard to dietary intake patterns, a strong positive correlation existed between markers of bone resorption (n-telopeptide [NTX], deoxypyridinoline, and pyridinoline) and the ratio of animal protein to potassium intake during bed rest. Figure 22 shows that a positive correlation existed between urinary NTX excretion and the ratio of animal protein to potassium intake during 4 weeks of bed rest. No relationship was found between the ratio of vegetable protein to potassium and markers of bone metabolism. There tended to be a positive association between these variables before bed rest and during weeks 1 and 2 of bed rest, but the relationship was not significant, likely because of high variability among the population and small sample size [756].

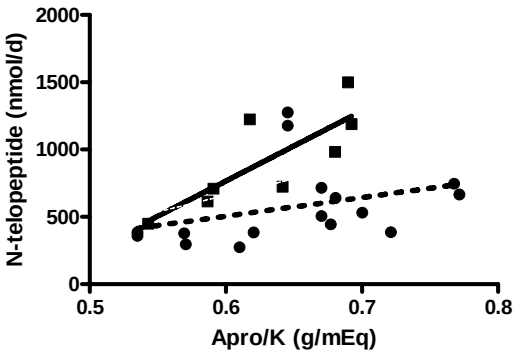

Figure 22. The bone resorption marker n-telopeptide (NTX) was positively correlated with the ratio of animal protein to potassium intake (APro/K) during week 4 of bed rest (solid line, squares), while no relationship was observed in ambulatory subjects (dashed line, circles). Adapted from Zwart et al. [756].

The results above, showing that the ratio of animal protein to potassium intake was less related to bone metabolism markers in the exercising group and more related to bone markers at the end of bed rest, when calcium excretion was highest, support the argument that calcium status could have an important role in determining the effect of protein on bone. If calcium is being resorbed from bone, then acid load can have a more detrimental effect on bone, similar to what has been observed in other studies of the effect of high-protein diets on bone [126, 127].

The idea that the levels of acid and base precursors in the diet can affect bone and calcium metabolism is supported by the results of studies testing the ability of a supplement containing essential amino acids and carbohydrate (45 g/d essential amino acids and 90 g/d sucrose) to mitigate muscle loss [757]. The supplement contained 1.5 g methionine, which is about 1.13 times the recommended daily intake (supplementing the amount of methionine provided in the diet). The sulfur in methionine is converted in the body to sulfuric acid, and thus methionine is an acid precursor in the diet. It was evident that more methionine was broken down than was used by the body because urine pH decreased in the amino acid-

supplemented group (Figure 23). It was hypothesized that this low-grade metabolic acidosis [708] contributed to the higher urinary concentrations of bone resorption markers (Figure 24) and calcium excretion (Figure 25) in the supplemented group.

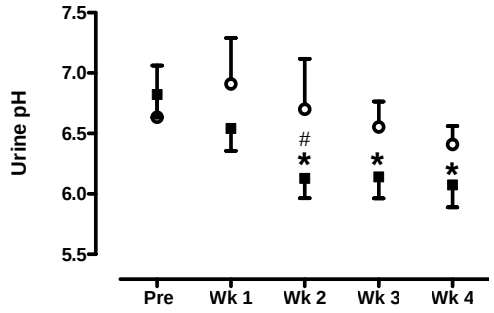

Figure 23. Urine pH (mean ± SD) of amino acid-supplemented (■) and placebo (○) groups during 4 weeks of bed rest. *Significantly different from before bed rest (Pre), $P < 0.05$. #Significant difference between groups, $P < 0.05$. Figure is from Zwart et al., J Appl Physiol 2005 [757].

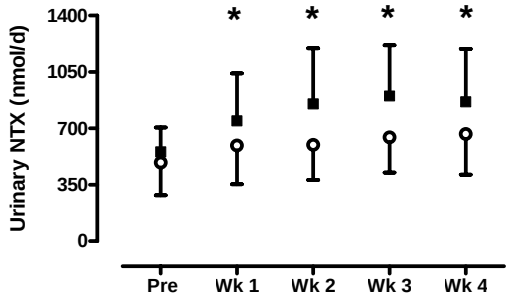

Figure 24. Urinary n-telopeptide (NTX) excretion (mean ± SD) of amino acid-supplemented (■) and placebo (○) groups during 4 weeks of bed rest. *Significantly different from before bed rest, $P < 0.05$ (no significant differences between groups). Figure is from Zwart et al., J Appl Physiol 2005 [757].

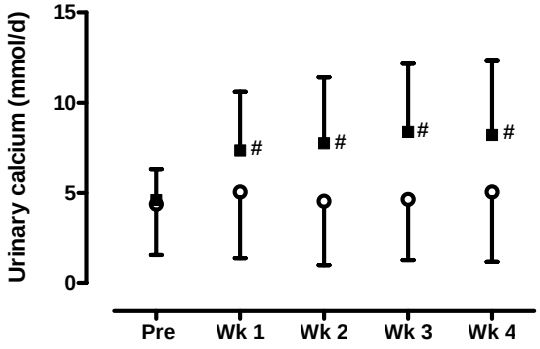

Figure 25. Urinary calcium excretion (mean ± SD) of amino acid-supplemented (AA, ■) and placebo (○) groups during 4 weeks of bed rest. #AA values were significantly different from pre-bed rest values, $P < 0.05$. Figure is from Zwart et al., J Appl Physiol 2005 [757].

In a separate study, 13 volunteers were subjected to 60 to 90 days of 6º head-down-tilt bed rest [761]. Net acid excretion, as determined by dietary acid and base components, was positively correlated with NTX during but not before bed rest (Zwart et al., unpublished data). Net acid excretion has also been associated with calcium loss using meta-analysis techniques [164].

6. Dietary Intake and Requirements

Maintaining a proper protein intake is vital, as both low-protein and high-protein diets can cause harm (and, at the extreme, death). A low-protein diet (below the recommended dietary allowance) for up to 4 weeks can decrease calcium absorption and cause increased secretion of parathyroid hormone in otherwise healthy subjects [307, 308]. The impact of chronically low protein intake is not well understood; however, several studies suggest that low-protein diets are associated with loss of bone density [187, 520].

The current documented space flight requirement for protein intake is 0.8 g/kg per day, not to exceed 35% of the total daily energy intake [460]. About 2/3 of the total amount of protein is to be provided in the form of animal protein, and 1/3 of the total should be in the form of vegetable protein. In the U.S., the recommended dietary allowances (RDAs) for those in the age range of the astronaut population are 56 g/d for men and 46 g/d for women [279]. The acceptable range for protein intake is 10% to 35% of total energy intake [279]. For historical reference, the space flight daily protein requirements were defined in 1991 for missions of 30 to 120 days, and were defined similarly in 1995 for missions up to 360 days as 10% to 15% of total energy intake [457, 458].

Actual intakes of protein typically exceed these recommendations, as shown in Table 2 (page 15). European studies have shown that on long missions reaching (or exceeding) nominal protein intakes is common, but that on short flights (Shuttle missions) protein intake is less than the recommended amount because of insufficient food intake [242].

7. Risks on Exploration Missions

The risks associated with protein intake come from deficiency or excess. Deficiency of protein leads to muscle loss, weakness, wasting, tissue breakdown, inability to perform the job (including getting out of the spacecraft), and ultimately death. Low-protein diets can have negative consequences for bone [307, 309-311]. Excess protein exacerbates increased excretion of calcium and the risk of renal stone formation, and is detrimental to bone. Specific amino acids may additionally increase these risks.

8. Remaining Questions

Research continues on the effects of amino-acid supplementation as a means to mitigate muscle loss. This needs to continue in order to refine the details (such as dose and timing) and assess the viability of this countermeasure.

Further research is also required to better understand the effects of protein source (animal vs. vegetable, and the effect of sulfur amino acid content) on bone loss and renal stone risk [460, 758]. The concept of using these effects as nutritional countermeasures has long been advocated [171], but it has yet to be evaluated.

C. CARBOHYDRATE

1. Background

Carbohydrates play an important role in the body because they supply the primary source of energy as well as a readily available source. This energy is oxidized and used by various organs and cells in the body, particularly the brain and red blood cells, which depend solely on carbohydrate for energy.

Dietary carbohydrates are classified into a number of different categories, all based on the number of sugar units present. Monosaccharides are composed of only 1 sugar unit, such as glucose or fructose. Disaccharides are composed of 2 sugar units; examples are sucrose (glucose + fructose) and lactose (glucose + galactose). Longer chains of sugar units, up to 10, are known as oligosaccharides, and polysaccharides contain more than 10 sugar units. Examples of polysaccharides are starch and glycogen, which are the storage forms of carbohydrate for plants and animals, respectively.

The human body stores about 150 to 500 g of carbohydrate as glycogen, in the liver and skeletal muscle [388]. Most of the body's glycogen is in skeletal muscle. Muscle glycogen stores are used mainly by muscle, whereas the smaller glycogen stores in the liver are used to maintain, store, and export blood glucose. Glycogen stores, especially those in the liver, fluctuate greatly during the day in response to food intake, and these fluctuations may be involved in the regulation of food intake [650]. Liver stores of glycogen are depleted after 12 to 18 hours of fasting [388]. In skeletal muscle, glycogen synthesis is triggered by a rise in insulin after the consumption of carbohydrates. De novo synthesis of glucose from noncarbohydrate precursors can and does occur in the body, if needed. This allows the liver to maintain adequate blood glucose concentrations. Insulin is required for the uptake of glucose into cells, and various transporter systems are found in different types of tissues that utilize glucose.

As long as the intake of protein and fat is adequate, the lower limit of dietary carbohydrate that is compatible with life is zero. The level of carbohydrate required to provide optimal health is not as clearly defined.

2. Findings from Space Flight and Ground-Based Research

Carbohydrate should make up the most significant portion of the diet because it is the main energy source. Requirements for carbohydrate in space are thought to be similar to those on Earth. However, to date, few investigations have been conducted on the effects of microgravity on the metabolism of dietary carbohydrate, and those studies have had conflicting results.

Early studies documented increases in blood concentrations of both insulin and glucose at landing after Apollo (Figure 26) and Skylab (Figure 27, Figure 28) flights.

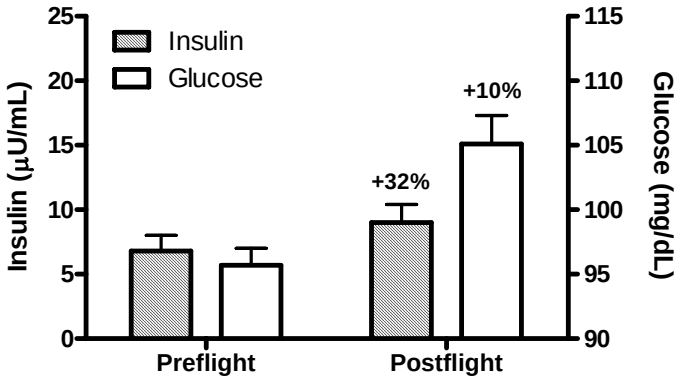

Figure 26. Plasma insulin (n = 22) and glucose (n = 33) in Apollo crewmembers before and after flight. Data are from Leach et al., 1975 [366].

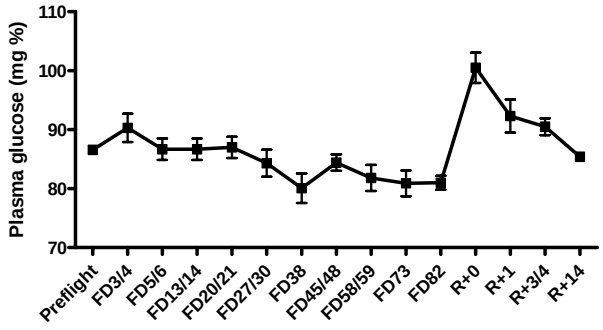

Figure 27. Plasma glucose in Skylab crewmembers (n = 9) before, during, and after flight. Data are from Leach and Rambaut, 1977 [361] .

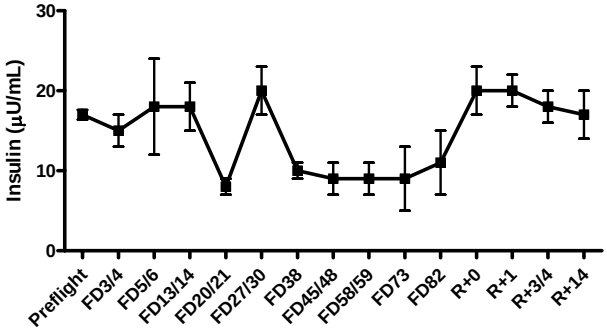

Figure 28. Plasma insulin in Skylab crewmembers (n = 9) before, during, and after flight. Data are from Leach and Rambaut, 1977 [361].

On the Shuttle, studies by German investigators showed no impact of 7 days of flight on glucose tolerance tests [406]. Additionally, a Russian study documented a reduction in fasting plasma glucose after 60 or 88 days of flight on a Salyut-Soyuz spacecraft complex, and a reduced peak of blood glucose in glucose tolerance tests [6, 592]. Insulin resistance (lack of sensitivity to insulin) has been found to result from simulated weightlessness (bed rest) [49, 56, 648, 696]. Using C-peptide excretion as a proxy, Stein et al. found evidence of insulin resistance during actual and simulated spaceflight [624]. Efforts to maintain muscle mass (and presumably correct the insulin resistance) continue, but little research has been done to pursue this as a nutritional issue.

3. Dietary Intake and Requirements

The current documented requirement for carbohydrate intake during space flight is 50% to 55% of the total daily energy intake. In the U.S., the acceptable macronutrient distribution range for dietary carbohydrate is defined as 45% to 65% of the total dietary energy intake [558]. A minimum intake of 140 g/d is required to maintain the needs of organs that require carbohydrate for energy production [408]. For reference, the daily carbohydrate requirement for male and female astronauts was originally defined in 1991 for missions of 30 to 120 days as 50% of total energy intake [457], and in 1995 for missions up to 360 days as 50% to 55% of total energy intake [458]. The 1995 requirement included an admonition that most of the carbohydrate should be provided as complex carbohydrates, with less than 10% of total carbohydrate provided as simple sugars.

Macronutrient intake by space crews is relatively high in protein and carbohydrate content (close to 60% of calories) [350], as shown in Table 2 on page 15. Some have speculated that this may represent a shift in macronutrient preferences, but it may also simply be related to the high sugar content of many of the available beverages in the U.S. food supply [346].

4. Risks on Exploration Missions

Suboptimal carbohydrate intake before and during space flight may have consequences for the crew's productivity and impede their ability to respond in emergency situations [345]. Deficiency of carbohydrate leads to ketosis. A ketotic state would likely impair performance of crewmembers, as seen in studies conducted by the military [507], as well as increase renal stone risk secondary to reduced urinary pH [508, 509, 751]. Other aspects of the mission would also be at risk (for example, the life-support systems may not be able to remove exhaled ketones from the air). Toxicity of carbohydrate has not been well studied, and would likely be an issue only because it would displace other nutrients (protein and fat) from the diet.

5. Remaining Questions

Few data are currently available to assess the impact of space flight on carbohydrate metabolism. Observations from space flight as well as ground-based bed rest studies show subtle changes in insulin secretion, insulin resistance, and glucose intolerance [142, 393, 648, 696]. Even subtle changes in such important metabolic processes make it critically important to consider the likelihood, nature, and consequences of altered carbohydrate and insulin metabolism for exploration missions.

D. DIETARY FIBER

1. Background

Dietary fiber consists of nondigestible food components that are typically carbohydrate and plant-based. Nonstarch polysaccharides, including cellulose, gums, pectins, mixed-linkage β-glucans, and hemicelluloses, are the major components of dietary fiber. Lignan is also included even though it is a noncarbohydrate component.

Evidence exists that dietary fiber plays a role in decreasing plasma cholesterol, modifying the response of blood glucose to food (the glycemic response), improving large-bowel function, and decreasing the bioavailability of some nutrients. Epidemiological evidence also points to relationships between diets high in fiber and decreased incidence of cardiovascular disease and bowel cancer [287].

2. Findings from Space Flight and Ground-Based Research

Changes in gastrointestinal function and gut transit time during space flight have been described. Because mouth-to-cecum transit times are slower on orbit [345], adequate dietary fiber will be essential to maintain gastrointestinal function and decrease the incidence of constipation.

3. Dietary Intake and Requirements

The current documented requirement for dietary fiber intake in space flight is 10 to 14 g/1000 kcal. In the U.S., acceptable daily requirements for dietary fiber intake [279] are, for those aged 19 to 50 years, 38 g/d for men and 25 g/d for women, and for individuals aged 51 to 70 years, 30 g/d for men and 21 g/d for women.

For reference, the daily total fiber requirements for male and female astronauts were defined in 1991 for missions of 30 to 120 days as 10 to 15 g, in soluble and insoluble forms [457], and in 1995 for missions up to 360 days as 10 to 25 g, in soluble and insoluble forms [458].

4. Risks on Exploration Missions

Inadequate dietary fiber, in combination with low fluid intake, may lead to constipation. An open question exists about the effect of fiber on vitamin K synthesis by colon microflora (and its availability) during space flight (see vitamin K section).

5. Remaining Questions

Several studies have shown that specific dietary fatty acids and types of dietary fiber can reduce animals' risk of getting radiation-induced cancer [122, 682]. Further research is warranted to investigate the potential protective effects of fiber on the risk of radiation-induced cancer in humans exposed to high-linear energy transfer radiation during space flight.

E. FAT

1. Background

Fat is the most energy-dense of all the nutrients, and therefore is a major energy source for the body. Chemically, dietary fat is mainly in the form of triacylglycerols, which contain a glycerol backbone with as many as 3 fatty acids attached. Many types of fatty acid exist, including saturated, monounsaturated, polyunsaturated, and trans. Dietary fat assists in the absorption of fat-soluble vitamins and supplies the body with the 2 essential fatty acids, linoleic acid and linolenic acid. These essential fatty acids are necessary for growth and development as well as many other biochemical processes, including production of eicosanoids (physiologically active substances derived from arachidonic acid). Lipids, in the form of phospholipids, make up a large proportion of the structural components of the cellular membrane bilayer. Energy stored as fat is released in the process of fatty acid oxidation, and fat supplies more energy than any other macronutrient because of its higher content of carbon-to-hydrogen bonds.

Body stores of fat are located mainly in adipose tissue as triacylglycerols. Adipose tissue is dispersed throughout the human body, its distribution differing slightly between genders.

According to case studies, people following fat-free diets can exhibit symptoms of essential fatty acid deficiencies after only 1 month. An infant consuming fat-free total parenteral nutrition for 3 months developed skin lesions and had polyunsaturated fatty acid levels less than 10% of control values [501]. In another study, an adult who consumed fat-free total parenteral nutrition for 7 months developed a severe dermatitis by the end of the first month. Omega-3 (n-3) fatty acids made up 0.01% of the fatty acids of this person's plasma phospholipids, which means that the patient was almost completely depleted of n-3 fatty acids [266].

2. Findings from Space Flight and Ground-Based Research

While few, if any, studies have been conducted to look at dietary fat, plasma lipid levels, and related factors in space flight, voluminous data exist from routine medical examinations conducted before and after flight, along with annual medical exams (Figure 29, Figure 30, Figure 31).

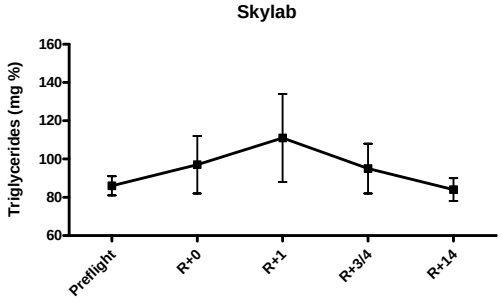

Figure 29. Plasma triglycerides in Skylab crewmembers (n = 9) before and after flight. Data are from Leach and Rambaut, 1977 [361].

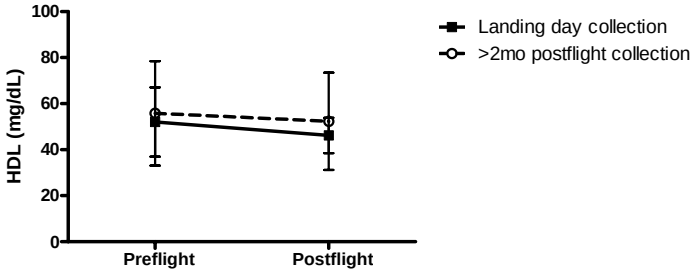

Figure 30. Serum high-density lipoproteins (HDL) in ISS crewmembers (n = 12) before and after flight. Postflight data are from landing day or 2 to 12 months after flight. Because HDL is not a routine measurement at landing, some data were available only at the next medical exam.

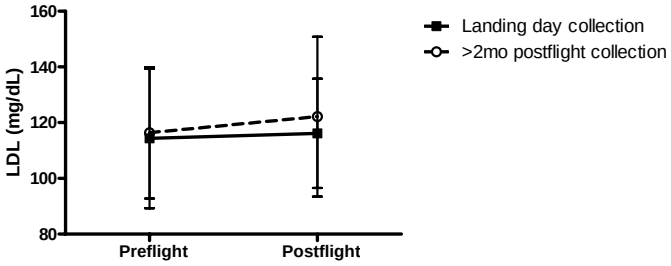

Figure 31. Serum low-density lipoprotein (LDL) in ISS crewmembers (n = 12) before and after flight. Postflight data are from landing day or 2 to 12 months after flight. Because LDL is not a routine measurement at landing, some data were available only at the next medical exam.

Contrary to the typical lipoprotein response to weight loss, low-density lipoprotein (LDL) concentrations tended to increase in long-duration crewmembers who lost weight during the flight. This relationship seemed to return to normal by the subsequent medical exam (according to available data, 50 to 257 days after landing) (Figure 32).

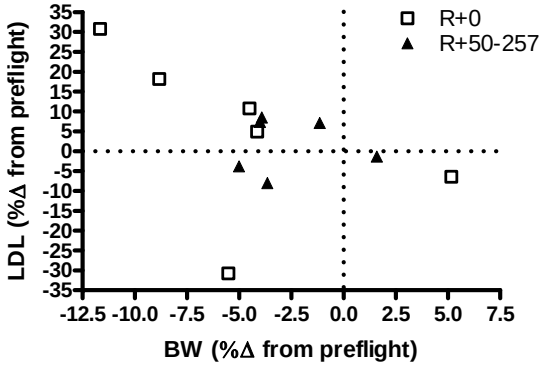

Figure 32. Relationship between the loss of body mass observed after landing and the change in serum LDL in ISS crewmembers (n = 12). Because LDL is not a routine measurement at landing, some data were available only at the next medical exam, which ranged from 50 to 257 days after landing.

Bed rest studies have documented alterations in fuel homeostasis, including gender differences [56]. Specifically, lipogenesis was increased during bed rest, to a greater extent in women than in men. Additionally, men had increased carbohydrate oxidation [56]. Given these data, and the insulin, leptin, and other endocrine changes noted in bed rest and space flight [409, 630, 631], changes in fuel homeostasis in bed rest clearly warrant additional investigation.

3. Dietary Intake and Requirements

The current documented space flight requirement is for dietary intake of fat to make up 25% to 35% of the total daily energy intake [460]. Dietary intake of n-6 and n-3 fatty acids is to be 14 g/d and 1.1 to 1.6 g/d, respectively. Saturated fat should be < 7% of total calories, trans fatty acids < 1% of calories, and cholesterol intake < 300 mg per day. In the U.S., currently no RDA or adequate intake level has been set for total fat because data are insufficient to determine the level of dietary fat that may put one at risk for inadequacy or may contribute to the prevention of chronic disease [279]. The acceptable distribution range for fat intake is 20% to 35% of total energy intake [279]. For reference, the daily total fat requirement for male and female astronauts was defined in 1991 for missions of 30 to 120 days to be 30% to 35% of total energy intake [457], and in 1995 for missions up to 360 days to be 30% to 35% of total energy intake [458].

Actual in-flight intakes of total fat are typically 25% to 30% of calories, as shown in Table 2 (page 20). Intake of specific types of fat has yet to be documented during flight.

4. Risks on Exploration Missions

Deficiency of fat leads to essential fatty acid deficiency and ultimately death. Toxic levels of fat lead to high serum cholesterol, obesity, atherosclerotic plaques, and ultimately coronary heart disease, and ultimately death.

5. Remaining Questions

Alterations in fuel homeostasis and regulatory hormones have been noted in space flight and ground-based studies. The implications of these findings in long-duration exposures are not well understood.

The role of n-3 fatty acids in cancer prevention is currently being investigated in animal models of space flight radiation effects [122]. Not only do n-3 fatty acids (in combination with pectin) show promise in alleviating cancer risk [94, 122, 267, 557, 682], but these fatty acids also have well-documented cardiovascular benefits. Abundant data show that eicosapentaenoic acid can successfully prevent muscle atrophy in other muscle-wasting circumstances, such as cancer or sepsis [40, 595, 672-675, 727, 728, 732, 733], indicating the likelihood is high that eicosapentaenoic acid will have the same beneficial effects on muscle atrophy during space flight or in ground-based analogs including bed rest. Thus, further research on eicosapentaenoic acid is warranted.

Recent preliminary analysis of data from bed rest studies has revealed a negative correlation between n-3 fatty acids and bone loss during bed rest. Although this is still being evaluated, it provides additional evidence of the importance of evaluating fish oils as a countermeasure for muscle, bone, and radiation risks of space flight.

F. FLUID

1. Background

Adequate fluid intake is necessary to maintain the body's normal hemodynamic state and normal fluid osmolality, which is important for cardiovascular health and for maintenance of fluid and electrolyte homeostasis. Water is a structural component of the body and the solvent for transportation of nutrients and waste. Fluid and electrolytes may be lost from the body by a variety of routes and for a variety of reasons. They are excreted in sweat, urine, and feces, and in abnormal situations excessive amounts can be lost by these routes and others. Significant losses may occur through the gastrointestinal tract as a result of diarrhea, vomiting, or gastric drainage. Loss through the skin increases with fever, increased metabolism, sweating, and burns [485].

Total body water makes up about 50% to 70% of body mass [561]. Fluid requirements increase with metabolic rate and heat stress. Death from dehydration can occur within weeks of depriving the body of all water [655].

2. Findings from Space Flight and Ground-Based Research

Fluid and electrolyte homeostasis is significantly altered during space flight, and this has been extensively reviewed [130, 145, 146, 365, 367, 368, 370, 371, 373, 601]. The hypothesis originally proposed to explain this was that upon entering weightlessness, the human body would experience a headward shift of fluids, with subsequent diuresis and dehydration. A series of flight experiments was conducted to assess fluid and electrolyte homeostasis during space flight; the most comprehensive of these took place on the 2 Spacelab Life Sciences missions in the early 1990s. Despite much research, the hypothesis of diuresis and subsequent dehydration secondary to the headward fluid shifts has never been confirmed during actual space flight [145, 198, 365, 480, 481, 601].

Within hours of the onset of weightlessness (the earliest available data point), a reduction in both plasma volume and extracellular fluid volume had occurred, accompanied by the "puffy" faces typically observed early in flight [365, 468]. Initially, the decrement in plasma volume (~17%) was larger than the decrement in extracellular fluid volume (~10%), suggesting that interstitial fluid volume (the other four-fifths of extracellular fluid) is conserved proportionally more than plasma volume [365]. The idea that interstitial fluid volume is conserved is supported by rapid decreases in total circulating protein, specifically albumin [365], indicating that protein, and associated oncotic pressure, shifted from the intravascular to the extravascular space. This would have facilitated the initial changes in plasma volume [365].

Following the initial adaptation, extracellular fluid volume further decreased between the first days of flight and 8 to 12 days after launch, from the initial ~10% below preflight levels to ~15% below preflight levels [365]. Plasma volume was partially restored during this period, from the initial ~17% below preflight levels to ~11% below preflight levels [365], and it has been found to remain 10% to 15% below preflight levels even for extended-duration flights [290].

It is hypothesized that the shift of protein and fluid to the extravascular space represents an adaptation to weightlessness, and that after several days, some of the extravascular albumin has been metabolized, with a loss of oncotic force and a resulting decreased extracellular fluid volume and increased plasma volume [365, 481]. This loss of extracellular protein (intra- and extravascular) and the associated decreased oncotic potential probably play a role in postflight orthostatic intolerance, which has been considered to result partly from reduced plasma volume at landing [77]. Furthermore, the loss of protein may in part explain why fluid loading alone does not restore circulatory volume [274, 698], as no additional solute load exists to maintain the fluid volume. Another potential (or perhaps partial) explanation for the failure of fluid loading is that because astronauts' diets are high in sodium, additional salt cannot help increase plasma volume or extracellular fluid volume. This has been documented in bed rest [Heer et al., 2009].

The effect of space flight on total body water has been evaluated to assess hydration. Shuttle and Skylab astronauts had decreases of about 1% in total body water during flight [364, 365, 665], and the percentage of body mass represented by water did not change. Thus, the often-proposed weightlessness-induced dehydration does not exist. This has also been shown by European investigators on Shuttle and Mir missions [144, 145, 480-482].

Diuresis is also typically not observed during flight [32, 144, 196, 197, 291, 373, 480, 481, 601], for a number of possible reasons. Operational constraints have made it difficult to

document urine volume accurately on the first day of space flight. However, on the Spacelab Life Sciences missions, urine volume on the first 3 days of flight was significantly less than preflight volume, and urine volume tended to be less than preflight volume throughout the flight [365]. Urine volumes on a week-long flight to Mir were also less than preflight volumes [196]. During the first week of the 59- and 84-d Skylab flights [361], urine volume was less than it was before flight, and for the remainder of the missions it was unchanged from preflight levels. Decreased fluid intake likely accounts for the decreased urine volume, which was accompanied by little or no change in total body water. Adequate urine volume during flight is important for reducing the risk of renal stone formation [226, 729-731].

As mentioned above, the percent of body mass represented by total body water is relatively unchanged during flight [365]. However, on a volume basis, the change in extracellular fluid volume was found to be greater than the change (or lack of change) in total body water [365]. Thus, by difference, intracellular fluid volume increased during space flight. This had been previously hypothesized from ground-based studies [211] and observed in postflight studies of Apollo crewmembers [291]. The mechanism for a space flight-induced increase in intracellular fluid volume is unknown. One possible explanation is that a shift in fuel utilization results in increased glycogen storage, a condition known to increase cellular water content.

Diuresis has been documented to occur in bed rest studies [478, 479, 697]. Urinary albumin, a marker of kidney function, has been shown to be reduced in both space flight (compared to before flight) and bed rest (compared to the ambulatory state) [100-102]. However, space flight, but not bed rest, results in reduced urine flow rates [480]. Taken together, these data suggest that differences in fluid metabolism exist between analog studies and actual space flight [145, 197, 198, 478, 480-482]. Such differences do not seem to be a simple effect of abnormal renal function, and thus require further investigation [533].

3. Dietary Intake and Requirements

In the U.S., the recommended total intake of water (including that contained in food, beverages, and drinking water) is 3.7 L/d for men (19 years and older), and 2.7 L/d for women (19 years and older) [280]. This is considered “adequate intake.” Since 1991 [457, 458], the space flight requirement for fluid has been 1 to 1.5 mL/kcal, with a minimum intake of 2000 mL/d. Actual fluid intakes meet this minimum (> 2 L) requirement on average, but every crewmember does not meet it every day, as shown in Table 2 (page 15).

4. Risks on Exploration Missions

Although no space flight-induced dehydration occurs, care must be taken to ensure adequate fluid intake and hydration status. Inadequate fluid intake increases the risk of dehydration and renal stone formation. Fluid intake during flight is typically less than preflight intake, and often below the recommended quantity. In closed flight vehicles, water is often a limiting resource, but rationing of water should be avoided.

Deficiency of fluid leads to dehydration and ultimately death. Likewise, an excess of fluid intake leads to water intoxication and ultimately death. Obviously, the risk of this occurring during space flight, where water is a limited commodity, is extremely low.

5. Remaining Questions

Decreased fluid intake during space flight may be a consequence of reduced thirst during flight [345], but the reason for reduced thirst is unknown.

Studies described above have documented that total body water is unchanged during flight, but apparently a shift of fluid from the extracellular to the intracellular compartment occurs. The effect of this on cell size and cell function (such as the effect of a change in the density of receptors on cell membranes) has not been evaluated. This might be responsible for some of the microgravity-induced changes noted in other systems (such as the endocrine, cardiovascular, and immune systems).

G. SODIUM AND CHLORIDE

1. Background

Sodium is the major cation of extracellular fluid [485]. Together with chloride, sodium is utilized by the body to maintain normal water distribution, osmotic pressure, and anion-cation balance in the extracellular fluid compartment [669]. Electrolyte concentrations in the body are essential for proper cardiovascular function and are under renal and hormonal control [516]. Increases in blood sodium levels can be caused by diabetes, renal polyuria, diarrhea, insufficient water intake, excessive sweating, or increased dietary sodium intake. Sodium levels decrease with edema, excessive water intake, vomiting, diarrhea, diuretic therapy, renal tubular damage, hyperaldosteronism, or lower dietary intake.

For the normal adult, total body sodium averages about 60 mmol/kg body weight. Forty to 45 percent of total sodium resides in bone, with the balance found in extracellular and intracellular fluid. These sodium stores are classified as either exchangeable (42 mmol/kg body weight) or nonexchangeable, the exchangeable stores being composed of all cellular sodium and less than half of bone sodium [512]. Exchangeable sodium becomes available by diffusion when plasma sodium levels become low, and in states of edema, the exchangeable sodium stores absorb sodium.

Animal studies show that symptoms of sodium deficiency occur after 3 to 4 weeks of dietary sodium restriction [405]. During acute starvation, urinary sodium excretion decreases to less than 0.2 g within 10 days [45], and can be affected by the amount of sweat [313]. Plasma sodium levels are maintained fairly well during acute starvation: an initial decrease is followed by a return toward normal values [193]. Maintenance of blood sodium is also observed during semi-starvation. During the Minnesota Experiment, plasma sodium levels in samples taken after the 6-month semi-starvation period were 0.6 ± 7.3% higher than baseline levels (n = 4) [313]. Six days of undernutrition resulted in large negative balances of sodium chloride (–12.8 ± 3.6 g/d), likely related to changes in water balance [313].

2. Findings from Space Flight and Ground-Based Research

Pre-, in-, and postflight plasma sodium and chloride data are available from Apollo (Figure 33, Figure 34), Skylab (Figure 35, Figure 36), and Shuttle (Figure 37) flights, and have been reviewed extensively [198, 239, 242, 481, 601].

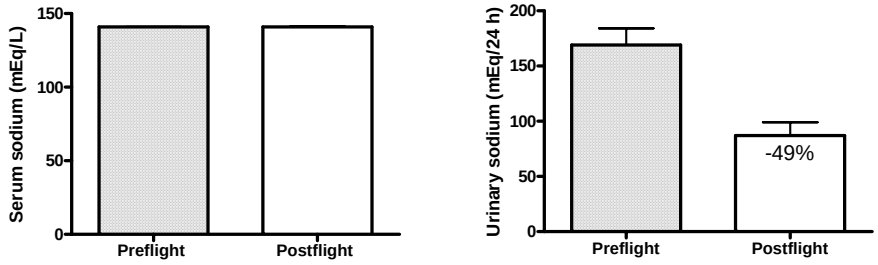

Figure 33. Serum (n = 33) and urinary (n = 30) sodium from Apollo crewmembers. Numbers in bars represent the percent change from preflight values. Adapted from Leach et al., 1975 [366].

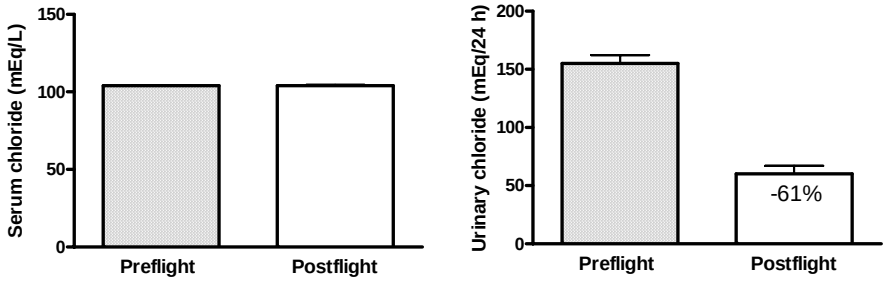

Figure 34. Serum (n = 33) and urinary (n = 30) chloride from Apollo crewmembers. Numbers in bars represent the percent change from preflight values. Adapted from Leach et al., 1975 [366].

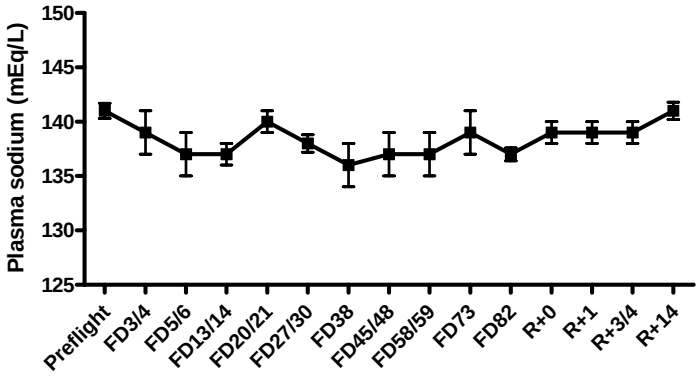

Figure 35. Plasma sodium of Skylab crewmembers (n = 9) before, during, and after flight. Data are from Leach and Rambaut, 1977 [361].

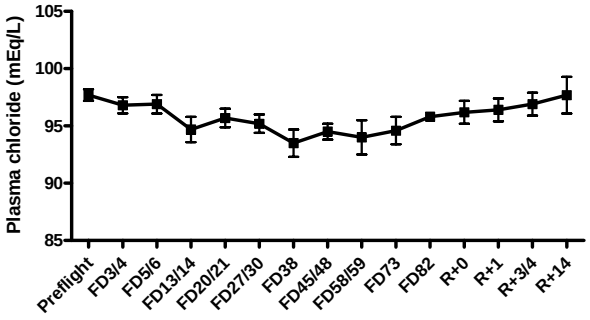

Figure 36. Plasma chloride of Skylab crewmembers (n = 9) before, during, and after flight. Data are from Leach and Rambaut, 1977 [361].

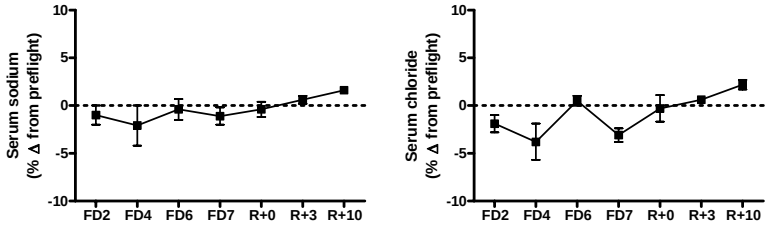

Figure 37. Serum sodium (left panel) and chloride (right panel) of Shuttle crewmembers (n = 2 to 6) during and after flight, expressed as a percent change from preflight values. Data are from Leach-Huntoon et al., 1987 [359].

In-flight sodium intakes (Figure 38) during Skylab and Shuttle missions averaged 4 to 5 g, and were similar to the astronauts' preflight intakes [62]. The current food system is high in dietary sodium, and typical intakes on the ISS have been in excess of 4.5 g, even with suboptimal food intake [610]. Intakes as high as 7 to 10 g of sodium per day have been observed. Sodium homeostasis and blood sodium levels are maintained during real and simulated space flight [352], but the high sodium content of the current space food system makes it important to monitor and restrict dietary sodium intake of astronauts to maintain their bone and renal health.

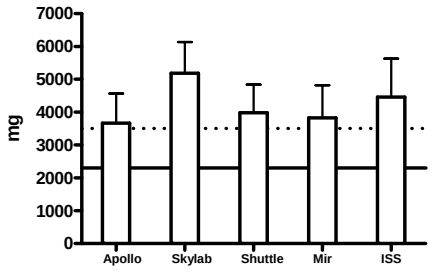

Figure 38. In-flight dietary sodium intake (mg/d) across space programs. Apollo n = 33, Skylab n = 9, Shuttle n = 32, Mir n = 7, ISS n = 23. Apollo and Skylab data are from Bourland et al., 2000 [62]. Figure is adapted from Smith and Lane, 2008 [611], with additional data from Smith et al., 2005, and Smith and Zwart, 2008 [610, 612].

European studies with Mir crewmembers documented positive sodium balance during space flight, in a non-osmotic fashion (that is, without a concomitant increase in fluid compartments) [198, 242, 481]. These data were confirmed in a series of ground-based studies, documenting an increase in mRNA expression of some of the enzymes required for glycosaminoglycan syntheses in the skin, the displacement of sodium by hydrogen in the glycosaminoglycans, and a subsequent acidosis [248].

On Earth, excessive sodium intake has been associated with increased bone turnover [155, 207, 208]. Dietary sodium is known to affect calcium homeostasis [92, 107, 238, 259, 472, 474]. A predictable relationship exists between urinary sodium and calcium; that is, for each 100 mmol of sodium excreted in urine, 1 mmol of calcium is excreted [318]. This phenomenon is expressed at high levels of dietary sodium.

Over 90% of dietary sodium is absorbed, even when intake is high [240]. Sodium is excreted mostly in the urine, but about two-thirds of the sodium filtered by the kidney is reabsorbed by mechanisms thought to involve solvent drag and electrochemical gradients. The sodium-dependent calcium transport system uses the energy stored in the electrochemical gradient of sodium to drive calcium into the lumen of the proximal renal tubule, and ultimately leads to increased calcium loss secondary to increased sodium excretion. In the distal tubule, calcium is preferentially reabsorbed, an event stimulated by parathyroid hormone (PTH) and cyclic adenosine monophosphate (cAMP) [3]. Cyclic AMP also influences reabsorption of sodium [110].

A small amount of sodium is excreted in feces. When 500 mmol sodium was ingested each day for 7 days, the average fecal excretion was 1.8 ± 0.4% of the total dose, and when smaller amounts of sodium were ingested (50 mmol/d), an average of 6.0 ± 1.0% was excreted in the feces (Figure 39).

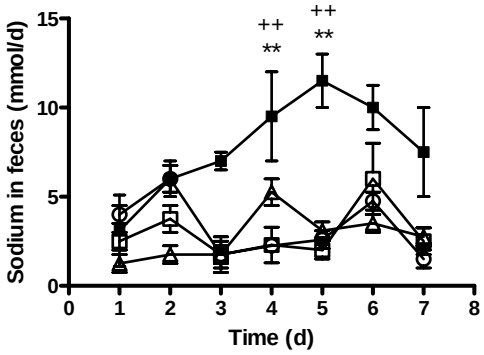

Figure 39. Fecal sodium excretion in 4 groups with different sodium intake (Δ: 50 mmol NaCl/d; □: 200 mmol NaCl/d; ○: 400 mmol NaCl/d; ■: 550 mmol NaCl/d). Values are mean ± SEM (n = 8). Fecal sodium excretion increased significantly with increasing sodium intake. **Significantly different from the 50 mmol NaCl/d group. $^{++}$Significantly different from the 200 mmol NaCl/d group ($P < 0.01$). Adapted from Heer, 1996 [240].

Salt loading alone increases intestinal calcium absorption. In hypoparathyroid patients, dietary salt increased intestinal calcium absorption in one study by Meyer [427] but not in another study by Breslau [69]. In Breslau's study, calcium absorption correlated with serum 1,25-dihydroxyvitamin D. Thus, conclusions about the role of PTH in the increase in intestinal calcium absorption after a sodium load are speculative.

Studies in premenopausal women suggest that increased intestinal calcium absorption, rather than increased bone resorption, compensates for sodium-induced hypercalciuria in subjects whose adaptive processes related to bone metabolism are intact [201, 392]. Ginty et al. [201] examined the effects of 7 days of high or low dietary sodium on bone markers in young women. Although urinary calcium was increased with high (180 mmol/d) sodium intakes, the effect of high sodium on markers of bone resorption was not different from the effect of low (80 mmol/d) sodium intakes. Lietz et al. [392] also found no effect of intakes of 170 mmol/d or 60 mmol/d of sodium for 8 days on bone resorption markers in postmenopausal women. However, Evans et al. [155] reported that postmenopausal women ingesting 300 mmol sodium per day for 7 days had greater excretion of bone resorption markers than those ingesting 50 mmol sodium per day. These differences were not observed in a premenopausal group [155]. These results suggest that bone resorption is increased in situations where the adaptive responses of bone are limited or altered, as they are after menopause.

Data from human and animal studies suggest that high dietary sodium chloride leads to bone loss due to increased bone resorption [54, 227-229, 419, 420, 573], and even that restriction of dietary sodium will reduce bone resorption [475]. In a review of the interactions between dietary salt, calcium, and bone, Massey and Whiting [420] suggested that habitual excessive salt intake contributes to bone loss. Other reviewers have come to the conclusion that increased dietary sodium chloride intake negatively affects acid-base balance, with subsequent loss of calcium [132, 184].

Massey and Whiting [420] found that the effect of excessive salt intake on bone loss is modulated in specific subpopulations. For example, people who tend to form renal calcium stones are more responsive to changes in dietary salt than are non-stone formers. Although sodium intakes of stone formers are typically similar to those of controls [163, 679], the detrimental effects of high sodium intakes on renal stone risk have been well documented [54, 132, 573]. Increasing sodium intake from 50 mmol/d to 300 mmol/d increased renal stone risk by elevating urinary saturation of calcium phosphate and monosodium urate, and reducing inhibition of calcium oxalate crystallization [554].

Work by Goulding [207, 208] and Matkovic [421] has generated interest in the effect of dietary sodium on bone mass. High levels of dietary sodium are not only major predictors of urinary calcium and hydroxyproline excretion, but are also associated with greater loss of bone with age, unless dietary calcium is supplemented [134]. Work by Dr. Heer's group has also documented the resorptive response to high dietary sodium, and the role of acid-base balance in this process [188].

Dietary sodium also seems to exacerbate the calciuric responses to musculoskeletal unloading in weightlessness. Bed rest subjects consuming a low-sodium diet (100 mmol/d) had no change in urinary calcium, while those on a high-sodium diet (190 mmol/d) had hypercalciuria [23]. A more recent bed rest study by Heer et al. documented that the high-sodium-induced increase in bone resorption exceeded the bed rest-induced increase, through a mechanism mediated by acid-base balance [188-190]. A symposium was held recently in Germany (and proceedings published in 2008) regarding the impact of acid-base balance on health issues [708], including the role of sodium in bone loss [24, 78, 185].

3. Dietary Intake and Requirements

In the U.S., the recommendation for adequate intake of sodium for men and women ages 19 to 50 years is 1.5 g/d, and for men and women ages 51 to 70 years it is 1.3 g/d [280]. The current documented space flight requirement for dietary sodium is 1500 to 2300 mg/d (1.5 to 2.3 g/d) for both women and men. The ISS sodium requirement was slightly higher at 3500 mg [458] (Table 1), although typical intakes exceeded this (Table 2).

4. Risks on Exploration Missions

High sodium intakes in flight can exacerbate bone loss and lead to increased risk of renal stone formation. In and of itself, excess sodium can lead to hypernatremia, hypertension, and even death. Although it has not been a concern to date, too little sodium or a deficiency of this electrolyte during flight could lead to hyponatremia, hypotension, and even death.

5. Remaining Questions

Further research is required to investigate potential effects of high sodium intake during space flight, since the space food system currently has very high sodium levels. The impact of high sodium intake on bone, calcium, and pH is not well understood, and adjustments in sodium intake may serve as a viable countermeasure to bone loss. Furthermore, the role of a high-sodium diet in potassium homeostasis is not well understood. This may prove to be an area where nutrition and cardiovascular effects of space flight may interact, and study of the interaction may produce a dietary countermeasure.

H. POTASSIUM

1. Background

As the major intracellular cation, potassium has a significant role in several physiological processes [516]. It is crucial to regulation of acid-base balance, energy metabolism, blood pressure, membrane transport, and fluid distribution within the body. It is also involved in the transmission of nerve impulses and cardiac function [320]. Potassium metabolism that is disordered because of excessive or deficient circulating levels has negative consequences for cardiac, muscle, and neurological function.

Total body potassium averages 45 mmol/kg body weight, totaling about 3150 mmol (1230 g) of potassium in a reference 70-kg person. Two percent of body potassium (~60 mmol) is distributed in the extracellular fluid, and intracellular fluid levels are typically maintained at 140 to 150 mmol/L).

Potassium levels cannot be maintained at intakes under 10 to 20 mmol/d [505]. Moderate depletion of potassium in humans is associated with clinically significant impaired active relaxation of the left ventricle [621]. In the referenced study, healthy adults were placed on a

potassium-depletion diet for 7 days. At the end of that time, isovolumic relaxation time and deceleration time of flow through the mitral valve were significantly increased.

Deficiency of potassium leads to hypokalemia, muscle weakness, constipation, and fatigue, or even death. There is no evidence of adverse effects associated with toxicity of potassium from naturally occurring sources. However, supplemental intake may cause hyperkalemia (and associated weakness, cardiac arrest, and paralysis), metabolic acidosis [708], decreased neuromuscular function, or even death.

2. Findings from Space Flight and Ground-Based Research

Serum and urinary levels of potassium were both decreased after space flight on Apollo (Figure 40) [366], and there is evidence of a similar decrease on Skylab [361].

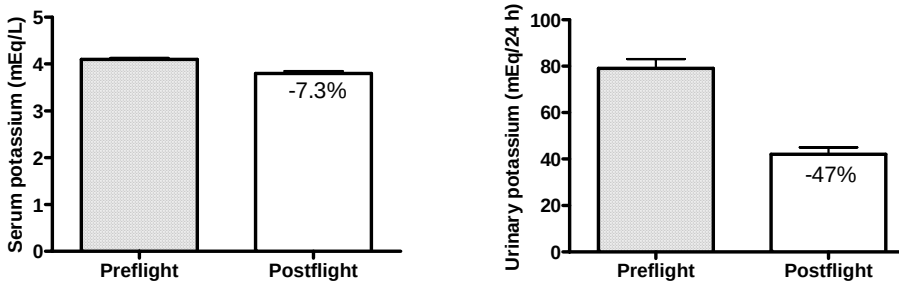

Figure 40. Serum (n = 33) and urinary (n = 30) potassium of Apollo crewmembers. Numbers in bars represent the percent change from preflight values. Adapted from Leach et al., 1975 [366].

Potassium loss (both total body potassium and exchangeable potassium) was observed in Apollo crewmembers (Figure 41) [366]. Increased levels of urinary potassium during space flight may be related to muscle disuse atrophy and inadequate intake [352]. In the initial days of bed rest, excess dietary sodium was shown to be potassium-depleting (Heer et al., unpublished observations).

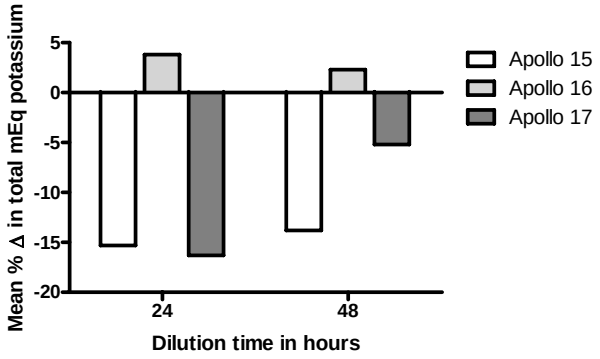

Figure 41. Exchangeable potassium of Apollo 15, 16, and 17 crewmembers after flight, as the percent change from preflight values. Data are from Leach et al., 1975 [366].

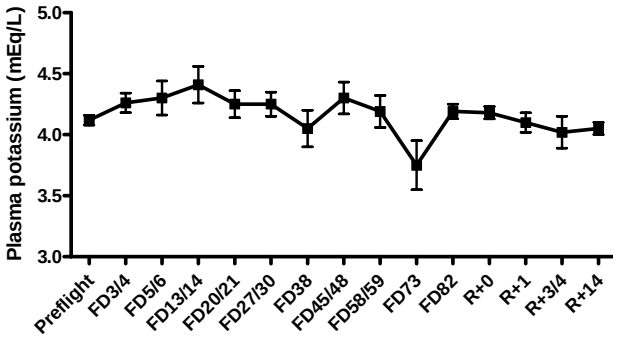

Figure 42. Plasma potassium of Skylab crewmembers (*n* = 9) before, during, and after flight. Data are from Leach and Rambaut, 1977 [361] .

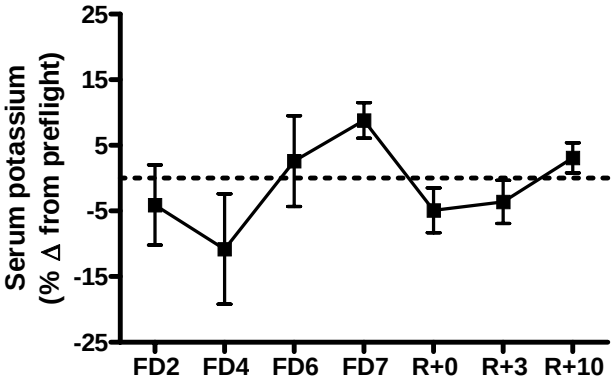

Figure 43. Serum potassium of Shuttle crewmembers (*n* = 2-6) during and after flight, expressed as the percent change from preflight values. Data are from Leach-Huntoon et al. 1987 [359].

3. Dietary Intake and Requirements

Dietary intake of potassium for long-duration ISS crewmembers is, on average, 3.2 g per day, which is lower than the recommended daily amount of 3.5 g for ISS crewmembers. The current documented space flight requirement for potassium is 4.7 g/d, the same as the U.S. recommendation for adequate intake of potassium for men and women 19 to 70 years [280]. The ISS potassium requirement was slightly lower at 3.5 g [458] (Table 1).

4. Risks on Exploration Missions

Loss of lean body mass, along with high sodium intake, may result in potassium depletion. As mentioned on page 52, the implications of potassium depletion for cardiac, musculoskeletal, and other systems are extremely serious.

5. Remaining Questions

The relationship between bone health and the protein:potassium ratio in the diet needs to be further investigated, along with the role of potassium in cardiovascular health during flight.

VI. FAT-SOLUBLE VITAMINS

A. VITAMIN A

1. Background

Less concern is expressed about adequacy of fat-soluble vitamin intake than about intake of water-soluble vitamins because the body can store larger quantities of fat-soluble vitamins. However, recent findings about previously unknown functions of some of these vitamins, as well as unique aspects of space flight, provide specific challenges for maintaining optimum status of these nutrients.

Vitamin A is a general term that refers to a family of fat-soluble compounds that are structurally similar to retinol and share its biological activity. Among these are retinol, α-carotene, β-carotene, and retinyl palmitate. Trans-retinol is the primary biologically active form of vitamin A. Many carotenoids, including β-carotene, can be converted to trans-retinol and thus contribute to vitamin A activity. Collectively, these carotenoids are termed provitamin A carotenoids and they are measured in retinol equivalents (REs).

Vitamin A is directly involved in vision, gene expression, reproduction, embryonic development, and immunity. Vitamin A and β-carotene serve as biological antioxidants and have been shown in multiple studies to reduce the risk of cancer and coronary heart disease [325, 693]. Vitamin A also plays a role, albeit sometimes indirectly, in the function of almost all of the body's organs [490].

Vitamin A is stored mainly (80%) in the liver, with the remainder stored in peripheral organs and tissues. Total body stores range from 1.05 to 3.14 nmol (300 to 900 mg) in normal adults [618].

Liver stores of vitamin A are severely depleted when their content is less than 20 μg [549]. A study of vitamin A depletion in baboons found a 59% decrease in hepatic vitamin A after 4 months of a chronic ethanol diet [386]. After 24 to 48 months, the researchers found a 95% decrease in hepatic vitamin A stores, accompanied by fibrosis and cirrhosis of the liver. Alcoholism is often associated with vitamin A deficiency because retinol and ethanol are competing substrates for the same enzymes [385].

Deficiency of vitamin A leads to xerophthalmia, loss of appetite, drying and keratinization of membranes, infection, or even death. Acute toxicity of vitamin A leads to

nausea, vomiting, headache, blurred vision, and muscular incoordination. Chronic toxicity of vitamin A leads to rapid reduction in bone mineral density, liver abnormalities, or even death.

2. Findings from Space Flight and Ground-Based Research

There is a significant interaction between the effects of landing site and space flight on serum levels of both retinol and retinol-binding protein (Figure 44) [610]. Russian landings are different from U.S. landings in that blood samples are usually collected several hours later because of the logistics of the landing site.

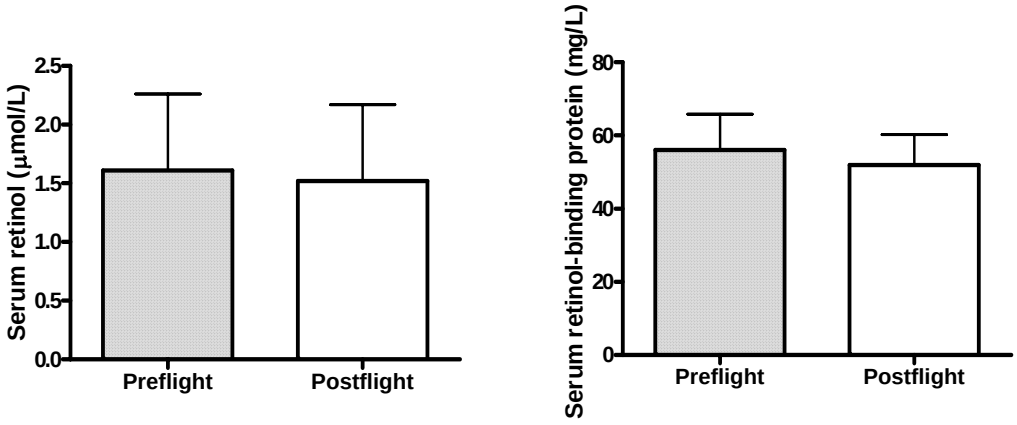

Figure 44. Serum retinol (n = 23) and retinol-binding protein (n = 18) in ISS crewmembers before and after long-duration space flight. Data are from Smith et al., 2005 [610].

Serum retinol decreased from 0.73 ± 0.17 μg/mL to 0.59 ± 0.13 μg/mL when landings were in Russia, and increased from 0.52 ± 0.09 μg/mL to 0.63 ± 0.12 μg/mL when landings were in the U.S. Similarly, retinol-binding protein decreased from 61.4 ± 5.6 to 50.92 ± 8.41 mg/L when landings were in Russia, and increased from 49.2 ± 9.2 to 53.0 ± 8.7 mg/L when landings were in the U.S. These differences in landing sites could be related to the time delay in sample collection, the fact that crewmembers might have consumed food during the time delay, or even a difference in the stress response at different sites. These data, however, do not seem to provide clear evidence that there is a deficiency of any sort for vitamin A.

3. Dietary Intake and Requirements

In the U.S., the recommended dietary allowance for vitamin A is 900 μg RE/d for men aged 19 and older, and 700 μg RE/d for women aged 19 and older [181]. Upper limits also exist for vitamin A (3000 μg RE/d), and β-carotene supplementation is advised only in situations where there is a risk of vitamin A deficiency. The current documented space flight requirement for vitamin A intake is 700 to 900 μg/d.

4. Risks on Exploration Missions

Oxidative stress is increased during space flight, and this could affect cardiovascular health and cancer risk. Vitamin A status may play a critical role in maintaining antioxidant health during space flight.

As with many antioxidants, the desire to supplement with high doses in the hope of staving off one disease is high, but unwarranted and potentially counterproductive. Excess vitamin A, in levels on the order of twice the recommended daily intake, has been shown to increase bone resorption and fracture risk [284, 426, 429, 497].

5. Remaining Questions

Vitamin A content and stability in the space food supply should be determined. The role of vitamin A as an antioxidant has not been investigated.

B. VITAMIN D

1. Background

The best-understood role of vitamin D is its involvement in calcium metabolism. One of the major functions of this vitamin is to maintain normal blood levels of calcium and phosphorus. The liver converts vitamin D to 25-hydroxyvitamin D. Typically the gold-standard measurement for determining vitamin D status (Figure 45), 25-hydroxyvitamin D is converted to 1,25-dihydroxyvitamin D in the kidney, and from there it is transported systemically to target organs. Classic target organs include bone, intestine, and kidney.

In recent years, noncalcitropic functions of vitamin D have been identified [48, 237, 431, 477, 713]. Although 1,25-dihydroxyvitamin D is the biologically active form for these pathways also, 25-hydroxyvitamin D must be available in sufficient quantities for the 1-hydroxylase enzyme in nonrenal tissues to synthesize 1,25-dihydroxyvitamin D. Besides kidney cells, other cell types, including epithelial cells, monocytes, and antigen-presenting cells, also synthesize 1,25-dihydroxyvitamin D [257]. Numerous tissues are affected by vitamin D status because their cell nuclei contain receptors for 1,25-dihydroxyvitamin D [48]. Some of these tissues are adipose tissue, bone marrow, brain, breast, cancer cells, cartilage, lung, muscle, ovary, placenta, prostate, stomach, testis, thymus, and uterus [476].

It has been suggested that the newly discovered functions of vitamin D help elucidate the relationship between 25-hydroxyvitamin D levels and many chronic diseases not normally associated with its calcitropic functions, such as cancer, diabetes, and multiple sclerosis [220, 230, 262, 265, 657]. Similarly, the noncalcitropic functions of vitamin D may help explain why a robust set of reproducible data shows an inverse correlation between sun exposure and several types of cancer [5, 209, 210].

People who are normally exposed to sunlight make vitamin D in their skin (Figure 45). Ultraviolet B light, a component of sunlight, converts 7-dehydrocholesterol to 25-hydroxyvitamin D_3 in the skin [263]. Although sunlight has a positive effect on health

through its role in making vitamin D, caution must still be exercised to avoid too much sun exposure [199, 200, 445].

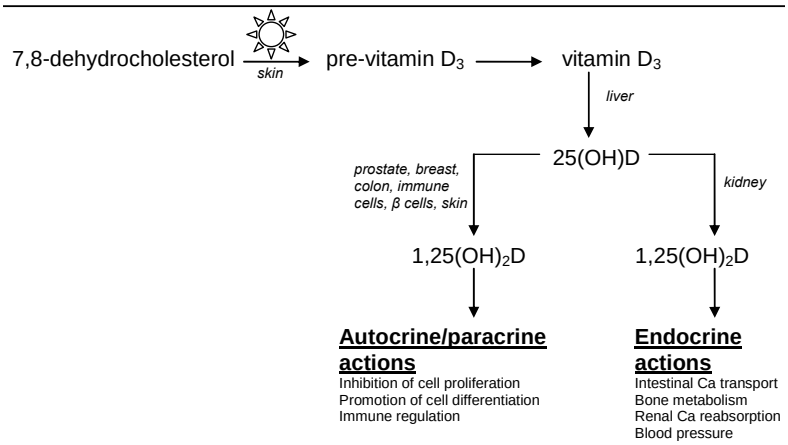

Figure 45. Vitamin D synthesis, activation, and catabolism. Dusso et al., Am J Physiol Renal Physiol 2005 [149], adapted with permission.

In the U.S., the recommendation for adequate intake (AI) of vitamin D by the 1998 Food and Nutrition Board of the Institute of Medicine was 200 IU/d (5 µg/d) for adults < 51 years. For adults > 51 years, the AI was defined as 400 IU/d (10 µg/d) [179]. The 2005 Dietary Guidelines for Healthy Americans report that optimal serum 25-hydroxyvitamin D levels should be at least 80 nmol/L, the level that maximally suppresses serum parathyroid hormone concentration [137]. These guidelines recommend that people in high-risk groups (such as those who are elderly, have dark skin, or are exposed to little sunlight) need to have substantially higher intakes of vitamin D (25 µg or 1000 IU) to maintain serum 25-hydroxyvitamin D values at 80 nmol/L [137]. Increasing serum 25-hydroxyvitamin D levels to 80 nmol/L from < 50 nmol/L is associated with not only serum parathyroid hormone suppression, but also a two-thirds greater calcium absorption efficiency, a one-third decrease in osteoporotic fracture risk, greater bone mineral density, and reduced rates of bone resorption and loss [52, 96, 235, 570].

Since the discovery of vitamin D, a vitamin D "deficiency" has been defined with the endpoints of rickets or osteomalacia. Today, it is clear that serum 25-hydroxyvitamin D must be high enough to allow 1,25-dihydroxyvitamin D production in kidney and other cells, and the disease index for vitamin D should not be limited to short-latency diseases such as rickets. From the large body of data relating parathyroid hormone concentrations to circulating 25-hydroxyvitamin D [97, 153, 662], the general consensus is that the lower end of an acceptable normal range for 25-hydroxyvitamin D should be defined as ~80 nmol/L.

2. Findings from Space Flight and Ground-Based Research

Spacecraft typically shield crewmembers from the ultraviolet B radiation that forms 25-hydroxyvitamin D_3 in the skin (the only exception being the rare quartz windows). Crewmembers on the longest Skylab mission (Skylab 4, 84 days), but not the shorter missions

(28 and 59 days), had decreased serum 25-hydroxyvitamin D at landing [361] despite taking daily 400-IU vitamin D supplements (Figure 46). Supplementation with this amount of vitamin D also did not prevent a decrease in vitamin D status after flight in ISS crewmembers [610].

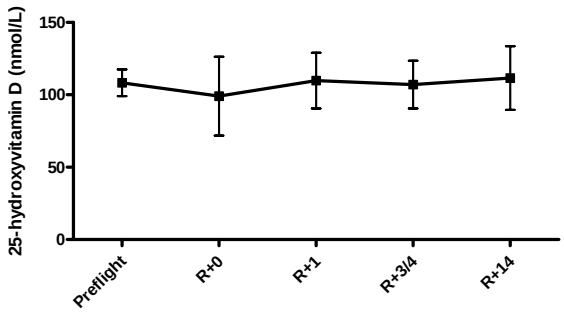

Figure 46. Plasma 25-hydroxyvitamin D of Skylab crewmembers (n = 9) before and after flight. Data are from Leach and Rambaut, 1977 [361].

Indeed, decreased vitamin D status is one of the most striking nutritional changes that occurs during space flight [609, 610]. The mean preflight serum 25-hydroxyvitamin D concentration for U.S. ISS crewmembers is 62 ± 14 nmol/L (Figure 47). In several studies, crewmembers on the Russian space station Mir had serum 25-hydroxyvitamin D_3 concentrations that were 32% to 36% less during and after long-duration (3- to 4-month) missions than before the missions [603, 609]. The serum 25-hydroxyvitamin D concentrations of ISS astronauts have typically been 25% to 30% lower after 4- to 6-month space flights [610], and in several ISS crewmembers, serum 25-hydroxyvitamin D has decreased to levels considered clinically significant (Figure 47) [610].

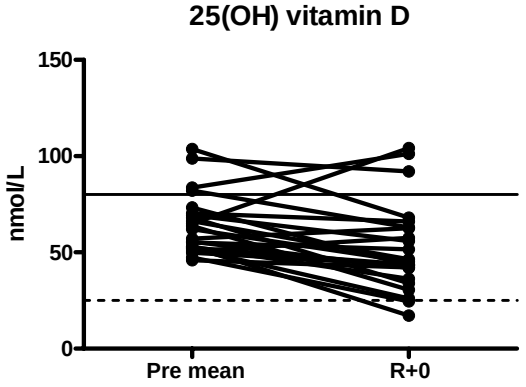

Figure 47. Serum 25-hydroxyvitamin D concentrations before and after 4- to 6-month space flights on the International Space Station (n = 23). Each line represents 1 crewmember. The "Pre mean" point on each line is the average of data collected about 6 months and about 6 weeks before launch. R+0 = Recovery plus zero days, that is, landing day. These samples are typically collected 2 to 8 hours after landing. Adapted from Smith and Zwart, Adv Clin Chem 2008 [612].

Another important observation from the ISS nutritional status assessment was related to the relationship between parathyroid hormone (PTH) and 25-hydroxyvitamin D before and after ISS missions. Before launch, 25-hydroxyvitamin D was inversely correlated with PTH (r = –0.72, P < 0.05) (Figure 48), but this relationship was not evident after landing, suggesting that the body's normal response to changes in vitamin D was altered [610].

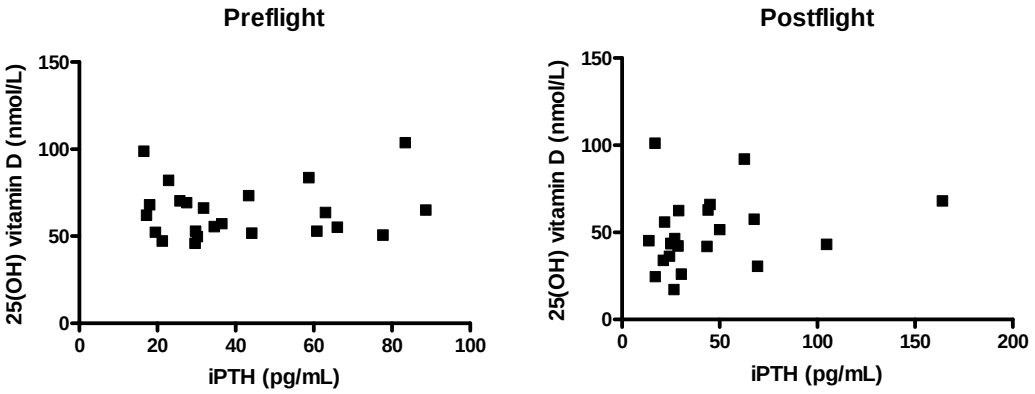

Figure 48. Serum 25-hydroxyvitamin D and parathyroid hormone concentrations before (average of data from samples collected about 6 months and 6 weeks before launch) and after (landing day, typically collected 2 to 8 hours after landing) 4- to 6-month space flights on the International Space Station. Each symbol represents 1 crewmember. Adapted from Smith and Zwart, Adv Clin Chem 2008 [612].

Results from ground-based studies of bed rest subjects [607] and subjects living in closed-chamber facilities or submarines for extended periods suggest that these subjects are also at high risk of having vitamin D deficiency [140, 148, 604]. Ground-based models with limited sunlight exposure are valuable for performing vitamin D supplementation trials.

Perhaps an ideal ground-based model for individuals lacking ultraviolet light exposure is the Antarctic, where winter levels of ultraviolet B radiation are essentially zero. We recently completed a study at McMurdo Station, Antarctica, to determine the daily dose of vitamin D needed to sustain serum levels of 25-hydroxyvitamin D during a 5- to 6-month period when there is little to no ultraviolet B (UV-B) exposure [613].

The environment in the Antarctic is quite unique. Seasonal changes in ultraviolet B light exposure are more extreme than in any other part of the world. The sun does not rise for 42 days during winter (June 1 to July 12), and the sun does not set for 60 days during the summer months (Nov 22 to Jan 20). During the Antarctic winter, scientists and visitors are typically isolated, and no fresh fruits or vegetables are available. As a result of being in close quarters and having limited food choices throughout the year, most scientists at a particular research station have homogeneous food intakes and physical activities. Not only is Antarctica a good model for studying vitamin D metabolism because of the limited sunlight exposure [281], but also the Antarctic science station model has been used successfully as a ground-based analog for space flight in studies of behavior, immune response, and latent virus reactivation [451, 452, 585].

It is well documented that vitamin D status is decreased among subjects who live in Antarctica for an extended period [395, 489, 511, 741, 748]. One research group examined

25-hydroxyvitamin D status of 31 members of an Antarctic wintering team who stayed at the Japanese Antarctic station, Syowa, for 14 months. For 1 week in May and 1 week in July, food items were weighed before they were cooked and vitamin D intake was estimated to be 488 IU/d. Serum 25-hydroxyvitamin D was lowest during April to October (~19.0 ± 4.4 ng/mL, or ~47.5 nmol/L) [741]. Because the subjects had no source of UV-B during the winter months, it can be concluded from this study that 488 IU/d is not enough to prevent a decrease in serum 25-hydroxyvitamin D levels. Olvieri and colleagues also studied bone metabolism in wintering individuals for 1 year and found that the mean 25-hydroxyvitamin D level in Argentine Antarctic wintering researchers was 10 ng/mL (25 nmol/L) during the winter months [489]. On a different 1-year expedition to Antarctica, both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were significantly decreased about 25% during the winter months [748].

To our knowledge, only 1 supplementation trial has successfully maintained serum 25-hydroxyvitamin D in subjects living in Antarctica during the summer [395]. Despite the sunlight in the summer, temperatures still keep skin exposure to the sun at a minimum. Twenty-two healthy males were randomly divided into 2 groups: supplemented with 1000 IU vitamin D_3 per day, and nonsupplemented controls. Both groups ingested less than 500 mg/d calcium. Blood was sampled at intervals of 22 days during the Antarctic summer months. Serum 25-hydroxyvitamin D levels were significantly decreased in the control group but did not change in the supplemented group. In the latter group, however, a significant decrease in PTH occurred. This study showed that 1000 IU/d vitamin D was enough to maintain vitamin D status during the summer months in Antarctica.

Although these data suggest that 1000 IU/d vitamin D may be enough to offset changes in vitamin D status in subjects with limited sun exposure such as astronauts, they shed no light on the efficacy of 1000 IU/d during the winter months in Antarctica, the time when Antarctica most closely models space flight. In the winter months, there is little to no UV-B exposure. The mean monthly amount of total UV-B radiation at the Syowa station in Antarctica is greatest in December (49,540 J/m^2) and smallest in June and July (0 J/m^2) [741]. In Tsukuba, Japan, which is similar in latitude to the Midwest in the United States, the maximum UV-B total daily is about 20,550 J/m^2 and the lowest is about 5,010 J/m^2 [741]. Astronauts aboard the International Space Station and those who will travel to Mars will not be exposed to any UV-B because spacecraft successfully block UV-B radiation [536]. The zero UV-B radiation exposure and zero availability of fresh fruits and vegetables due to forced isolation makes the winter months in Antarctica a better model for space flight than the summer months, when many researchers work outdoors (temperatures range from – 5 to +6 °C).

In addition to a decrease in vitamin D status, wintering residents in Antarctica show signs of impaired cognitive function and changes in psychosocial behavior [162, 531]. Although there is some evidence that a vitamin D deficiency may be related to changes in cognitive function [204], further research is needed to determine if these changes are related to nutritional issues or other reasons.

Glerup and colleagues compared vitamin D status in sunlight-deprived individuals (veiled Arab women living in Denmark, veiled Danish Muslim women, and nonveiled Danish women) and found a severe vitamin D deficiency among veiled Arab women (serum 25-hydroxyvitamin D was 7.1 ± 1.1 nmol/L) [203]. Twenty-six percent of the veiled Arab

women reported a change in gait compared with 9% of nonveiled Danish controls, and muscle pain was felt by 88% of Arab women. These women had a very low vitamin D intake (1.04 μg/d) and limited sun exposure. Veiled Danish Muslims had a high vitamin D intake [13.53 μg/d, (~600 IU/d)] but limited sun exposure, and they were still vitamin D deficient (serum 25-hydroxyvitamin D was 17.5 ± 2.3 nmol/L). These data suggest that 600 IU/d vitamin D is not enough to maintain 25-hydroxyvitamin D levels in individuals with little or no sun exposure. In another study with 51 submariners on deployment, 400 IU vitamin D was not enough to prevent a decrease in vitamin D status after 76 days [148].

One Russian study of the effects of gamma or proton radiation on vitamin D showed a slight (2.3% and 4.6%, respectively) decrease in vitamin D content of supplements [80] after irradiation.

3. Dietary Intake and Requirements

As mentioned above, the 1998 Food and Nutrition Board of the Institute of Medicine defined an adequate intake of vitamin D at 200 IU/d (5 μg/d) for adults < 51 years, and for adults > 51 years, the AI was defined as 400 IU/d (10 μg/d) [179]. The 2005 Dietary Guidelines for Healthy Americans recommended substantially higher intakes of vitamin D (25 μg or 1000 IU). Given the volume of data reported on vitamin D and health in recent years, a call has gone out for reconsideration and reevaluation of these recommendations [739].

The current documented space flight requirement for dietary intake of vitamin D is 25 μg per day [460], an increase from the original ISS recommendation of 10 μg per day [458] (Table 1). The ISS food system provides less than half of this amount (4 μg per day on average, Table 1). Given this shortfall, and because astronauts in space are shielded from sunlight, considering them to be in a high-risk group seems appropriate. It is currently recommended that ISS crewmembers take 800 IU of vitamin D per day during long-duration space flight.

4. Risks on Exploration Missions

Deficiency of vitamin D leads to osteomalacia and osteoporosis, which could lead to life-threatening fractures and even death. Furthermore, decreased vitamin D status has been associated with increased risk for multiple diseases, including cancer, cardiovascular disease, diabetes, multiple sclerosis, and infections [4, 125, 141, 237, 262, 431, 471, 510, 615, 713]. This is likely related to the fact that cells in a variety of tissues contain 1,25-dihydroxyvitamin D_3 nuclear receptors [99, 446].

As noted above, vitamin D deficiency is linked to calcium metabolism, and in severe cases leads to osteomalacia and osteoporosis in adults (and rickets in children). Throughout the ISS program, supplemental vitamin D has been provided to astronauts to ensure optimal vitamin D status.

Efforts to provide vitamin D supplements are misinterpreted to infer that this might be a viable bone loss countermeasure, but this is not the case. Even when vitamin D stores during

flight are adequate, the circulating concentration of the active form of vitamin D, 1,25-dihydroxyvitamin D, is decreased [603, 609]. As described in the section on calcium, this is likely the result of the increased release of calcium from resorbed bone, and results in decreased intestinal absorption of calcium. Adequate stores of 25-hydroxyvitamin D will not affect this. Any attempt to directly provide the 1,25-dihydroxyvitamin D, or as in some cases on Earth, excess 25-hydroxyvitamin D levels, may lead to hypercalcemia, renal stones, soft tissue calcification, and even death. Controlled trials in bedridden subjects have also proven that several months of supplementation fail to affect bone metabolism. In one trial, bedridden elderly people took supplemental vitamin D (400 or 1200 IU/d compared to placebo) for 6 months. Little effect was found on parathyroid hormone, and no effect on bone markers [53]. In a similar 40-week trial of 1000 IU of vitamin D_2 or D_3 (two groups), neither had an effect on bone markers [619]. The problem of weightlessness-induced bone loss must be solved, but vitamin D is not the answer. Nevertheless, even if bone loss is not stemmed, ensuring an adequate amount of vitamin D will remain important.

Since the current space food system includes very few dietary sources of vitamin D, and vitamin D cannot be synthesized endogenously due to lack of UV light, decreased vitamin D status is a serious concern for exploration missions that could last 1000 days.

Toxicity of vitamin D is typically less likely to occur than a deficiency [231, 668, 703, 704], but use of supplements would increase its likelihood. Excessive blood levels of vitamin D can lead to hypercalcemia, which can lead to nephrocalcinosis, arteriosclerosis, irreversible calcification of soft tissue, or even death.

5. Remaining Questions

Vitamin D levels in the food system need to be determined, and the stability of vitamin D in the food system needs to be investigated. Additional research is needed to understand whether supplementation (and what level of supplementation) can maintain vitamin D stores. This is very important for long-duration crewmembers, and is of the utmost importance for exploration-class missions.

C. VITAMIN E

1. Background

Vitamin E is a lipid-soluble, chain-breaking antioxidant found in body tissues, and is also the first line of defense against lipid peroxidation reactions. Eight naturally-occurring compounds have vitamin E activity: 4 tocopherol derivatives (α-, γ-, δ-, and β-tocopherol) and 4 tocotrienol derivatives (α-, γ-, δ-, and β-tocotrienol) [676]. The tocopherols that are most abundant in biological systems are α- and γ-tocopherol, but small amounts of δ-tocopherol and α-tocopheryl quinine are also present. About 90% of the tocopherol found in human plasma is in the form of α-tocopherol [278].

Vitamin E helps protect cell membranes in the early stages of free-radical attack because of its free-radical-quenching activity. Free radicals attack polyunsaturated fatty acids found in

membrane phospholipids, causing damage to cellular membranes and possibly cell death. The interception of a free radical by vitamin E produces a tocopheroxyl radical that can be reduced by vitamin C or another reducing agent to return vitamin E to its reduced state. The extent of regeneration and recycling of vitamin E in human tissue has not been well established [617, 676].

Vitamin E is stored mainly in adipose tissue but is also found in phospholipid membranes. Results of studies conducted to determine vitamin E tissue levels have shown that tissue α-tocopherol concentrations are largely reflected by changes in plasma α-tocopherol concentrations [304].

Vitamin E deficiencies in humans are rare; however, fat malabsorption syndromes, genetic abnormalities, and protein-energy malnutrition are specific conditions in which a vitamin E deficiency is likely to occur. Symptoms include neurological problems associated with nerve degeneration in the extremities [278]. Vitamin E depletion has been detected when markers of lipid peroxidation were elevated. However, the lowering of levels of these lipid peroxidation markers has not been shown to have any health benefits, and therefore they have not been used to establish α-tocopherol requirements.

Deficiency of vitamin E leads to neurological disorders, hemolytic anemia, retinopathy, and abnormal platelets and lymphocytes, or even death. Toxicity of vitamin E from naturally occurring sources has not been shown to occur.

2. Findings from Space Flight and Ground-Based Research

After ISS crewmembers had spent 4 to 6 months in space, their plasma γ-tocopherol was 50% less than preflight levels [610]. No change in α-tocopherol occurred in these subjects.

Recent animal studies have documented the ability of vitamin E to mitigate muscle atrophy, apparently through genetic regulation of proteolysis [576]. Additionally, animal hindlimb unloading studies have shown that supplemental vitamin E can have a positive influence on bone, potentially through the vitamin's antioxidant properties [594]. Although, as always, such results are intriguing, the ability of these studies to translate into effectiveness in humans has yet to be determined.

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of vitamin E is 15 mg/d for men and women, the same as the U.S. recommendation for adequate intake of vitamin E. No upper limit has been established because the highest level of daily intake is not likely to pose serious health risks to the majority of individuals [278]. Although no striking changes occurred in plasma vitamin E concentrations, the space flight menus provide only about 60% of the documented requirement for vitamin E (see Table 1, page 18).

4. Risks on Exploration Missions

Oxidative stress can increase in microgravity and high-radiation environments [161, 633, 634], and the antioxidant properties of vitamin E may help to counteract the free-radical damage caused by high-linear energy transfer radiation in space. Pretreatment with antioxidants may help decrease radiation damage during missions [503], and it may be necessary to provide enough vitamin E for astronauts' blood levels of the vitamin to be higher during space flight than on Earth. However, knowledge gaps weaken the evidence for use of vitamin E as a countermeasure (see below).

5. Remaining Questions

Vitamin E content of space foods, along with the stability of vitamin E in these foods, needs to be determined. After learning about the promising antioxidant effects of supplemental vitamin E, many people on Earth did not hesitate to take vitamin E supplements to prevent cancer. But the protective effects were not borne out in controlled studies, highlighting the difficulties of defining a specific antioxidant countermeasure for space travelers without the luxury of having data from epidemiological studies to provide an evidence base for space flight.

D. VITAMIN K

1. Background

Vitamin K occurs naturally in 2 forms: phylloquinone (vitamin K_1) and menaquinone (vitamin K_2). Menaquinones are produced by bacteria, while phylloquinone is synthesized in plants. Phylloquinone represents the main source of dietary vitamin K in Western countries [491].

The function of vitamin K was originally assumed to be strictly limited to involvement in blood coagulation, but an increasing amount of evidence indicates that this vitamin affects multiple physiological systems. Vitamin K is a cofactor in the posttranslational synthesis of γ-carboxyglutamic acid (GLA). γ-Carboxyglutamic acid is a constituent of all vitamin K-dependent proteins, and its role is related to increasing the affinity of the proteins for calcium [166]. Vitamin K-dependent proteins include blood coagulation proteins (prothrombin; factors VII, IX, and X; and proteins C and S) and bone proteins (osteocalcin, matrix GLA protein, and protein S).

The main storage depot for vitamin K in the body is the liver. Large amounts of vitamin K are also present in cortical and trabecular bone [260]. However, vitamin K stores are very small compared to those of other fat-soluble vitamins, and hepatic vitamin K is rapidly depleted when dietary vitamin K is restricted [689].

Anticoagulants such as warfarin, a coumarin-based anticoagulant, are administered to create a partial vitamin K deficiency to reduce risks of abnormal blood clotting [417]. Dosing with warfarin must be closely monitored for optimal efficacy and safety. High or low intake

of vitamin K can interact with the actions of warfarin to yield nontherapeutic anticoagulation or life-threatening hemorrhagic complications [233, 305].

2. Findings from Space Flight and Ground-Based Research

Data from 11 U.S. astronauts on ISS Expeditions 1 to 8 (mission durations of 128 to 195 days during 2000–2004) revealed that on landing day their serum phylloquinone (vitamin K_1) was 42% lower than it was before flight (Figure 49), whereas urinary γ-carboxyglutamic acid did not change [610]. In one study, undercarboxylated osteocalcin was elevated (a sign of vitamin K insufficiency) as early as the 8th day of space flight, and remained high during 21- and 180-d missions [85]. Studies on the EuroMir 95 mission showed that markers of vitamin K status were decreased after 12.5 weeks of space flight, and vitamin K supplementation (10 mg/d for 6 weeks) reversed these effects [695]. Vitamin K supplementation elevated γ-carboxyglutamic acid and decreased undercarboxylated osteocalcin, suggesting that vitamin K status was lower during space flight and was improved by supplementation [85, 695].

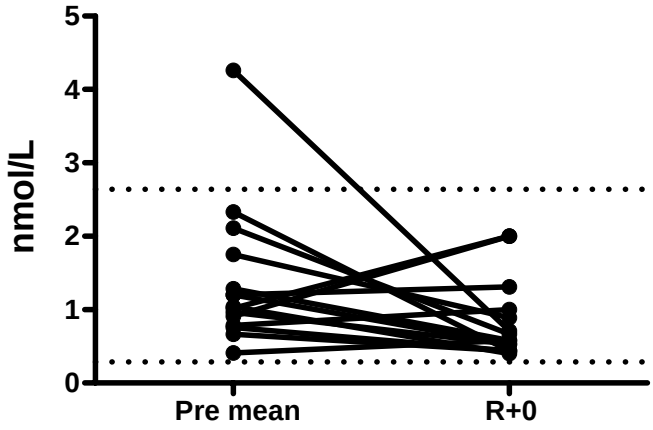

Figure 49. Serum phylloquinone before and after 4- to 6-month space flights on the International Space Station. Each line represents 1 crewmember (n = 15). The "Pre Mean" point on each line is the average of data collected about 6 months and about 6 weeks before launch. R+0 = Recovery plus zero days, that is, landing day. These samples are typically collected 2 to 8 hours after landing. Data are from Smith et al. [610].

Elevated undercarboxylated osteocalcin has been associated with increased fracture risk in certain populations, and evidence exists that vitamin K antagonists increase the risk of fracturing vertebrae and ribs in a time-dependent manner [90, 582].

Recent publications have shown a link between carboxylation of osteocalcin and insulin resistance and energy metabolism. Space flight has been shown to increase the percentage of undercarboxylated osteocalcin [85, 694, 695], which according to Lee and Karsenty [383] should increase insulin sensitivity. However, space flight or disuse is accompanied by an increase in insulin resistance (decrease in insulin sensitivity). Yashida et al. [743] have reported that daily supplementation of 500 μg of vitamin K decreases insulin resistance. The

nature of any relationship between insulin sensitivity and the carboxylation of osteocalcin must be considered unknown for now, and it could be a concern for exploration missions.

3. Dietary Intake and Requirements

The current documented space flight requirements for dietary intake of vitamin K are 90 and 120 μg per day for women and men, respectively. These are the same as the U.S. adequate intake recommendations for vitamin K [181]. No upper limit has been established.

4. Risks on Exploration Missions

Decreased vitamin K status has serious implications for space flight because it is related to bone health. Space flight data, including data from Mir [85, 694] and ISS crewmembers [610], suggest that vitamin K status during long-duration space flight is suboptimal.

5. Remaining Questions

Deficiency of vitamin K is not common in adults, as the intestinal microflora synthesize vitamin K. The reliability of this source of vitamin K during flight is unknown, and expert panels have recommended having higher intake requirements because of this uncertainty [460]. It has been hypothesized that microflora production of vitamin K may be altered in space, but few or no data are available to support this. The use of vitamin K as a bone loss countermeasure has been proposed and is under investigation [243, 652]. Given that the amount of space flight data documenting the improvement in bone marker status with vitamin K supplementation is limited, clearly more needs to be known before exploration missions are undertaken. Furthermore, the vitamin K content of the space food system and its stability should be determined.

VII. WATER-SOLUBLE VITAMINS

Water-soluble vitamins are a key concern for space travelers, because of the limited endogenous storage of many of these nutrients. They must be replenished from food that may have been stored for a long time (9 to 18 months) under suboptimal conditions, including the space radiation environment.

A. FOLATE

1. Background

Folate is the general term used to describe folic acid and compounds that have activity similar to that of folic acid [30]. Folic acid is the form of the vitamin used in vitamin supplements and fortified food products, but it is rarely found to occur naturally in food.

About 50% of all folate is stored in the liver. The average liver concentration of folate is about 8 μg/g [268]. Estimated total body folate stores are 12 to 28 mg [277]. Very little folate is excreted in the urine or feces. Most of the absorbed folate is secreted by the liver into the bile, which is then reabsorbed through enterohepatic recirculation. Most of the folate excreted in feces is synthesized by intestinal bacteria.

The reduction of folic acid and dihydrofolate by a cytosolic enzyme produces the active form of folate, tetrahydrofolate (THF). Tetrahydrofolate accepts single-carbon groups from reactions in amino acid metabolism to form active derivatives of THF [30]. These derivatives function in amino acid metabolism, specifically in the reversible reactions of serine synthesis from glycine, methionine synthesis from homocysteine, and histidine metabolism. Folate is essential in cell division because the THF derivatives play important roles in purine and pyrimidine synthesis. Tetrahydrofolate derivatives play a major role in the formation of thymidylate, which is a substrate needed for DNA synthesis [30].

Radiation exposure and inadequate dietary consumption can lead to inadequate intake of folate [277]. Deficiency of folate leads to megaloblastic anemia or even death. Low folate intake will cause red blood cell folate concentrations to diminish within 4 months. Bone marrow cells become megaloblastic (that is, they take on a nucleated, embryonic form), and anemia occurs after 4 to 5 months of low folate intake [218]. Folate deficiency in humans has been described as a 4-stage process [254, 255], including changes in serum folate (Stage 1), changes in red blood cell folate (Stage 2), defective DNA synthesis and elevated homocysteine (Stage 3), and clinical folate deficiency (Stage 4), manifested by

macroovalocytosis (many large, oval cells in the blood), elevated mean corpuscular (red blood cell) volume, and large, nucleated embryonic cells.

Folate deficiency is associated with irritability, forgetfulness, and hostile or paranoid behavior [255]. It has been suggested that folate may influence the metabolism of certain neurotransmitters, but this may be related to the neurotoxicity of homocysteine, which is elevated in folate deficiency. Hyperhomocysteinemia also has detrimental cognitive and neurodegenerative effects [256].

2. Findings from Space Flight and Ground-Based Research

It is evident that folate status is decreased after long-duration space flight (4 to 6 months) (Figure 50) [604, 610]. To date, only pre- and postflight assessments of nutrient status have been possible, although the recently initiated Nutritional Status Assessment Supplemental Medical Objective experiment will provide in-flight data as well [612].

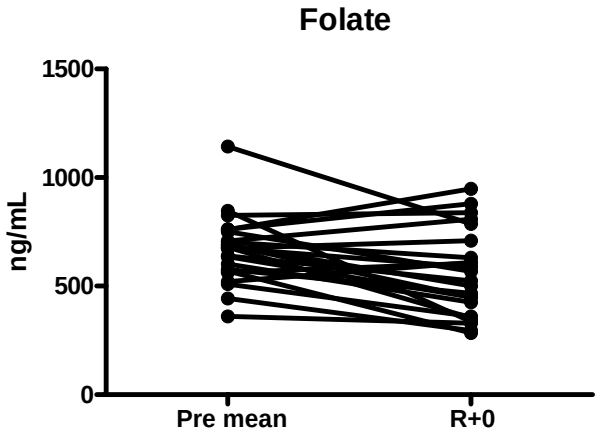

Figure 50. Red blood cell folate concentrations before and after 4- to 6-month space flights on the International Space Station (n = 23). Each line represents 1 crewmember. The "Pre mean" point is the average of data collected about 6 months and 6 weeks before launch. R+0 = Recovery plus zero days, that is, landing day. These samples are typically collected 2 to 8 hours after landing. Adapted from Smith and Zwart, 2008 [612].

Recent bed rest studies did not document any change in red blood cell folate status during or after short (3-week, [762]) or long (60- to 90-day [761]) bed rest. A 14-day exposure to increased atmospheric pressure (saturation diving) did not significantly affect red blood cell folate [608].

3. Dietary Intake and Requirements

The current documented space flight requirement for folate intake is 400 μg/d [460], unchanged from ISS requirements [458] (Table 1). In the U.S., the RDA for all individuals aged 14 and older is 400 μg/d of dietary folate equivalents (DFEs). Using DFEs adjusts for

the 50% reduction in food folate bioavailability compared to that of folic acid: 1 μg DFE = 0.6 μg of folic acid from fortified food, or as a supplement taken with meals; 1 μg DFE = 1 μg of food folate = 0.5 μg of a supplement taken on an empty stomach. An upper limit of folate intake during space flight is set at 1000 μg/d.

4. Risks on Exploration Missions

As with many nutrients, folate deficiency on an exploration mission would be catastrophic. Animal studies have shown that low folate status increases chromosome damage resulting from radiation exposure [42, 115, 151, 152]; however, it should be noted that excessive folate supplementation provided no additional benefit [151]. Similarly, cell models have shown that folic acid deficiency increases sensitivity to chromosome breakage from ionizing radiation [42]. Antioxidant properties of folate have been studied, and folate was found to scavenge a diverse array of reactive oxygen species efficiently [299]. Cell models also show the ability of folate to reduce iron toxicity in cases of iron overload, by oxidizing free or chelated iron [299]. Folate status may be even more important during exploration missions than on the ISS because of known increases in iron storage during long-duration space flight [610] and exposure to ionizing radiation.

5. Remaining Questions

It is unknown whether the decrease in folate status during space flight is related to the folate content of food, the stability of folate in food during flight, or alterations in absorption, metabolism, or excretion. Folate levels in the space food system need to be determined. If the diet does in fact provide 400 μg/d, then further research should be done to understand the stability of folate during radiation exposure. If neither folate content of food nor folate stability in food is an issue, then evaluations of folate metabolism during space flight are warranted to ensure that the body's requirements are understood.

B. THIAMIN

1. Background

Thiamin functions as a coenzyme in the metabolism of carbohydrates and branched-chain amino acids [39]. The coenzyme form of thiamin, thiamin pyrophosphate, functions in the decarboxylation of pyruvate and α-ketoglutarate. Without these decarboxylations, synthesis of both adenosine triphosphate (ATP) and acetyl-coenzyme A would be inhibited. Thiamin pyrophosphate also functions as part of the hexose monophosphate shunt, the pathway by which 6-carbon sugars are converted to pentoses and NADPH (the reduced form of nicotinamide adenine dinucleotide phosphate) [39]. Thiamin pyrophosphate is also involved with neural function, although the mechanism is not completely understood [39].

About 30 mg of thiamin is stored in the human body [277]. About half of the body's thiamin is stored in the skeletal muscle, with the rest being stored in the heart, liver, kidney, and brain. Thiamin in excess of tissue needs and storage capacity is excreted in the urine. The biological half-life of thiamin is in the range of 9 to 18 days.

Deficiency of thiamin ultimately leads to beriberi (enlarged heart, muscle weakness, anorexia, apathy, reduction in nerve impulse transmission) or even death. No toxicity symptoms of excess thiamin are known.

2. Findings from Space Flight and Ground-Based Research

Evaluation of erythrocyte transketolase activity, an index of thiamin status [81], before and after space flight did not yield any abnormal data [610].

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of thiamin is 1.2 and 1.1 mg/d for men and women, respectively [460] (Table 1), the same as the U.S. RDAs for men aged 19 and older and for women [277]. The ISS thiamin requirements were slightly higher at 1.5 mg, and without gender differences [458] (Table 1).

4. Risks on Exploration Missions

It is well known that thiamin is highly susceptible to destruction by radiation [80, 183, 706] and processing in foods [79]. It will be crucial to determine if thiamin can survive a 3-year-plus mission to deep space.

5. Remaining Questions

The thiamin levels in the space food supply and their stability need to be determined, particularly since thiamin is highly susceptible to degradation from radiation exposure.

C. NIACIN

1. Background

The term "niacin" includes nicotinamide, nicotinic acid, and their derivatives that have the biological activity of nicotinamide [277, 286]. In its coenzyme forms, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), niacin has many different metabolic roles in the human body. The nicotinamide moiety accepts hydride ions in numerous biological redox reactions. NAD functions in respiration and as a co-dehydrogenase with enzymes involved in the oxidation of fuel molecules [286].

NAD is converted to NADH, which transfers electrons from the Krebs cycle through the electron transport chain. NAD also acts as a donor of adenine dinucleotide phosphate-ribose for the posttranslational modification of proteins [218]. The coenzyme NADP has a role in fatty acid, cholesterol, and steroid syntheses, and as a co-dehydrogenase in the pentose phosphate pathway. Conversion of folate to its active forms also requires NADP.

Niacin is stored in the liver as NAD. This stored NAD can result from conversion of tryptophan, nicotinic acid, or plasma nicotinamide.

Limited data show that after 80 to 135 days of ingesting a low-niacin diet, subjects' urinary excretion of N^1-methylnicotinamide is at a level representing deficiency status [180]. On a niacin-deficient diet, symptoms begin to appear after 50 to 60 days [286].

Deficiency of niacin leads to dermatitis, glossitis, growth retardation, pellagra and its associated three "d"s (diarrhea, dermatitis, dementia), and ultimately death. Niacin deficiency has also been associated with increased damage to DNA after an oxidative stress, but it was not related to glutathione peroxidase levels [659].

Niacin in the amount of 3 g/d or more has been associated with toxic effects [277]. Niacin toxicity from mega doses of niacin can cause vasodilatory effects (flushing), gastrointestinal distress, hepatotoxicity, glucose intolerance, and blurred vision [286]. However, many of these toxic effects have been shown to occur only after treatment over long periods and in amounts that far exceed the RDA. The tolerable upper intake limit is defined as 35 mg of niacin equivalents per day. This is the upper limit of where no risks or adverse effects are expected [286].

2. Findings from Space Flight and Ground-Based Research

Niacin status of astronauts during and after flight has not been measured.

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of niacin is 16 mg niacin equivalents/d (NE/d) [460], slightly lower than the originally defined ISS requirement of 20 mg NE/d (Table 1) [458]. The ISS menu was estimated to provide intakes of almost 30 mg NE/d on average (Table 1). In the U.S., the niacin requirement for men aged 19 and older is 16 mg/d of niacin equivalents, and for women aged 19 and older the requirement is 14 mg/d of niacin equivalents [277]. One niacin equivalent is equal to about 60 mg of the amino acid tryptophan and can be obtained from 6 grams of high-quality protein [218]. The RDA for niacin can be met from the actual niacin content of the diet or by metabolic conversion of tryptophan in the diet.

4. Risks on Exploration Missions

Very little is known about niacin metabolism during space flight. One concern for exploration missions is the stability of niacin in the food system, particularly because of

reports showing that the niacin content of foods decreases after exposure to 6 kGy of radiation [129].

5. Remaining Questions

Niacin content and stability in the space food supply need to be determined. The role of niacin in protection from oxidative damage should also be evaluated as part of a larger search for an oxidative damage countermeasure.

D. RIBOFLAVIN

1. Background

Riboflavin's primary role in the body, like that of many water-soluble vitamins, is as a coenzyme [544]. The most important biologically active forms of riboflavin are flavin mononucleotide and flavin adenine dinucleotide (FAD). These cofactors participate in a range of redox reactions in numerous metabolic pathways [514, 544]. Some of these pathways are niacin-dependent and niacin-independent dehydrogenations, reactions with sulfur-containing compounds, hydroxylations, oxidative decarboxylations, dioxygenations, and reduction of oxygen to hydrogen peroxide [544]. The riboflavin cofactors also play a role in the formation and function of some other vitamins, including folate, vitamin B_{12}, and vitamin B_6 [514].

Unbound flavins are labile and are rapidly hydrolyzed to release free riboflavin. Excess free riboflavin is excreted in the urine [514].

The highest concentrations of stored riboflavin are found in the liver, kidneys, and heart [277], and almost all riboflavin in tissues is enzyme-bound, such as FAD covalently bound to succinic dehydrogenase [590]. The total body stores of riboflavin are enough to meet the demands of the body for 2 to 6 weeks [277].

Riboflavin deficiency affects ferritin iron mobilization and iron absorption. Symptoms of riboflavin deficiency include peripheral nerve demyelination, neurologic abnormalities, and anemia.

2. Findings from Space Flight and Ground-Based Research

After flight on the International Space Station, erythrocyte glutathione reductase (EGR) activation, an index of riboflavin status [81], was unchanged compared to preflight values [610].

A 14-day exposure to increased atmospheric pressure (saturation diving) did not have a statistically significantly effect on EGR activation, but activation values during and after the dive tended ($P = 0.07$) to be lower than before the dive [608].

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of riboflavin is 1.3 mg/d [460], lower than the initial requirements of 2.0 mg/d defined for ISS crewmembers [458]. Regardless of the requirement, the menu provides about 2.2 mg/d on average (Table 1). In the U.S., the RDAs for riboflavin for men and women aged 19 and older are 1.3 and 1.1 mg/d, respectively [277].

4. Risks on Exploration Missions

Cataract incidence is higher in space travelers than in the general population [119, 297], and cataracts have also been described in riboflavin-deficient animal models [270, 514]. Although no evidence exists to date that riboflavin status changes during space flight, the possibility that this nutrient could be involved in cataract formation cannot be ignored.

Riboflavin is relatively heat-stable, but it is readily degraded by light [38, 514]. It does not seem to be degraded by gamma irradiation of foods [183, 342], which reduces concern about long-term stability.

5. Remaining Questions

No evidence exists that riboflavin status is altered during 4- to 6-month space flights [610]; however, riboflavin content in the space food supply needs to be investigated to ensure that a) enough is available, and b) riboflavin will not degrade during long-duration storage.

E. VITAMIN C

1. Background

The term “vitamin C” actually refers to 2 different compounds, both of which have activity against scurvy: ascorbic acid and dehydroascorbic acid [294]. Vitamin C functions as an antioxidant because it acts as a reducing agent for most physiologically relevant reactive oxygen species, reactive nitrogen species, singlet oxygen, and hypochlorite. It serves as a cofactor for enzymes involved in the biosynthesis of collagen, carnitine, and neurotransmitters [294]. Vitamin C also provides antioxidant protection by returning α-tocopherol to its biologically active state during lipid oxidation. The reducing agents glutathione and either reduced nicotinamide adenine dinucleotide (NADH) or reduced nicotinamide adenine dinucleotide phosphate (NADPH) regenerate the oxidation products of ascorbate [294].

It has been suggested that vitamin C requirements should be greater for persons who are under excessive physical or emotional stress, given the role of ascorbate in the biosynthesis of steroid hormones and neurotransmitters. However, no substantial data show that vitamin C metabolism is altered in healthy subjects under mental or emotional stress [278].

The total body pool of vitamin C varies with intake. Higher concentrations are found in the pituitary and adrenal glands, liver, spleen, heart, kidneys, lungs, pancreas, leukocytes, eye tissues and humors, and the brain, while lower concentrations are found in the saliva, muscle, and plasma. Blood cell and tissue concentrations become saturated at intakes from 100 to 140 mg/d, and steady-state plasma vitamin C concentrations occur with intakes of 200 mg/d. Catabolic turnover varies from 10 to 45 mg/d, and with low intake, turnover is reduced. Maximum body pools of ascorbate are ~2 grams.

Vitamin C has been related to cataract and cancer incidence [663, 716, 742], both of concern for space travelers. Although higher vitamin C intake in the Framingham Study was found to be associated with lower bone mass [553], the significance of this association was marginalized when adjusted for potassium intake. This suggests that vitamin C may be a secondary factor related to fruit and vegetable reduction in bone loss [356, 407, 465, 466], as described elsewhere in this text.

Vitamin C deficiency most commonly presents itself as any of an array of symptoms commonly referred to as scurvy. Scurvy is seen in adults within 45 to 80 days of stopping vitamin C intake. Intake below the RDA can cause a deficiency once the body pools fall below ~300 mg of ascorbic acid. The length of time until scurvy symptoms develop when intake is suboptimal depends on the size of the individual's body pool of vitamin C before intake was decreased.

Deficiency of vitamin C leads to fatigue, depressed immune function, scurvy (fatigue, muscle cramps, bruised and/or bleeding gums), and eventually even death. As noted in the introduction, scurvy resulted in more sailor deaths during the age of sail than all other causes of death combined [66]. Toxicity of vitamin C leads to gastrointestinal distress, and has been reported in subjects consuming more than 1000 mg/d [663].

2. Findings from Space Flight and Ground-Based Research

Vitamin C status of crewmembers has not been reported to date, at least not to our knowledge. Vitamin C assessments of ISS crewmembers have been initiated, but have yet to be reported. A recent short-duration bed rest study documented no statistically significant change in vitamin C (Figure 51), but results showed a trend for an increase, which might be related to dietary intake during the study compared to the subjects' nominal intake [762].

The stability of vitamin C has been studied in food supplies, and it is generally unstable at a neutral or alkaline pH, and in high-oxygen environments [253]. Vitamin C is also unstable when exposed to light or heat [253], and in irradiated foods [160, 555]. Salem [555] found that gamma irradiation of fresh onion bulbs significantly reduced their vitamin C content. This group also found that vitamin C content of onion bulbs had decreased about 50% after 6 months of storage. The destructive effects of gamma irradiation (10 kGy) on vitamin C were also evident in commercial spices such as basil, black pepper, cinnamon, nutmeg, oregano, parsley, rosemary, and sage [86]. Exposure of these spices to gamma rays for > 3 months resulted in a marked increase in quinone radicals.

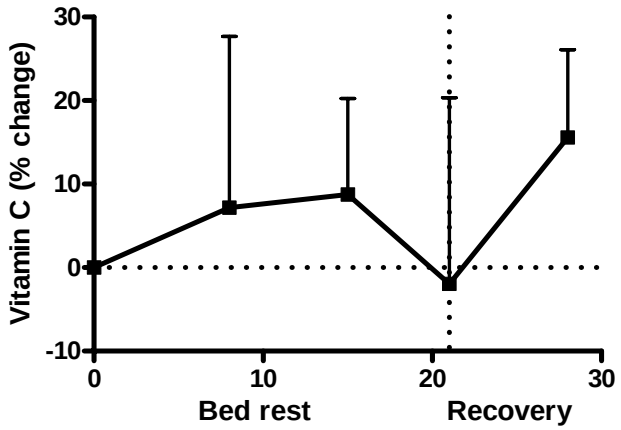

Figure 51. Plasma vitamin C in 7 subjects during 21 days of bed rest. Data, from Zwart et al. [762], are expressed as percent change from before bed rest.

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of vitamin C is 90 mg/d (Table 1). In the U.S., the RDAs for vitamin C for men and women aged 19 and older are 90 mg/d and 75 mg/d, respectively. They are set by assuming a coefficient of variation of 10 percent because information about the standard deviation is unavailable. The RDA is defined as equal to the estimated average requirement (EAR) plus twice the coefficient of variation, to cover the needs of at least 98% of the population [278]. Because of the increased level of stress predicted for orbiting crews, the requirement for vitamin C in space crews was initially defined as 100 mg/d for males and females [457, 458], at a time when the U.S. RDA was 60 mg/d.

4. Risks on Exploration Missions

A major concern for space flight is the possibility that vitamin C could be degraded in foods during extended-duration missions when space foods are exposed to large amounts of radiation and undergo long-term storage (foods may be sent to Mars in advance of the crew, and left there for up to 5 y). This could be catastrophic.

Free-radical formation is increased in space because greater amounts of radiation are present than on Earth. Because of this and increases in other oxidative stressors, antioxidants such as vitamin C are in greater demand by the body to act as buffers and minimize the oxidative damage. Studies have shown that supplementation with vitamin C and other antioxidants can modify human tissue radiosensitivity and protect DNA against damage [82, 288]. Just as important to consider, however, is the possibility that vitamin C could induce DNA damage. Cai and colleagues [82] found that vitamin C can act as an antioxidant to prevent DNA damage caused by ionizing radiation, but in the presence of copper, it can also act as a reducing agent to induce DNA damage. Because vitamin C can reduce redox-active metals such as iron and copper, this “antioxidant” can increase the pro-oxidant chemistry of

these metals [76]. Thus, vitamin C can serve as both a pro-oxidant and an antioxidant, and the amount of it required by exploration crewmembers needs to be carefully addressed (as does the amount of almost all nutrients).

5. Remaining Questions

Vitamin C content and stability in the space food supply need to be determined. Evaluation of the impact of vitamin C supplementation during exposure to oxygen or high-linear energy transfer radiation should be investigated before recommendations can be made for supplement use during flight. This should be evaluated in a coordinated effort to find an antioxidant profile for space travelers. After data have been gathered regarding vitamin C status during and after flight, and preferably after data are available regarding the influence of space flight-induced stress on vitamin C, an evaluation of intake requirements needs to be made.

F. VITAMIN B_6

1. Background

Vitamin B_6 comprises a group of 3 compounds and their 5′-phosphates (P): pyridoxal (PL) and PLP, pyridoxine (PN) and PNP, and pyridoxamine (PM) and PMP [423]. These "vitamers" of B_6 serve as coenzymes in many transamination reactions by forming a Schiff's base with the ε-amino group of lysine and the carbonyl group of PLP [277, 423]. They can also function in decarboxylation reactions, such as the formation of γ-aminobutyric acid from glutamate and serotonin from 5-hydroxytryptophan, and they function in trans- and desulfhydration, by which cysteine is synthesized from methionine and pyruvate is generated from cysteine, respectively. The vitamers also function in cleavage reactions, racemization of D- and L-amino acids, synthesis of multiple compounds, glycogen catabolism (where vitamin B_6 is required for the activity of glycogen phosphorylase), and steroid hormone action (where the vitamers decrease the actions of steroids) [218].

About 80% of vitamin B_6 is stored in muscle tissue and 10% is stored in the liver, with the rest being stored in the blood plasma pool. Research data have shown that total body stores are about 1,000 μmol or 167 mg [277]. Overall body half-lives of the vitamers of vitamin B_6 are about 25 days [277, 580].

Deficiency of vitamin B_6 leads to dermatitis, microcytic anemia, convulsions, altered mental status, hyperhomocysteinemia, or even death. Toxicity of vitamin B_6 leads to sensory neuropathy or even death.

2. Findings from Space Flight and Ground-Based Research

The variables used to assess vitamin B_6 status are red blood cell transaminase, plasma PLP, and urinary 4-pyridoxic acid. No change occurred in the activation of red blood cell

transaminase of astronauts on 4- to 6-month space flights [610]. To date, plasma PLP has not been determined after long-duration space flight or bed rest.

Weightlessness has been shown to reduce the cross-sectional area of muscle fibers and is associated with a change from type I to type II muscle fibers [333]. Since vitamin B_6 is stored mainly in muscle tissue [105], a decrease in muscle cross-sectional area could reduce the amount of the vitamin that is stored. Increased excretion of 4-pyridoxic acid (4-PA) during bed rest, a finding observed in short- [762] and long-duration bed rest studies [106], likely reflects this loss of muscle stores of vitamin B_6.

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of vitamin B_6 is 1.7 mg/d [460], slightly lower than the original requirement defined for ISS missions [458]. In the U.S., the vitamin B_6 requirement for all adults over age 19 years is 1.3 mg/d [277]. The ISS food system is estimated to provide adequate (2.3 mg/d average) vitamin B_6 (Table 1).

4. Risks on Exploration Missions

Given the changes observed in vitamin B_6 metabolism during bed rest, vitamin B_6 status during and after long-duration space flight warrants further attention. A deficiency in vitamin B_6 causes a decrease in the synthesis of serotonin and catecholamines, which has been shown to be associated with depression [272]. Excess vitamin B_6 can lead to neuropathy [37, 195, 303].

5. Remaining Questions

Vitamin B_6 levels and stability in the space food supply need to be determined, along with an assessment of its stability in an environment with increased levels of radiation.

G. VITAMIN B_{12}

1. Background

Vitamin B_{12} functions in many enzymatic reactions, and deficiencies result in anemia, as well as neurological disorders. Vitamin B_{12} functions as a coenzyme in 2 metabolic forms: adenosylcobalamin and methylcobalamin [622]. Vitamin B_{12} works as a cofactor for 3 different enzymatic reactions: 1) the conversion of homocysteine to methionine, 2) the conversion of L-methylmalonyl-coenzyme A (CoA) to succinyl-CoA, and 3) the isomerization of L-leucine and β-leucine. Vitamin B_{12} deficiency may cause the accumulation of folate in the serum because of a reduction in B_{12}-dependent methyltransferase, also known

as the methyl-folate trap [584]. Vitamin B_{12} also functions in the synthesis of choline, which can be converted to the neurotransmitter acetylcholine.

Unlike other water-soluble vitamins, vitamin B_{12} can be stored in the body for years. It is stored predominantly in the liver, but smaller amounts can also be found in the muscles, kidneys, bones, heart, brain, and spleen. About 2 to 5 mg of vitamin B_{12} is stored in the body [277]. The size of B_{12} stores remains relatively stable, partly because urinary and fecal excretion decrease in direct relationship to decreases in the body pools. The half-life of vitamin B_{12} in humans is 350 to 400 days [277].

No evidence of toxicity has been found with vitamin B_{12} supplementation in amounts greater than the RDA [277], and no adverse effects are reported to be caused by an excess of vitamin B_{12}. If a person went for many years without adequate intake and/or supplementation, body stores could be depleted. Other factors that could contribute to a vitamin B_{12} deficiency include a decrease in gastric acidity, the presence of atrophic gastritis, and uncontrolled growth of bacteria accompanied by malabsorption of food-bound B_{12} [691]. Deficiency of vitamin B_{12} leads to pernicious anemia and demyelination of the central nervous system, and can lead to death [622].

2. Findings from Space Flight and Ground-Based Research

No data are available on vitamin B_{12} status during or after long-duration space flight, although the recently initiated Nutritional Status Assessment Supplemental Medical Objective experiment will provide determinations of homocysteine, methylmalonic acid, and related metabolites. These determinations will allow not only diagnosis of vitamin B_{12} deficiency, but also differentiation between vitamin B_{12} and folate deficiencies.

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of vitamin B_{12} is 2.4 μg/d [460], slightly higher than the original requirement defined for ISS missions [458]. This is the defined required amount of vitamin B_{12} in the U.S. for both men and women aged 19 years and older [277]. The ISS food system is estimated to provide 4.6 μg vitamin B_{12} per day (Table 1).

4. Risks on Exploration Missions

Virtually nothing is known about the status of vitamin B_{12} during or after space flight, or its relationship to other factors. Alterations in the metabolism of this vitamin or the requirements for it during long-duration flights could have critical health implications for crewmembers.

5. Remaining Questions

Determinations of homocysteine (and related metabolites) before, during, and after flight should help resolve (or increase) any concerns about vitamin B_{12} in space crews. Vitamin B_{12} concentrations and stability in the space food supply should be determined.

H. BIOTIN

1. Background

Biotin is a required cofactor for pyruvate carboxylase, acetyl-CoA carboxylase isoforms 1 and 2, propionyl-CoA carboxylase, and β-methylcrotonyl-CoA carboxylase [88]. The 5 biotin-dependent enzymes are involved in carbohydrate, fatty acid, and amino acid metabolism [88].

Biotin exists in a free state or bound to proteins. About 81% of biotin in the human body is free biotin in serum, and 10% is free in tissues [440].

Low-biotin diets administered to 10 healthy subjects who also consumed large amounts of avidin (an egg-white protein that binds biotin very tightly) showed signs of decreased biotin status by the third day [444]. At that time urinary excretion of 3-hydroxyisovaleric acid had increased significantly. Urinary excretion of biotin and its metabolites decreased significantly only after 7 to 17 days. Serum biotin did not decrease significantly, and it was suggested that serum biotin is not a sensitive indicator of marginal biotin deficiency [442]. The earliest and most sensitive indicator of a biotin deficiency is 3-hydroxyisovaleric acid excretion. Urinary biotin excretion, however, was used in animal studies as an indicator of a biotin deficiency, generally reported to occur about 2 to 3 weeks after beginning consumption of a biotin-free diet [389, 443].

Despite the observation that frank signs of deficiency are rare, there is growing appreciation of genetic, physiologic, and pharmacologic conditions that marginally impair biotin status [334, 441, 530]. This suggests that the lack of physiologic manifestations of biotin deficiency may not be a reliable measure to gauge biotin status. Marginal changes in biotin status have been shown to affect a range of metabolic factors, from carboxylase activity to the expression of non-biotin-dependent enzymes such as glucokinase, ornithine transcarbamylase, and phosphoenolpyruvate carboxykinase [59, 120, 411].

Frank biotin deficiencies are associated with neurological and dermatological manifestations, which are likely caused by the loss of function of biotin-dependent enzymes. Seizures, hearing loss, optic atrophy, dermatitis, and aciduria (associated with elevated blood concentrations of organic acids) are common symptoms of a frank biotin deficiency. There is no evidence of toxicity of biotin at high intake levels.

2. Findings from Space Flight and Ground-Based Research

No data currently exist regarding biotin intake or status during or after space flight.

3. Dietary Intake and Requirements

The current documented requirement for dietary intake of biotin during space flight is 30 μg/d. In the U.S., the dietary reference intake for biotin has been based only on adequate intake (AI) data [180]. To date, no RDA has been reported for biotin due to lack of data and a general consensus that colon bacteria synthesize biotin that contributes to the daily supply. Because microbial synthesis of biotin takes place in the lower part of the intestine, where nutrient absorption is limited, controversy exists about how much of the biotin produced by colon bacteria is available for host metabolism. The AI for adults is extrapolated from the AI for healthy infants consuming breast milk, and has been determined to be 30 μg/d for men and women > 19 years.

4. Risks on Exploration Missions

Nothing is known about biotin as related to space flight. While risk of deficiency on Earth is rare, alterations in synthesis metabolism or requirements during long-duration flights, or the occurrence of drug/nutrient interactions, could have significant health implications for the crew.

5. Remaining Questions

Biotin levels in the space food system need to be determined. Biotin status of astronauts during and after flight, and the fact that gastrointestinal changes during space flight may lead to changes in microbial synthesis of biotin, warrant further study. Furthermore, the interaction of biotin with some pharmacological agents (such as phenobarbital) included in the medical kit supplied to astronauts during space flight has been shown to yield biotin deficiencies in other populations [334].

I. PANTOTHENIC ACID

1. Background

The primary function of pantothenic acid is in its role as a precursor of coenzyme A and as a component of acyl carrier protein [433]. Pantothenic acid, in the form of coenzyme A and acyl carrier protein, is required for numerous lipid, carbohydrate, and protein metabolic reactions. Coenzyme A is necessary for acetyl and acyl transfer reactions associated with catabolism, and it acts as a precursor to acyl carrier protein. Acyl carrier protein is also a coenzyme in fatty acid synthase complex.

Free pantothenic acid is found in various parts of the body: 10 to 15 μmol/L in the liver, ~100 μmol/L in the heart, 1 to 5 μmol/L in plasma, 50 to 100 μmol/L as coenzyme A, and 10 μmol/L as acyl carrier protein. About 70% to 90% of coenzyme A is found in the mitochondria. Any excess pantothenic acid is excreted in urine [433].

Since pantothenic acid is widely distributed in foods of both plant and animal origin, deficiencies have been reported only in cases where semisynthetic diets or antagonists to the vitamin were used, or in cases of multiple nutrient deficiencies [433]. Individuals became deficient after 63 days on a diet virtually devoid of pantothenic acid [191]. Deficiency of the vitamin is frequently associated with multi-nutrient deficiencies, making it difficult to detect specific symptoms of pantothenic acid deficiency [433]. There is no conclusive evidence that adverse effects occur from high intakes of pantothenic acid [433].

The requirement for pantothenic acid in a variety of metabolic reactions explains why a deficiency of the vitamin can cause neurological, immunological, hematological, reproductive, and gastrointestinal dysfunctions. Specific symptoms include dermatitis, growth retardation, numbness and burning of hands and feet, impaired antibody production, headache, fatigue, insomnia, increased sensitivity to insulin, and intestinal disturbances [433].

2. Findings from Space Flight and Ground-Based Research

No data regarding pantothenic acid intake or status during or after space flight are currently available.

3. Dietary Intake and Requirements

The current documented requirement for dietary intake of pantothenic acid during space flight is 30 mg/d [460]. In the U.S., the dietary reference intake for pantothenic acid has been based only on adequate intake (AI) data [180]. No RDA has been reported for pantothenic acid. The AI for adults is based on mean intakes and is 5 mg/d for men and women > 19 years. No upper limit has been reported for pantothenic acid, but doses of the vitamin as high as 10 to 20 g/d have been well tolerated, with occasional diarrhea reported [433]. Estimates of pantothenic acid in the ISS food system indicate that the requirements are being met (Table 1).

4. Risks on Exploration Missions

The stability of pantothenic acid under conditions of long-term space flight (such as extended storage time and exposure to high-linear energy transfer radiation) will have to be determined in order to minimize risk for pantothenic acid deficiency symptoms.

5. Remaining Questions

Pantothenic acid levels in the space food system should be determined. Given the lack of information, and rarity of deficiency, at this point, no specific research is required.

VIII. MINERALS

A. CALCIUM AND BONE

1. Background

Calcium is essential for maintaining the body's structural and mechanical functions, and it makes up 37% to 40% of the bone mineral hydroxyapatite in the body [234, 719]. In addition to its obvious role in the musculoskeletal system, calcium has a critical role in modulating the function of important proteins and regulating metabolic processes. Calcium binding is responsible for the activation of a wide range of proteins, including those involved in cell motility, blood coagulation, muscle contraction, neural transmission, glandular secretion, and cell division [559, 717, 719]. Circulating calcium levels are under tight control and are maintained within a narrow range [473].

Bone acts as the body's reserve for calcium, and contains almost 99% of the calcium in the body [719]. Total skeletal calcium is on average 1100 to 1500 g, and inadequate calcium intake has significant impact on adult bone [276]. About 1% of the body's calcium stores resides in the intracellular structures, cell membranes, and extracellular fluids [559].

During acute starvation, urinary calcium remains constant; the largest amounts of calcium loss occur in feces, with much of the mineral lost apparently coming from bone [313]. Blood calcium levels are extremely resistant to starvation, with no change found after 4 days of starvation in children [193], or 44 days of total fasting [285]. Studies in dogs and cats indicate that significant changes occur only when more than 35% of body mass is lost [448]. Blood calcium levels in humans after chronic semi-starvation are variable, but most studies indicate that plasma or serum calcium levels decrease [313]. Controlled calcium balance studies during semi-starvation provide more variable results, with individual calcium balances ranging from positive to negative [313].

Calcium depletion is not uncommon in many subgroups of the population. Calcium absorption may be decreased in a variety of disease states, including Crohn's disease, diabetes, chronic renal failure, and malabsorption syndromes [559]. Although the daily calcium intake requirement rises with age, many elderly people and those in other population groups have inadequate intakes. Assessment of calcium deficiency by clinical laboratory analyses is difficult because circulating calcium is tightly regulated over a wide range of intakes [559, 719]. Imaging techniques (such as dual-energy X-ray absorptiometry and

quantitative computed tomography) that enable determination of bone mineral content may provide a good indicator of long-term calcium nutritional status.

Deficiency of calcium leads to reduced bone mass and osteoporosis. An excess of absorbed calcium leads to kidney stones, hypercalcemia, and ultimately renal insufficiency or even death. Increased dietary (as opposed to absorbed) calcium intake is not only not related to increased renal stone risk, it has been associated with reduced risk [236]. Intakes up to 2500 mg/d are considered safe under normal conditions [559, 719].

2. Findings from Space Flight and Ground-Based Research

Bone loss is a significant health concern for long-duration space flight [91, 261, 382, 588]. As a result of skeletal unloading during flight [378, 484, 528, 598, 651, 726], bone mineral is lost, leading to increased urinary excretion of calcium [598, 725, 726]. It is often estimated that the rate of bone mineral loss during space flight is about 0.5% to 1% per month [379, 702, 718]. Averaged losses across all sites were estimated to be 2% to 9% [586]. The bone loss and an increased risk of renal stone formation during and after flight [508, 509, 729, 730, 750] are significant.

The Skylab studies showed that during space flight, bone mineral was not uniformly lost from all parts of the skeleton. Loss of bone tissue was greatest in weight-bearing bones such as the os calcis. Of the 3 men aboard the 59-day Skylab 3 mission, 1 lost a significant amount of os calcis bone mineral (–7.4%) but the other 2 did not (+2.3% and +1.4 %). Calcium excretion in the urine was 200% of the preflight value for the man who lost os calcis mineral and 50% of the preflight values for the other 2 men [598]. This subject-to-subject variability remains a hallmark of space flight-induced bone loss [382], and may provide insight to finding a means to mitigate this loss.

Negative calcium balance was observed during the Skylab [361, 498, 598, 722, 724-726] and Mir [603, 609] missions. During the 84-d Skylab 4 mission, calcium balance was –200 mg/d [498, 525, 725], but no significant calcium losses occurred during the 28-d Skylab 2 mission [598, 718]. Increased urinary and fecal calcium excretion accounts for most of the deficit in calcium [361, 598, 603, 609, 722, 725, 726, 730]. During the Skylab 4 mission, calcium losses correlated roughly with mineral losses in the *os calcis* [723] and increases in the excretion of hydroxyproline [382, 525].

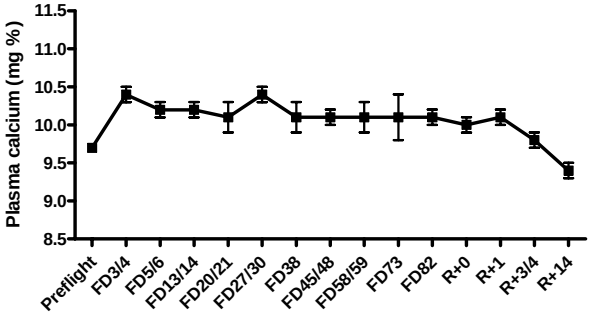

Figure 52. Plasma calcium of Skylab crewmembers (n = 9) before and after flight. Data are from Leach and Rambaut, 1977 [361].

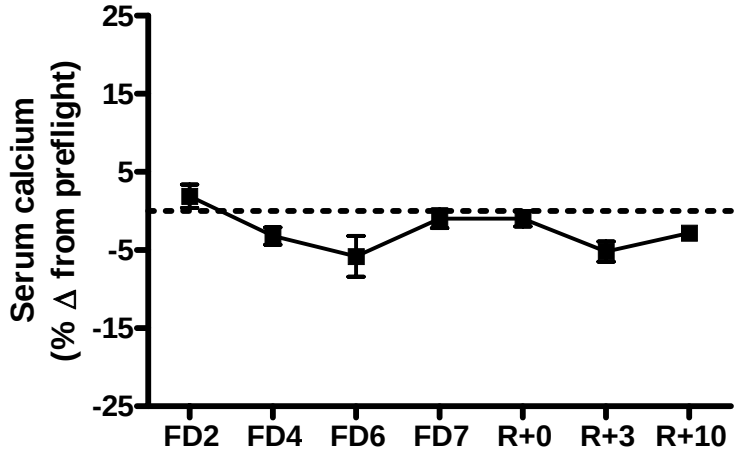

Figure 53. Serum calcium of Shuttle crewmembers (n = 2-6) during and after flight, expressed as a percent change from preflight values. Data are from Leach-Huntoon et al., 1987 [359].

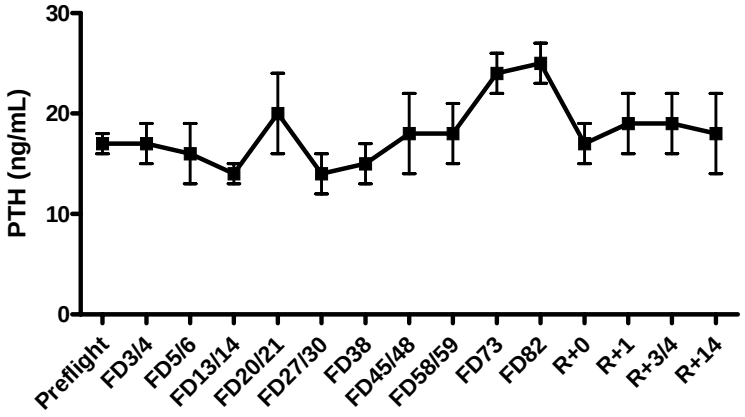

Figure 54. Plasma parathyroid hormone (PTH) concentrations of Skylab crewmembers (n = 9) before and after flight. Data are from Leach and Rambaut, 1977 [361].

Because of the nature of calcium metabolism, the source of calcium loss from bone and increased urinary calcium excretion cannot easily be identified. Calcium excretion can be affected by dietary changes, alterations in absorption of calcium from the diet, secretion of calcium into the gastrointestinal tract, the rate of bone calcium deposition (that is, bone formation), and bone resorption. For space flight-induced bone loss to be mitigated, the mechanism must be known. Although early animal studies suggested that the primary change in bone metabolism was related to bone formation, the identification of markers specific to bone resorption in the late 1980s [156, 684] and the availability of commercial immunoassays in the 1990s [546, 577] allowed resolution of this matter: bone resorption increases during space flight and bone formation decreases or does not change significantly.

3. Bone

Bone resorption increases during space flight, as shown by the concentrations of bone resorption markers [84, 108, 575, 602] and by the results of calcium tracer kinetic studies [603, 609]. Urinary hydroxyproline was elevated during short-duration Shuttle flights [575] and longer duration Skylab flights [361, 362, 725]. Urinary collagen crosslinks, also markers of bone resorption [571], were elevated > 100% during space flight compared to preflight levels [602, 603]. Calcium tracer kinetics data indicated that bone resorption increased about 50% during flight [603].

Bone formation either remains unchanged or decreases during space flight [603, 609, 718]. As indicated by serum concentrations of bone-specific alkaline phosphatase and osteocalcin, bone formation was unchanged during Mir flights, but increased 2 to 3 months after landing [603, 609]. Trends toward decreased levels of bone formation markers were noted in 2 Mir studies with 1 subject each [84, 108]. The results of studies, using calcium tracer techniques, of bone formation in 3 Mir crewmembers [603, 609] were equivocal (formation unchanged or decreased). Together, increased resorption and decreased or unchanged formation yield an overall negative calcium balance [603, 609].

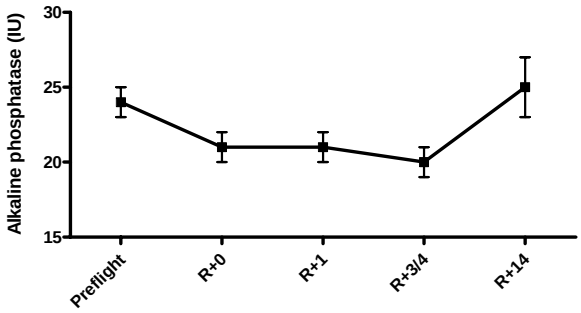

Figure 55. Plasma total alkaline phosphatase of Skylab crewmembers (n = 9) before and after flight. Data are from Leach and Rambaut, 1977 [361].

A number of related factors likely contribute to the loss of bone mineral during weightlessness. Mir astronauts were observed to have decreased calcium absorption [603, 609], which likely resulted from the decreased concentration of circulating 1,25-dihydroxyvitamin D that was also observed in these crewmembers [603, 609]. Although it is believed to be important to maintain calcium intake during flight, the lower calcium absorption during flight suggests that maintaining or increasing calcium intake is not a viable countermeasure for weightlessness-induced bone loss, a fact proven in bed rest studies [244, 619].

Space flight analog studies (such as bed rest) with humans have shown qualitative effects on bone and calcium homeostasis similar to those shown in flight studies [382, 502], with quantitative effects generally being of smaller magnitude. Effects include loss of bone mass [380, 620, 701, 749], decreased calcium absorption [376], increased urinary excretion of calcium and biochemical markers of resorption [22, 138, 143, 224, 245, 273, 374, 376, 620, 721, 726], increased risk of renal stone formation [138, 273, 751], and decreased serum concentrations of parathyroid hormone [22, 607] and 1,25-dihydroxyvitamin D [21, 22, 376, 607].

That bone resorption increases during bed rest has been shown by histomorphometry [300, 701] and measurement of biochemical markers. Excretion of hydroxyproline [143, 224, 376] increases during bed rest, and excretion of collagen crosslinks [376, 602, 607, 620] is elevated about 50% above control levels, compared with the increase of greater than 100% during flight [602, 603].

The concentrations of biochemical markers [376, 607, 749] indicate that bone formation is unchanged during bed rest, but histomorphometry data from bone biopsies show that bone formation decreases [22, 300, 701]. This difference likely reflects the difference between site-specific (biopsy) and systemic (biochemical markers) indices of bone formation. After ambulation begins following bed rest, bone formation generally increases [376, 749].

Bone loss and altered calcium metabolism occur in paralyzed individuals (as reviewed by Elias and Gwinup [150]), and a number of similarities can be found between these changes and those associated with space flight [319, 428, 454, 638]. The loss of bone that occurs after spinal cord injury seems to stabilize after about 25 weeks [438]. Studies of bone metabolism have not been possible during space missions of this duration, and the limited postflight bone assessment does not allow determination of the rate of loss.

If the rate of bone calcium loss is constant throughout a flight (a reasonable assumption judging by collagen crosslink excretion data [602, 603, 609]), then about 250 mg of bone calcium is lost per day during flight [217, 603, 609, 725].

Long-term follow-up data on bone recovery are far from complete [587, 670]. However, if the rate of postflight recovery estimated from biochemical data is also assumed to be constant (reasonable according to ground-based [380] and flight [603, 609] data), then the rate of recovery is about +100 mg/d [603, 609]. By these estimates, on flights up to about 6 months, it takes 2 to 3 times the mission duration to recover the lost bone. A recent analysis of bone recovery data from dual-energy x-ray absorptiometry analyses suggests that a 50% recovery of bone mass occurs in the initial 9 months after flight [587]. For longer exploration missions, however, the usefulness of these assumptions comes into question, as space flight data are not available for these durations. Although more data clearly are required to validate this hypothesis, it nevertheless has significant implications as mission durations increase.

4. Bone Loss Countermeasures

Many countermeasures to bone loss have been proposed and tested, from mechanical to pharmacological to nutritional forms.

A. Mechanical

Exercise countermeasures have been implemented during flight as far back as the Skylab missions (Skylab was the first vehicle to allow enough room for exercise). In addition to flight experiments, extensive ground-based testing has been done to evaluate the effectiveness of exercise as a countermeasure for muscle, bone, and cardiovascular maladaptations that occur during flight [112, 232, 502, 563]. For bone, the challenge remains to attain the force required to stimulate bone sufficiently to mitigate loss. Many types of exercises and devices have been studied, alone or in rare cases in combination, with mixed results. Although ground-based studies have demonstrated positive effects of exercise (for example, treadmill, flywheel, and weight stacks) on bone (assessed by various means from densitometry to

biochemistry) [47, 216, 542, 578, 607, 664, 714, 759], flight validation has not been achieved to date [354]. Many factors contribute to this lack of success, including the quantitative difference between bone loss during bed rest and space flight and the function, availability, and utilization of on-orbit hardware. The question of whether the same degree of exercise effectiveness can be reached during flight as in ground analogs is yet to be answered.

Vibration has also received much attention recently in the hope that it can provide a viable musculoskeletal countermeasure [44, 58, 550], and the initial ground-based evaluations are underway. As with all proposed countermeasures, vibration must first be proven effective in ground analog studies (such as bed rest), and if it is clearly successful, then in-flight validation studies can be conducted.

Under the assumption that lack of gravity is the stimulating factor in the bone loss of space flight, replacement of gravity by centrifugation ("artificial gravity") has been proposed as a countermeasure for multiple body systems [104, 700], particularly for bone. Some of the artificial-gravity studies have relied on short-radius centrifuges [213], others on rotating exercise devices [737, 738] intended to provide gravitational impact as well as physical exercise. Artificial gravity or hypergravity has been shown to positively affect bone, in human and some animal studies [283, 463, 464]. Vernikos and colleagues reported that intermittent exposure to 1 G_z (by standing or walking) during a 4-d head-down-tilt bed rest was effective in preventing the increase in urinary calcium that typically occurs during bed rest [699]. In a recent study, 1 hour per day of centrifugation resulting in 1 G_z at the heart and 2.5 G_z at the feet was ineffective for bone [614]. The optimal artificial gravity prescription for bone, including dose, duration, and frequency of centrifugation, remains to be clarified [103], along with its potential impact on nutrition and related systems [247].

B. Pharmacological

Pharmacological agents, the most common being the bisphosphonates, have also been tested for their ability to mitigate weightlessness-induced bone loss. Many ground analog studies of bisphosphonates (including bed rest studies and studies of patients immobilized because of spinal cord injury or other reasons) have been conducted, with generally positive findings [95, 216, 282, 381, 397, 415, 439, 487, 563, 581, 664, 701, 714]. However, ongoing discussion and debate surround the relative safety of these compounds for use in otherwise healthy individuals (astronauts), as opposed to the target population for whom the drugs were developed (patients with disorders such as osteoporosis). In addition to resolving safety concerns, investigators have yet to determine the optimal drug, dose, and schedule of administration during space flight. As noted above with exercise, given that the bone loss of bed rest is about half that of space flight, there is little reason to believe that the same dose of drug will have the same effectiveness in both environments. Moreover, data from animal studies suggest that the disuse- or space flight-induced increase in bone resorption cannot fully, or chronically, be mitigated by bisphosphonates [390, 391].

Endocrine therapies, including exogenous calcitonin administration [224, 563], have also been attempted, albeit unsuccessfully. In animal models, testosterone has also been suggested as a bone loss countermeasure [734, 735] because data have documented a reduction in testosterone concentrations during flight in human, animal, and cellular models [640-642, 644-647].

C. Nutritional

One of the most obvious nutritional countermeasures—providing calcium—does not protect against bone loss [755]. This result is likely related to the decreased calcium absorption seen during bed rest [376] and space flight [603, 609, 754]. Phosphate supplementation, used in an attempt to reduce calcium excretion, was also ineffective [271]. Combination therapy with calcium and phosphorus was also unsuccessful at mitigating bone loss and hypercalciuria [224].

Other nutrients, specifically sodium, protein, potassium, vitamin K, and omega-3 fatty acids, have also been proposed and/or tested as bone loss countermeasures [758]. These are discussed in detail in other sections of this book.

5. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of calcium during flight is 1200 to 2000 mg/d [460], higher than the initial ISS requirements of 1000-1200 mg/d [458]. In the U.S., adequate intake is defined as 1000 mg for men and women ages 31 through 50 years and 1200 mg for men and women 51 years and older [462]. The ISS menu provides about 1000 mg calcium/d, meeting the existing requirement. Meeting the higher intake requirement of 1200 to 2000 mg/d defined in 2005 [460] would help reduce the phosphorus:calcium ratio from the existing ratio of 1.8 (Table 1), a negative factor for bone health (see the Phosphorus section).

6. Risks on Exploration Missions

The ability to understand and counteract weightlessness-induced bone mineral loss will be vital to crew health and safety during and after extended-duration space station and exploration missions [20, 241, 447, 563, 587, 588, 612]. Changes in the endocrine regulation of bone metabolism seem to reflect adaptation to the weightless environment. Decreases in calcium absorption and plasma levels of parathyroid hormone and 1,25-dihydroxyvitamin D are responses that would be expected to occur if the resorption of bone increases as the body adapts to an environment in which bones bear less weight than on Earth. The evidence for these responses, and the lack of improvement provided by earlier dietary countermeasures, indicate that supplementation of the diet with nutrients such as calcium and vitamin D will not correct this problem [244]. Several other nutrients (for example, sodium, protein:potassium ratios, n-3 fatty acids, and vitamin K) do show promise as nutritional countermeasures, and both ground and flight testing of these are underway. In any event, adequate nutrition will be a required component in the success of whatever countermeasures are identified and implemented [239, 241].

For planetary missions, the ability of a partial terrestrial G force (such as Mars' 0.38 G) to reduce bone loss, or even allow recovery to begin, is unknown. Although no data on responses to partial G are available, the general consensus among investigators is that forces less than 0.5 G are likely to be of little value.

7. Remaining Questions

The effect of near-weightlessness on the human skeletal system is one of the greatest concerns in safely extending space missions [20, 241, 261, 282, 447, 486, 563, 587, 588, 606, 612]. Adequate intake of dietary calcium will be crucial for maintaining skeletal health. Both dietary protein (amount and type) and dietary sodium affect calcium metabolism. In addition, the use of pharmacological countermeasures against bone loss may have implications for calcium homeostasis. Specifically, the bisphosphonates exert their effects by inhibiting osteoclast-mediated bone resorption, and this inhibition lowers serum calcium in subjects who are normocalcemic or hypercalcemic [68]. It is recommended that subjects receiving bisphosphonates have adequate vitamin D status before therapy, and that their calcium status be monitored [46, 67, 506].

Although it is unlikely that diet is solely responsible for the bone mineral loss associated with space flight, even modest protective effects from a balanced diet would benefit crew health. Using diet modification as a countermeasure has several advantages, including no additional costs and no additional time required of astronauts during flight. The ratio of acid and base precursors in the diet could be an important predictor for the extent of bone loss during space flight, and could be determined from the menu choices before flight. Maintaining a diet balanced in acid and base precursors would involve food choices, and could be done with the help of a dietitian planning the menus. Furthermore, until in-flight resources for research are available, a pre- and postflight investigation of the relationship between diet and bone metabolism could provide a basis for defining optimal nutritional recommendations during recovery after space flight.

B. PHOSPHORUS

1. Background

Phosphorus is an important component of cell membranes and bone mineral. Phosphate accounts for about 60% of bone mineral [234], and most (85%) of the body's extracellular phosphorus is in bone [16]. Phosphorus is also an essential element of most enzymes, cellular messengers, and carbohydrate fuels.

Deficiency of phosphorus leads to hypophosphatemia, which causes cellular dysfunction and can lead to anorexia, muscle weakness, bone pain, and ultimately rickets, or even death. Osteomalacia, a defect in bone mineralization, often occurs as a result of long-term phosphorus deficiencies. Inadequate intake of phosphorus can cause the release of calcium from bone, cardiomyopathy, and a reduction in chemotactic, phagocytic, and bactericidal properties of granulocytes [324]. An excess of phosphorus leads to hyperphosphatemia, ectopic calcification of the kidney, or even death. Excessive phosphorus intake has been shown to affect calcium absorption by increasing excretion of endogenous calcium in the feces [123].

Human studies show that phosphorus can be depleted by daily antacid treatment with either magnesium-aluminum hydroxide (60 mL, 4 times per day) or aluminum hydroxide (30 mL, 4 times per day) [399]. Serum calcium of these subjects was elevated within 12 days of

treatment, and by day 20 phosphorus balance was negative [399]. Animal studies have demonstrated that removal of phosphate from the diet rapidly produces hypercalcemia, hypercalciuria, and hypophosphaturia. Rats fed a low-phosphate diet showed signs of deficiency after 11 days [289].

2. Findings from Space Flight and Ground-Based Research

Plasma phosphate was determined in Skylab crewmembers before, during, and after flight (Figure 56), and showed a tendency for increased circulating concentrations during flight.

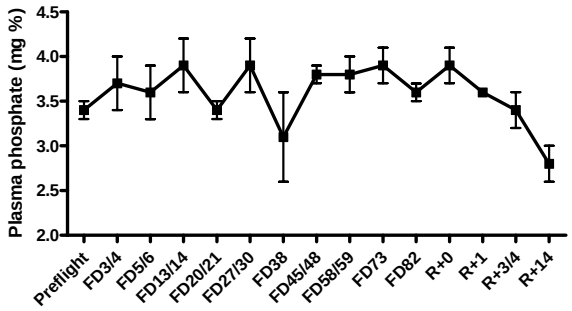

Figure 56. Plasma phosphate of Skylab crewmembers (n = 9) before, during, and after flight. Data are from Leach and Rambaut, 1977 [361].

Long-duration ISS space flight data showed that urinary phosphorus concentrations were about 45% less after landing than before launch (Figure 57) [610].

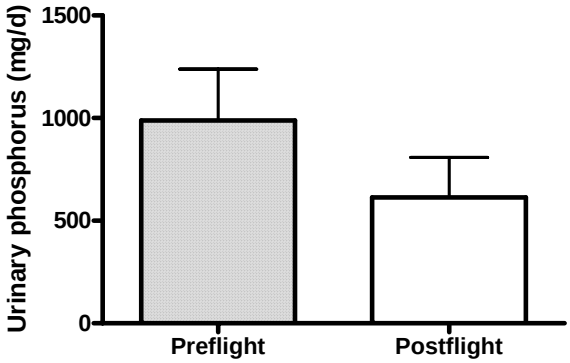

Figure 57. Urinary phosphorus of ISS crewmembers (n = 23) before and after long-duration space flight. Data are from Smith et al., 2005 [610].

Excretion of phosphorus during untreated bed rest was not changed [761] from ambulatory conditions. An earlier study of 3 subjects revealed increased urinary phosphorus and negative phosphorus balance [143]. In bed rest studies, investigators have attempted to use combination therapy with calcium and phosphorus to mitigate bone loss and hypercalciuria, with trends in the right direction but no significant changes [224].

3. Dietary Intake and Requirements

In the U.S., the RDA for phosphorus [276] is 700 mg/d for men and women 19 years of age and older. The current documented space flight requirement for dietary intake of phosphorus during flight is 700 mg/d, and phosphorus intake is not to exceed 1.5 times the calcium intake [460]. Although the ratio is the same as in initial ISS requirements, the phosphorus recommendation has been reduced [458]. The ISS menu provides an excess of phosphorus, with an average of 1856 mg phosphorus per day, and a phosphorus:calcium ratio of 1.8 (Table 1). Actual intakes from Apollo, Skylab, and Shuttle crews were closer to the desired 1.5 P:Ca ratio (Table 2).

4. Risks on Exploration Missions

Adequate phosphorus intake before and during flight will be crucial for preserving bone quality and quantity. In addition, a dietary phosphorus:calcium ratio greater than 1.5 is known to decrease calcium absorption, which could impair skeletal integrity. Serum phosphorus rises with increasing phosphorus intake, and if hyperphosphatemia occurs, it can result in calcification of the kidney. For this reason, ensuring optimal phosphorus intake during flight becomes very important [718]. Because phosphorus deficiency can cause muscle weakness and osteomalacia, maintaining adequate status of phosphorus during flight will be vitally important for preventing impaired performance on landing, which could limit crew capability for getting out of the spacecraft in an emergency.

5. Remaining Questions

Nominal determinations of phosphorus content of the space food system are required, as well as further investigation of the mechanism and implications of decreased phosphorus excretion after long-duration space flight. The implications of the existing dietary phosphorus:calcium ratio exceeding the guidelines should be evaluated.

C. MAGNESIUM

1. Background

Magnesium is the fourth most abundant cation in the body, and within the cell is second only to potassium [436, 707]. It is required as a cofactor for more than 300 enzyme systems and serves as a substrate for phosphate transfer reactions in all cells [707]. More than half of the body's magnesium is in bone, about 30% in muscle, and the remainder mostly in soft tissue [583].

While magnesium deficiency can be induced by many causes (from drug-nutrient interactions to plain inadequate intake), few studies have addressed experimental magnesium depletion in humans. Consuming a diet containing 10 mg/d for 110 days led to a steady

decline in plasma magnesium to levels 10% to 30% of control values, and urinary magnesium levels were negligible (< 1 mEq/d) within 7 days [583]. Abnormal neuromuscular signs occurred in 5 of 7 subjects after 25 to 110 days of magnesium deficiency [583]. Deficiency of magnesium leads to neuromuscular hyperexcitability, seizures, cardiac complications, or even death [276]. Adequate intake of magnesium is necessary to prevent hypocalcemia, resistance to vitamin D, and resistance to parathyroid hormone.

No evidence has been reported of adverse effects associated with toxicity from naturally occurring sources of magnesium, but very large doses may cause gastrointestinal distress. Furthermore, excessive intake from supplements has been shown to impair calcium absorption [583].

2. Findings from Space Flight and Ground-Based Research

Decreased urinary magnesium after flight, compared to before flight, seems to be a hallmark of space flight. Apollo serum and urinary magnesium are shown in Figure 58 [366]. Serum magnesium trends downward, as seen with in-flight and postflight Shuttle data shown in Figure 59.

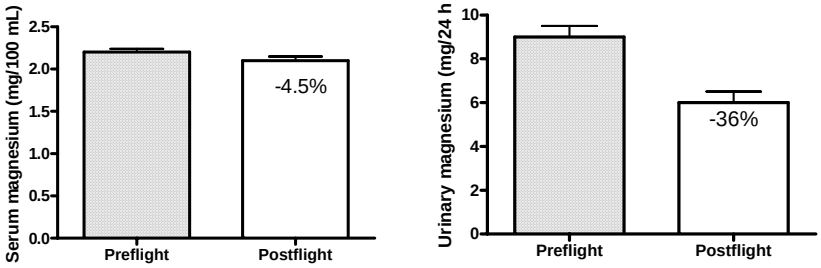

Figure 58. Serum (n = 32) and urinary (n = 23) magnesium from Apollo crewmembers. Numbers in bars represent the percent change from preflight values. Adapted from Leach et al., 1975 [366].

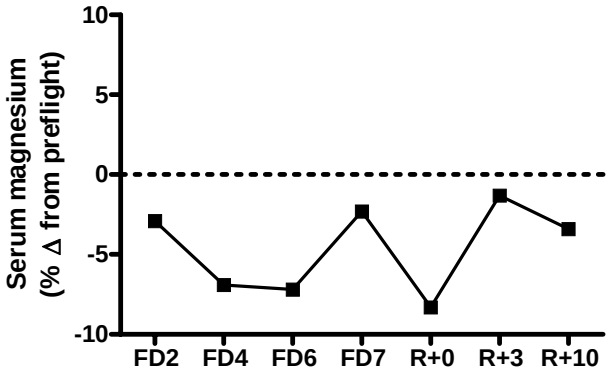

Figure 59. Serum magnesium of Shuttle crewmembers (n = 2-6) during and after flight, expressed as a percent change from preflight values. Data are from Leach-Huntoon et al., 1987 [359].

At landing, crewmembers on Skylab flights had lower plasma magnesium (Figure 60), but it had returned to normal by 2 weeks after landing.

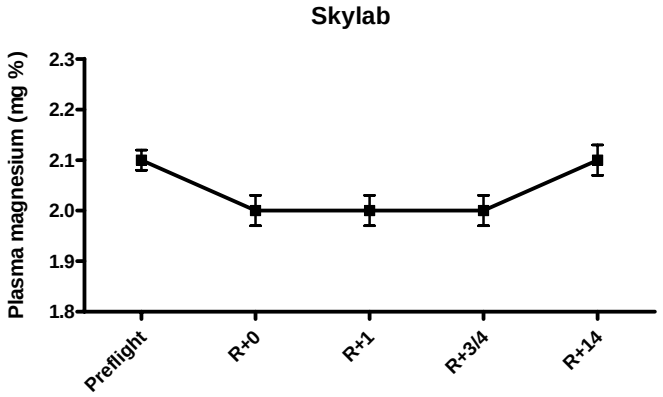

Figure 60. Plasma magnesium of Skylab crewmembers (n = 9) before and 0, 1, 3-4, and 14 days after flight. Data from Leach and Rambaut, 1977 [361].

Several studies show that magnesium metabolism may be altered during and after long-duration space flight [361, 372, 610]. After crewmembers had spent 4 to 6 months in space, their urinary magnesium was about 45% less than it was before flight [610]. The causes and implications of this are being evaluated in ongoing ground-based and flight studies.

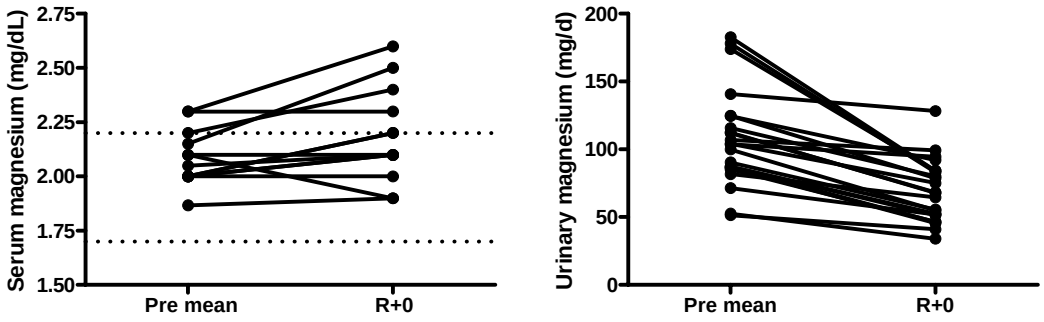

Figure 61. Serum (left panel) and urinary (right panel) magnesium before and after 4- to 6-month space flights on the International Space Station. Each line represents 1 crewmember. The "Pre mean" point on each line is the average of data collected about 6 months and about 6 weeks before launch. R+0 = Recovery plus zero days, that is, landing day. These samples are typically collected 2 to 8 hours after landing. Data are from Smith et al., 2005 [610].

A Russian report on the impact of space flight on the magnesium content of bones documented 12% to 32% lower concentrations in the compact layer of the femoral epiphysis and diaphysis, vertebral body, and sternum of Salyut-1 space station crewmembers than in nonflight controls [519]. These changes were reported as appearing "with a high degree of certainty." No changes were observed in the calcaneus. (Note: This study reported on the autopsy results after the tragic end of the 24-d Salyut-1 mission, compared to controls.)

Magnesium balance was slightly negative during extended-duration bed rest studies conducted in Russia [216], with little effect of exercise or bisphosphonate. Recent studies

conducted in the U.S. have shown a decrease in magnesium excretion in short- and long-duration bed rest [761, 762]. Artificial gravity had no effect on magnesium [762].

Magnesium shows promise for reducing the risk of renal stone formation [568]. In ground-based studies, potassium-magnesium citrate has proven effective in reducing bed rest-induced risk [751], but flight validation tests have yet to be conducted.

3. Dietary Intake and Requirements

The current documented requirement for dietary intake of magnesium during space flight is 420 and 320 mg/d for men and women respectively [460], compared to the original ISS requirement of 350 mg [458]. In the U.S., the RDA for magnesium [276] for men aged 19 to 30 years is 400 mg/d, and for men 31 to 70 years it is 420 mg/d. For women aged 19 to 30 years the RDA is 310 mg/d, and for those 31 to 70 years it is 320 mg/d. The ISS food system provides an average of 424 mg/d (Table 1).

4. Risks on Exploration Missions

Adequate magnesium intake before and during flight will be needed to reduce the potential for altered magnesium status, and to help preserve bone quality and quantity. Maintaining adequate magnesium status during flight will be critical for maintaining musculoskeletal structure and function and thus for preventing impaired performance on landing, which might limit crew capability for getting out of the spacecraft in an emergency.

5. Remaining Questions

Nominal determinations of magnesium content of the space food system are required. The significant decrease in urinary magnesium excretion after space flights (described above) also warrants further investigation.

D. Iron and Hematology

1. Background

Iron is an essential element involved in oxygen transport, oxidative phosphorylation in carbohydrate and lipid metabolism, and electron transport in cytochromes and cytochrome oxidase [41, 159].

Body iron is composed of essential iron compounds (70% of the total), which include hemoglobin (59%), functional tissue iron (myoglobin and metalloenzymes, 13%), and transport iron (bound to transferrin, < 0.1%); and nonessential storage iron (30%), which includes ferritin and hemosiderin [41]. Serum ferritin has been shown to be a sensitive indicator of iron stores [435]. Ferritin is exponentially correlated with storage iron, as

determined by quantitative phlebotomy in patients with iron overload [517]. Most investigators have looked at ferritin as an indicator of iron depletion, and it has been hypothesized to represent a rapidly mobilized iron pool, with hemosiderin being mobilized as the ferritin pool becomes depleted [435].

Iron is also thought to be involved in immune system function. Changes in serum ferritin and transferrin are observed during infection and as part of the inflammatory response. The inflammatory response is characterized by increased clearance of iron from plasma, increased uptake of iron by the reticuloendothelial system, and increased ferritin synthesis, inducing elevated serum ferritin levels [26]. The upper limit of serum ferritin in the presence of inflammation has been reported to be between 50 and 100 μg/L [55, 394].

Iron deficiency is the most common nutritional deficiency worldwide, but iron toxicity is also worthy of concern. Deficiency of iron leads to anemia, fatigue, reduced work capacity, impaired behavior and intellectual performance, cognitive deficits and memory loss, heart palpitations, impaired thermoregulation, decreased immune function, or even death [121, 402, 705]. Toxicity of iron may lead to tissue damage or cancer. High iron intakes have also been related to gastrointestinal distress. The toxic potential of iron derives from its ability to exist in 2 oxidative states (ferrous and ferric forms). Iron serves as a catalyst in redox reactions; however, when these reactions are not properly modulated by antioxidants or iron-binding proteins, cellular damage can occur [740]. The distinct relationship between iron stores and oxidative damage is clear [680]. Anemia has also been associated with inflammation [529].

Adaptation of iron metabolism in humans typically allows the maintenance of normal body iron in spite of disparate physiological requirements and dietary supply [113]. Body iron, about 4 g in the adult human, is determined by physiological iron demands, dietary supply, and adaptation [41, 113, 172]. Dietary iron is a function of both content and bioavailability of total food iron; bioavailability is lower in nonheme than in heme iron sources. Dietary factors that inhibit iron absorption include tea, coffee, bran, calcium, phosphate, egg yolk, polyphenols, and certain forms of dietary fiber [41]. Conversely, meat, fish, poultry, and ascorbic acid will enhance the bioavailability of nonheme iron.

Adaptation to variations in iron demand and supply is well documented [41, 172] in situations of iron deficiency and overload, and is regulated by alterations in transport, absorption, and storage of iron. Daily dietary iron absorption is 1 to 3 mg [41, 178], but the internal iron requirement is far in excess of this, with significant flux of iron through the system. Because a large percentage of body iron circulates in the red blood cells (RBCs), disordered RBC metabolism can cause marked changes in iron kinetics and metabolism.

Transferrin saturation is primarily a gauge of iron supply to tissues, but this test is subject to the large biological variation that occurs in serum iron concentration [41]. The delivery of iron to the erythroblast (RBC precursor) is mediated by the interaction of plasma transferrin with transferrin receptors located on the cell surface [114, 269]. The number of transferrin receptors is regulated by both iron status and formation of RBCs [43, 667]. Although ~80% of the transferrin receptors are located in the bone marrow where RBCs are formed, a truncated form of the receptor has been identified in human serum and plasma, and has been shown to be a reliable index of iron status [522]. Serum transferrin receptors may reflect the availability of iron for erythropoiesis (formation of RBCs) [165, 177, 317, 591]. Unlike serum ferritin, serum transferrin receptors are not influenced by infection or chronic inflammation [317, 339, 667]. Moreover, serum transferrin receptors have been shown to be sensitive to

(that is, decreased in the presence of) iron deficiency, inefficient erythropoiesis, and iron overload [43, 339].

Intracellular iron homeostasis requires coordination of processes of iron uptake, intracellular storage, and utilization [337]. Studies have shown that these processes occur under the aegis of regulatory factors that exert reciprocal control of the transferrin receptor and ferritin mRNA expression [337]. Storage (ferritin) and utilization (erythropoietic) pathways are stimulated and uptake pathways are depressed when intracellular iron status is replete, with the reverse occurring in the presence of intracellular iron depletion [337].

2. Findings from Space Flight and Ground-Based Research

Decreased red blood cell (RBC) mass is a consistent finding after short- and long-term flights [8, 290, 293, 347, 363, 683]. This "space flight anemia" was observed as early as Gemini missions in the 1960s [173]. The initial decrease in RBC mass occurs at a rate slightly greater than 1% per day, with an eventual loss of 10% to 15% within 10 to 14 days of flight [8, 363, 683]. During the first several days of space flight, hematocrit is either unchanged [600] or slightly elevated [8, 363, 683]. When elevation is noted, it is not as great as would be predicted from the decrease in plasma volume [365].

An early hypothesis for the cause of decreased RBC mass was that RBC synthesis in space was understimulated compared to synthesis on the ground [293]. Decreased release of mature RBCs into the circulation is associated with a decrease in circulating erythropoietin concentrations. Serum erythropoietin decreases in the first few days of space flight, but it returns to preflight levels later and iron turnover is unchanged during flight [8, 683], indicating that synthesis of RBCs and hemoglobin is unchanged.

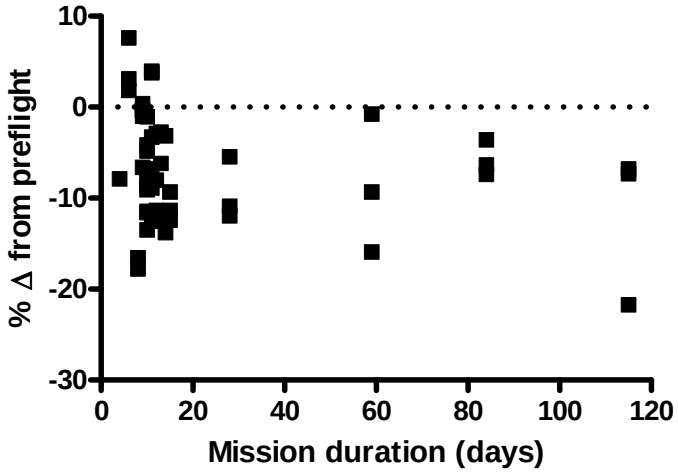

Figure 62. Red blood cell mass (mL/kg body mass) after space flight. Each point represents 1 crewmember. Data are expressed as percent change from preflight values. Adapted from Smith, 2002 [605].

Nevertheless, the release of new red cells is halted upon entry into weightlessness [7, 8, 540, 683], and newly released RBCs are selectively removed from the circulation [7]. These

nascent cells are larger than the more mature circulating RBCs, allowing them to be selectively destroyed [7]. Removal of mature red cells from the circulation is unchanged during flight [8].

Indices of iron metabolism and erythropoiesis return toward normal relatively quickly (days) after landing, although the replenishment of RBC mass may take several weeks. The repletion of RBCs usually occurs after the disproportionate return of plasma volume, so that a dilutional "anemia" often occurs after flight [600]. For example, a 3% to 5% decrease in hematocrit between landing (R+0 days) and R+3 days is common after both short- and long-duration flights [600].

Although the in-flight decrease in RBC mass is significant, the efficient postflight recovery suggests that it represents an adaptation to weightlessness. After the first weeks of flight, RBC mass and body fluid volumes reach new plateaus (lower than on Earth), as shown by data from long-duration flights [111, 347, 350, 360]. The triggering mechanism for these changes is unknown. One hypothesis is that the body senses a decreased requirement for blood volume and adapts accordingly. This may be related to changes in fluid (circulatory) dynamics and reduced gravitational strain on the circulatory system during flight, which may result in easier delivery of oxygen to tissues, or to the decreased plasma volume and increased concentration of RBCs in the first few days of space flight. The decrease in RBC mass has no documented functional consequences.

Serum iron concentrations are normal or elevated during and after flight [8, 683]. Serum ferritin concentrations increase during and after both short- and long-duration flights [10, 605].

Bed rest studies have not proven to be consistently reliable models for the hematological changes of space flight. Early bed rest studies showed a decrease in RBC mass during bed rest, but erythropoietin was unchanged and hematocrit increased [147], suggesting that the mechanisms that bring about hematological changes during bed rest are different from those that act during flight. If the reduced RBC mass during flight is caused by the reduced gravitational load on the circulatory system, it is reasonable to assume that bed rest alone would not alleviate these forces, but would only reposition them. More recent studies have shown small changes in iron status measurements, the most consistent being a drop in hematocrit and hemoglobin after reambulation [761, 762], suggesting an impact of plasma volume replacement, with a smaller role of hematopoiesis.

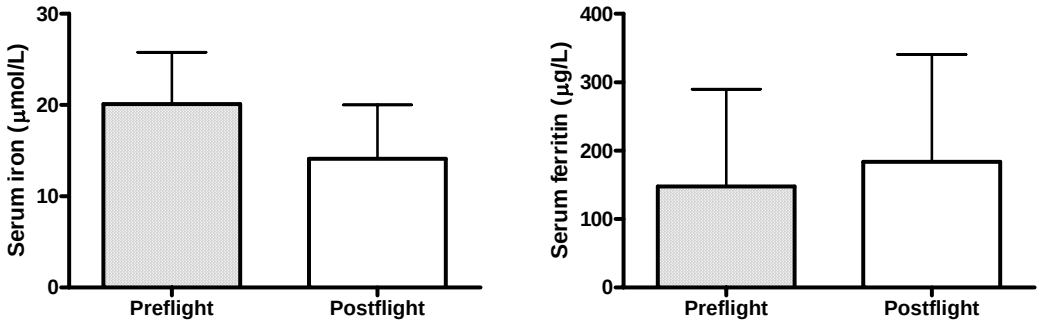

Figure 63. Serum iron and ferritin in ISS crewmembers (n = 23) before and after long-duration space flight. Data are from Smith et al., 2005 [610].

Another model is provided in studies involving changes in altitude, where the descent from high to low altitude induces changes similar to those observed for space flight (decreased red cell mass, increased iron storage) [539]. Exogenous erythropoietin prevented the changes [539], suggesting that it is involved in the regulating mechanism, as it may be in the initial change in space flight.

The NASA Extreme Environment Mission Operations (NEEMO) undersea environment provides an excellent space flight analog, specifically with respect to the environment in the NEEMO habitat [608]. Because of the increased air pressure in the habitat, crewmembers are exposed to higher oxygen pressures, which increase their risk for oxidative damage to DNA, proteins, and lipids [13, 27, 139, 548]. Probably because of the increased pressure and greater oxygen availability, newly formed red blood cells are destroyed in a process called neocytolysis (which also occurs in space flight) [9, 131, 538, 540], and body iron stores are elevated [605, 610]. As discussed above, excess iron can act as an oxidant and cause tissue damage [71, 202].

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of iron is 8 to 10 mg/d for men and women. In the U.S., the RDA for men 19 to 70 years is 8 mg/d, and for women aged 19 to 50 years it is 18 mg/d, dropping to 8 mg/d in women over 50. Historical space flight iron requirements for missions of 12 to 30 days were less than 10 mg/d [457, 458], matching the RDA at the time.

Dietary iron provided by the space food system has always exceeded the requirement, and intakes have often been much higher (intakes as high as 20 to 25 mg iron per day have been observed, and the menu provides an average of over 22 mg/d, Table 1). This gives reason for concern because of the potential for elevated tissue iron to cause deleterious effects, including oxidative damage [680]. This is a rare gender-based effect: women, who are at increased risk of iron deficiency on Earth, may actually be protected against iron overload during flight [226].

4. Risks on Exploration Missions

One consequence of the decreased RBC mass during space flight is that the iron released when new RBCs are destroyed is processed for storage. Increased iron storage and excess dietary iron intake during long-duration exploration missions pose a risk of iron toxicity and other effects of iron overload. Iron-related radical ions could form during iron-overload situations, and this could confound damage induced by ionizing radiation and inflammatory-immune injury [178]. Serum concentrations of ferritin and soluble transferrin receptor have been linked to evidence of DNA damage in ground-based models [680]. Furthermore, the formation of free radicals subsequent to elevation of iron stores has also been linked on Earth to cardiovascular disease and cancer. Although aspects of some of the evidence supporting this thesis contradict each other [25, 574], a correlation between coronary heart disease and iron status has been described in a number of recent studies [357, 556, 654], and an association between increased incidence of myocardial infarction and increased iron stores (as

measured by serum ferritin) has been observed [556, 653]. In a prospective Finnish study, increased risk of all cancer types combined and colorectal cancer in particular was associated with high iron stores [323]. The relationship between iron, lipids, and cancer has also been documented in the Framingham study [416]. A relationship has also been indicated between excessive iron stores and ascorbic acid deficiency; when reductions in ascorbic acid occur, vitamin A and selenium tend to exacerbate iron-induced peroxidation processes [565]. These data suggest that the alterations in erythropoiesis and iron metabolism that occur in microgravity could cause significant changes affecting crew health.

5. Remaining Questions

Better characterization of iron metabolism during flight is warranted because of the high levels of dietary iron and the potential for iron to act as an oxidizing agent during space flight, complicated by increased radiation levels. Iron absorption has yet to be determined during flight. Additionally, the relationship between iron storage and oxidative damage during flight has not been fully elucidated.

E. COPPER

1. Background

Copper is an essential cofactor for enzymes involved in energy production, metabolism of oxygen and iron, maturation of the extracellular matrix and neuropeptides, and neuroendocrine signaling [518]. Deficiencies in copper have implications for bone health, the nervous system, immune function, the cardiovascular system, and lipid metabolism [518]. Copper is involved in bone health, specifically related to lysyl oxidase function and collagen synthesis [497, 518].

Copper is not usually stored in tissues, but liver, brain, and kidney typically contain the largest amounts per unit tissue mass [518]. Total body copper is about 50 to 120 mg (0.79 to 1.9 mmol) [124]. Copper transport and regulation involve the blood protein ceruloplasmin.

Frank copper deficiency is rare in human populations consuming a normal diet; however, copper deficiencies have been noted in infants fed milk formulas, infants recovering from malnutrition and fed cow's milk, and patients receiving total parenteral nutrition for a prolonged period [181]. Six patients fed (through the gastrointestinal tract) a diet containing 15 μg copper/100 kcal for 12 to 66 mo [258] developed a copper deficiency.

When copper deficiency occurs it leads to normocytic, hypochromic anemia, decreased production of leukocytes and neutrophils, defects in connective tissue (specifically in collagen synthesis) that can lead to vascular and skeletal problems and central nervous system dysfunction, or even death [181]. Heartbeat irregularities have also been reported in cases of copper deficiency [437]. Deficiency symptoms, including macrocytic anemia, bone abnormalities, and decreased neutrophil production, have been reported in subjects with serum copper concentrations ranging from 0.9 to 7.2 μmol/L [258]. Toxic concentrations of copper lead to oxidative damage, gastrointestinal distress, liver damage, or even death [518].

2. Findings from Space Flight and Ground-Based Research

Serum copper and ceruloplasmin of ISS crews have been determined as part of the medical requirement to assess nutritional status in long-duration crewmembers [459, 610].

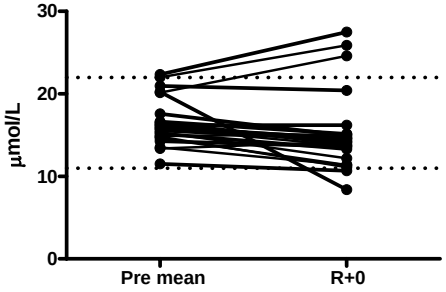

Figure 64. Serum copper before and after 4- to 6-month missions on the International Space Station. Each line represents 1 crewmember. The "Pre Mean" point for each line is the average of data collected about 6 months and about 6 weeks before launch. R+0 = Recovery plus zero days, that is, landing day. These samples are typically collected 2 to 8 hours after landing. Data are from Smith et al., 2005 [610].

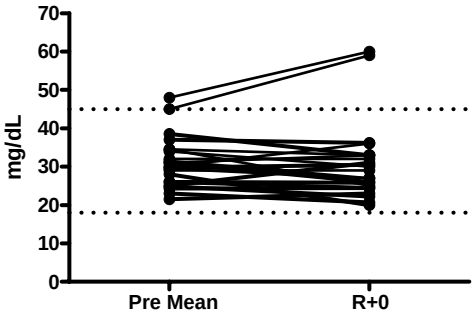

Figure 65. Serum ceruloplasmin before and after 4- to 6-month missions on the International Space Station. Each line represents 1 crewmember. The "Pre Mean" point on each line is the average of data collected about 6 months and about 6 weeks before launch. R+0 = Recovery plus zero days, that is, landing day. These samples are typically collected 2 to 8 hours after landing. Data are from Smith et al., 2005 [610].

One Russian report on the effect of space flight on copper content of bones [519] documented "non-uniform changes" in copper content of bone from different regions after flight compared to nonflight controls. Copper content of the femoral epiphysis was 81-159% greater, while the amounts of copper in the vertebral body and sternum were 36% and 58% less, respectively. (Note: This study reported on the autopsy results after the tragic end of the 24-d Salyut-1 mission, compared to controls.)

During a 17-week bed rest study, copper balance was unchanged, but after re-ambulation it increased [336]. During and after 3 weeks of bed rest, serum copper and ceruloplasmin were unchanged [762]. After 90 days of bed rest, serum copper was slightly elevated, but the change was statistically significant [761]. In 60- and 90-day bed rest studies, ceruloplasmin was unchanged [761].

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of copper is 0.5 to 9 mg/d [460], a wider range than the original ISS requirement of 1.5 to 3.0 mg/d (Table 1, [458]). In the U.S., the recommended dietary allowance for copper in men and women aged 19 to 70 years is 0.9 mg/d [181]. The ISS food system provides 3.6 mg/d on average (Table 1).

4. Risks on Exploration Missions

Changes in copper status could contribute to the effects of space flight on bone, red blood cells, and iron status. The changes in bone during space flight, described in this volume, could be exacerbated by copper deficiency and impaired collagen synthesis. Anemia of space flight is manifested as a reduction in circulating red blood cell mass with elevations in serum ferritin and iron concentrations [8, 350]. Since copper is required for iron mobilization and absorption, alterations in copper status may affect iron and red blood cell changes during flight.

Appropriate amounts of certain nutrients, copper in particular [65], are vital for maintaining normal immune function. The immune system seems to be altered during space flight [60, 118, 388, 660, 671], and this may have direct or indirect (when alterations are induced by stress or radiation) implications for nutrition and nutritional status as possible causes or effects [60, 135].

5. Remaining Questions

No information about copper absorption and metabolism during space flight is available, but, given the available ground data, obtaining such information is not a high priority at this point. Ensuring adequate copper content of the diet and verifying that the flight copper status data follow ground trends are important monitoring steps.

F. MANGANESE

1. Background

Manganese can function as an enzyme activator and as part of metalloenzymes. It becomes involved in activating enzyme-catalyzed reactions by causing conformational changes in the enzyme that it binds to. Manganese can also bind directly to the substrate.

All transferases, including kinases, hydrolases, oxidoreductases, ligases, and lyases, can be activated by manganese. However, in the presence of a manganese deficiency, these enzymes can be activated by other divalent cations. Activating these enzymes gives manganese a role in formation of components of connective tissue, urea formation, arginase activity, gluconeogenesis, the prevention of lipid peroxidation by superoxide radicals in the

mitochondria, and the conversion of pyruvate to oxaloacetate in the tricarboxylic acid cycle. Studies are currently being conducted to look at the role that manganese may play in second-messenger pathways in tissues and the regulation of calcium-dependent processes [218].

Only trace amounts of manganese are found in animal tissues. Humans store about 10 to 20 mg of the nutrient. Although it is found in most organs and tissues, the highest concentrations are in bone and in the liver, pancreas, and kidneys [218].

Signs of a manganese deficiency in humans have not been firmly established, partly because other cations can perform the same role. In one study, when adult men were fed a purified diet with only 0.11 mg manganese per day for 39 days, all of them developed a finely scaling rash, along with decreased serum cholesterol, increased serum calcium and phosphorus, and increased alkaline phosphatase [186].

It was initially believed that manganese was one of the least toxic trace minerals when taken orally. However, recent evidence shows a correlation between brain MRI manganese signals and neurological symptoms, including sleep disorders, found in patients with chronic liver disease [469]. The tolerable upper intake limit was based on these findings, and for adults that limit is 11 mg/d [181, 469].

Manganese and iron compete for binding sites. At low iron intakes, manganese is absorbed at a greater rate than at higher iron intakes, so that higher iron intake inhibits manganese absorption. Likewise, higher manganese intake can inhibit iron absorption.

2. Findings from Space Flight and Ground-Based Research

One Russian report on the effect of space flight on manganese content of bones [519] documented generally greater regional bone manganese content (26-187%) after flight than in nonflight controls. (Note: This study reported on the autopsy results after the tragic end of the 24-d Salyut-1 mission, compared to controls.)

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of manganese is 2.3 and 1.8 mg/d for men and women respectively, the same as the adequate intake of manganese for men and women aged 19 years and older [181].

4. Risks on Exploration Missions

Considering manganese's function in preventing lipid peroxidation and the increase in lipid peroxidation that occurs during space flight, ensuring adequate manganese intake on long space flights is vital to preventing and/or minimizing oxidative stress. Given the narrow range between adequate intake and toxicity concerns, however, crewmembers who select multivitamins need to take care to ensure that manganese intake is not excessive.

5. Remaining Questions

Existing knowledge of manganese metabolism seems adequate; other than the nominal determinations of manganese content of the space food system, no other specific research is required.

G. FLUORIDE

1. Background

Fluoride in bone exists in a rapidly exchangeable pool and a slowly exchangeable pool. In the rapidly exchangeable pool, fluoride is in the hydration shell on bone crystallites, where it is exchanged isoionically or heteroionically with other ions nearby [462]. The slowly exchangeable pool is mobilized during the process of bone remodeling. Fluoride has also been shown to influence the function of osteoblasts, enabling new bone to be made. An increase in fluoride absorption increases the amount absorbed by the hard tissue, but urinary excretion also increases.

Ninety-nine percent of fluoride is stored in mineralized tissues, predominantly in bone [469]. Because specific signs of fluoride deficiency have not been fully elucidated for higher animals and humans, it is not possible to estimate a relative time to depletion.

Fluoride deficiency increases the development of dental caries and may reduce the integrity of skeletal tissue [218]. Supplementation of fluoride (5 or 10 mg per day) in ambulatory subjects was shown to have no impact on calcium homeostasis, but did result in positive fluoride balance [413].

Toxicity with fluoride supplementation is rare but can occur with fluoride intakes greater than 10 mg/d for at least 10 years [276]. Toxicity of fluoride leads to fluorosis of the tooth enamel and skeleton, and osteosclerosis. High doses (> 40 mg per day) also result in side effects including bone pain and gastric irritation [541].

2. Findings from Space Flight and Ground-Based Research

No information about the effect of space flight on fluoride status of astronauts is available. Bed rest studies have documented that simulated weightlessness had no effect on fluoride balance [412], but this was in subjects consuming less than the recommended amounts of fluoride. Another study with similarly low fluoride intakes showed the same effect: bed rest alone does not affect fluoride balance [415], but balance is negative with insufficient intake.

In a follow-up study, fluoride supplementation was evaluated as a countermeasure for bone loss of osteoporosis and simulated space flight (bed rest). Although fluoride balance was positive when subjects were supplemented with 10 mg per day, there was no impact on calcium homeostasis, and both the fluoride-treated and untreated groups lost calcium during bed rest [414].

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of fluoride is 4 mg/d for men and 3 mg/d for women, the same as adequate intake of fluoride for men and women aged 19 years and older [181].

4. Risks On Exploration Missions

Care needs to be taken to ensure adequate, but not excessive, intake of fluoride.

5. Remaining Questions

Existing knowledge of fluoride metabolism seems adequate. Beyond the nominal determinations of fluoride content of the space food system (including water), no other specific research is required.

H. ZINC

1. Background

Zinc is a component of many enzymes, which depend on it for their catalytic activity. RNA polymerases, alcohol dehydrogenase, carbonic anhydrase, and alkaline phosphatase are all zinc metalloenzymes [116]. Tissue and cell growth, cell replication, skin integrity, cell-mediated immunity, and generalized host defense are all functions of zinc. Zinc is involved in bone metabolism, being required for bone formation and alkaline phosphatase activity, as well as collagen synthesis [497]. In tissue growth, zinc is involved directly with the regulation of protein synthesis. Cell membranes require zinc for protein-to-protein interactions and membrane proteins' conformation. Zinc may also affect the activity of enzymes attached to plasma membranes. Zinc prevents oxidation of the membrane by occupying sites that might otherwise be occupied by pro-oxidant metals and protects against oxidation by its role in the protein metallothionein. Zinc is an integral part of the hormone insulin and plays a role in carbohydrate metabolism.

About 1.5 to 2.5 grams of zinc is stored in the human body [181]. It is found intracellularly in all organs, tissues, and body fluids, but mostly in bone, liver, kidneys, muscle, and skin [116, 218]. More than 85% of zinc is found in skeletal muscle and bone [218, 315]. Even when dietary zinc is suboptimal, the zinc stored in muscle, brain, lung, and heart is not released. The apatite of bones releases zinc slowly, and this release does not greatly affect the zinc supply [181]. The greatest losses of zinc occur through the intestine. In men, the average daily loss of zinc from sources other than the intestine remains relatively constant at 1.27 mg/d, even when individuals consume an inadequate amount of the nutrient. For women, calculation of this value has been based on the difference in average surface area and menstruation, and is 1.0 mg/d [181].

Because the stores of zinc in the body are small, inadequate intake can quickly lead to exhaustion of the zinc supply. When this happens, plasma enzymes containing zinc and metallothionein are catabolized to provide the necessary zinc [116, 181], and this brings about a decrease in enzyme activity [218]. Zinc deficiency can also cause decreased glucose tolerance by decreasing insulin response. Basal metabolic rate has been shown to be decreased in individuals who were receiving a zinc-deficient diet [709]. Deficiency of zinc leads to arrested growth and development and decreased immune function.

There is currently no evidence of adverse effects associated with toxicity from naturally occurring sources of zinc. However, supplemental intake may cause suppression of immune response, decreased circulating high-density lipoprotein (HDL) cholesterol, reduced copper status, or even death. Acute toxicity has been shown to produce metallic taste, nausea, vomiting, epigastric pain, abdominal cramps, and bloody diarrhea. Long-term toxicity can cause copper deficiency because zinc and copper compete for absorption by the intestine [218].

2. Findings from Space Flight and Ground-Based Research

Zinc status of astronauts, as assessed by serum zinc and urinary zinc excretion, did not change after long-duration space flight (Figure 66, [610]). Circulating zinc levels are an imperfect tool to evaluate zinc status, as other physiological factors may affect them [116]. However, to increase the reliability of zinc status evaluation, more intensive and/or invasive techniques would be required.

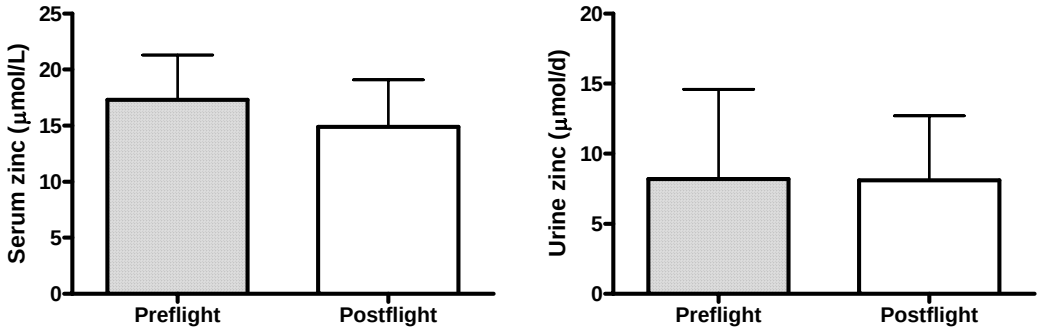

Figure 66. Serum and urinary zinc status from 11 ISS crewmembers before and after flight. Data are from Smith et al., 2005 [610].

The release of zinc from bones (as a result of demineralization) has been noted in bed rest studies [335, 336], and a similar increase in excretion of zinc was noted in Wistar rats flown during COSMOS 1129 (a 20-d space flight) [89]. This release of zinc associated with demineralization has raised concern that other metals, including lead, could also be released secondary to weightlessness-induced bone resorption [327, 328].

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of zinc is 11 mg/d [460], the same as the U.S. adequate intake for men (adequate intake is 8 mg/d for women) [181]. The space food system provides about 22 mg/d in the planned menu (Table 1), but actual in-flight intakes of Shuttle crewmembers are lower (12 mg/d on average) (Table 2, page 20).

4. Risks on Exploration Missions

Many compounds exist in food that can complex with zinc and decrease its absorption. Phytates, oxalates, polyphenols, fibers, and other nutrients including vitamins can all inhibit zinc absorption. In view of zinc's role in metabolism, ensuring that requirements are understood, and met, will be crucial on long-duration exploration missions.

Increases in urinary zinc with increased muscle catabolism have been noted in cases of starvation or trauma [181]. The importance of this phenomenon for space flight has not been evaluated (nor has the release of other heavy metals [such as lead] from bone during flight, although this has been modeled and proposed as a concern [327, 328]).

5. Remaining Questions

Existing knowledge of zinc metabolism seems adequate. Beyond the nominal determination of zinc content of the space food system, no specific research is required.

I. SELENIUM

1. Background

Selenium has been shown to play a role in the maintenance or induction of cytochrome P450, pancreatic function, DNA repair, enzyme activation, immune system function, and detoxification of heavy metals [656]. Selenium is also a cofactor for glutathione peroxidase (GPX). GPX plays a role in the reduction of organic peroxides and hydrogen peroxide. Selenium has also been shown to be necessary for iodine metabolism.

Total body selenium stores are in the amount of about 15 mg [218]. There are 2 selenium pools in the body: the selenium in selenomethionine and the selenium in GPX. Selenium absorption can be increased by vitamins A, C, and E and reduced glutathione, and decreased by chelation and precipitation of the mineral by heavy metals, such as mercury, and phytates.

Deficiency of selenium leads to decreased selenoenzyme activity, which may lead to biochemical changes that predispose to illness or even death. Selenium deficiency has been associated with Keshan disease, characterized by cardiomyopathy and heart tissue necrosis, and with Kashin-Beck's disease, characterized by osteoarthropathy of the joints and epiphyseal-plate cartilages of the legs and arms [218]. In rats, symptoms of acute selenium

deficiency have been shown to appear as early as 2 days after withholding selenium. The deficiency was shown as a reduction in GPX activity, but no change in blood enzymes was seen [278].

Selenium status has been related to cancer risk [656, 692], leading to much speculation about the ability of selenium supplementation to prevent cancer.

Toxicity of selenium is called selenosis. Nausea, vomiting, fatigue, hair and nail brittleness and loss, changes in nail beds, interference in sulfur metabolism, and inhibition of protein synthesis have all been demonstrated to result from selenium toxicity [656].

2. Findings from Space Flight and Ground-Based Research

The Clinical Nutritional Assessment profile [459] has documented a significant (10%) reduction in serum selenium concentrations after flight [610]. Whether this is related to intake or metabolism is not known.

3. Dietary Intake and Requirements

The current documented requirement for dietary intake of selenium during space flight is 70 μg/d. In the U.S., the recommended dietary allowance for men and women aged 19 years and older is 55 μg/d [278]. The space food system provides approximately double this amount (Table 1).

4. Risks on Exploration Missions

Deficiency of selenium can lead to impaired immune function, illness (Keshan disease and Kashin-Beck's disease, mentioned above), or even death. Excess of selenium can lead to problems affecting gastrointestinal, neurological, cardiopulmonary, and renal systems [656]. However, toxicity is not likely to occur except when selenium is consumed in large amounts in dietary supplements. Despite the relationship of selenium to cancer risk and antioxidant status, care must be taken to avoid toxicity.

5. Remaining Questions

Selenium levels in the space food system need to be determined. The potential role for selenium in protecting against oxidative stress during space flight should be further investigated.

J. IODINE

1. Background

Iodine performs its main function in its ionic form, iodide, as part of the thyroid hormones (triiodothyronine, or T_3, and tetraiodothyronine, T_4). About 15 to 20 mg of iodide is stored in the human body [753]. The thyroid gland traps the iodide, and it is here that 70 to 80 percent of the total body iodide is stored. The rest is stored in the salivary and gastric glands, with some iodide being found in the mammary glands, ovaries, placenta, and skin.

Iodine deficiency causes the iodine deficiency disorders, which include mental retardation, hypothyroidism, goiter (enlargement of the thyroid gland), cretinism, and other growth and development abnormalities, or even death [753]. During a 4-week study in which rats were subjected to varying degrees of iodine deficiency, the most severely depleted rats showed an increase in thyroid mass after 4 days [453].

No toxic side effects have been reported when 2.0 mg of iodine per day was ingested [218]. However, with intake greater than 18 mg/d for a prolonged period, the risk of goiter increases, as does the risk of thyroid cancer [181, 462]. Other symptoms of iodine toxicity, which occur when intake is on the order of several grams per day, include gastrointestinal distress, thyroiditis, goiter, sensitivity reactions, thyroid papillary cancer, or even death [462].

2. Findings from Space Flight and Ground-Based Research

Iodine intake on Shuttle missions has often been very high because iodine is used as a bactericidal agent in the water system [560]. Some changes in thyroid status that were potentially related to iodine excess were observed in ground studies and flight crews [424, 425, 456]. As a result, in the late 1990s a system to remove iodine from water was deployed on most missions. Iodine is not added to the ISS water, and as a result, pre- and postflight urinary iodine are similar (Figure 67).

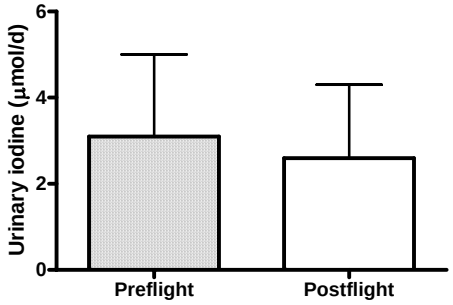

Figure 67. Urinary iodine excretion of ISS crewmembers before and after long-duration space flight (*n* = 23). Data are from Smith et al., 2005 [610].

3. Dietary Intake and Requirements

The current documented space flight requirement for the dietary intake of iodine during flight is 150 μg/d [460], the same as the U.S. recommended dietary allowance for iodine for men and women aged 19 years and older [181]. The tolerable upper intake level for iodine in adults is 1100 μg/d [181].

4. Risks on Exploration Missions

Although providing adequate amounts of dietary iodine is not a critical issue with regard to space flight, the possible effects of the iodine used in spacecraft water systems (where iodine is often used as a bactericide) are much discussed [425]. In earlier Shuttle missions and space programs, NASA used iodine concentrations in drinking water of 2 mg/L [560]. A report from the Food and Nutrition Board of the National Academy of Sciences states that in adults, daily iodine intake ranging from 50 to 2000 μg/d has no adverse effect [461]. With iodine as a bactericidal agent in the water, depending on water intake, iodine intake could easily exceed 2 mg/d. Given the current state of knowledge, it is assumed that iodine will not be used in exploration spacecraft water systems, or that these systems will be designed so that iodine will be removed before the water is consumed, or that levels of iodine will be used that would allow the iodine intake of crewmembers to remain below defined toxicity limits.

5. Remaining Questions

Existing knowledge of iodine metabolism seems adequate. It would be prudent to know precise iodine intake levels of crewmembers (from the diet and drinking water) so that potential hazards associated with iodine excess could be avoided.

K. CHROMIUM

1. Background

Chromium is thought to complex with nicotinic acid and amino acids to form glucose tolerance factor, which initiates the disulfide bridging between insulin and its receptor [218, 639]. This allows the insulin hormone to be more effective and therefore increases cellular glucose uptake and intracellular carbohydrate and lipid metabolism. Chromium may also play a role in pancreatic insulin secretion, internalization of insulin through decreasing membrane fluidity, and regulation of the insulin receptor. It also may increase sensitivity of tissues to insulin by activating insulin receptor kinase [639].

The human body can store 4 to 6 mg of chromium. Tissues having the greatest amounts of chromium are the liver, kidney, muscle, spleen, heart, pancreas, and bone [639]. It is possible that chromium is stored along with ferric iron because of its transport by transferrin, which can bind chromium as well as iron.

Deficiency of chromium leads to impaired glucose tolerance, or even death. Chromium deficiency may result in insulin resistance, which is characterized by hyperinsulinemia. This has been shown to be a risk factor for coronary heart disease. Several months of suboptimal chromium intake will lead to deficiency symptoms such as hyperglycemia and glycosuria [73]. One study found that 9 weeks on a low-chromium diet (5 μg/1000 kcal) was long enough to yield changes in glucose tolerance [17]. Severe trauma and stress may increase the need for chromium. Stress causes release of the stress hormones, including cortisol and glucagon. These hormones alter glucose metabolism and, in effect, chromium metabolism.

Toxicity of chromium leads to chronic renal failure, hepatic dysfunction, rhabdomyolysis (a disease of skeletal muscle), or even death. When they are ingested orally, Cr^{6+} is more toxic than Cr^{3+}. Liver damage, skin ulcerations, dermatitis, and respiratory disease may all result from a chromium intake greater than 1,000 μg/d [218].

2. Findings from Space Flight and Ground-Based Research

Little or nothing is known about chromium in space travelers. Chromium potentiates the action of insulin [403], and insulin resistance has been observed after space flight or bed rest [49, 648, 696]. Whether the insulin resistance associated with space flight is related to chromium is unknown.

3. Dietary Intake and Requirements

The current documented space flight requirement for dietary intake of chromium is 35 μg/d.

In the U.S., adequate intake of chromium is defined for men aged 19 to 50 years as 35 μg/d, and for those 51 years and older as 30 μg/d. Adequate intake is defined for women aged 19 to 50 years as 25 μg/d, and for those 51 years and older as 20 μg/d [181].

4. Risks on Exploration Missions

Although it may be plausible that changes in glucose metabolism during space flight are in part related to chromium, given that nothing is known about chromium during space flight, it seems premature to raise concerns about chromium at this point. Additionally, iron excess, in hemochromatosis, may affect chromium homeostasis [639], another reason to be concerned about iron excess during space travel.

5. Remaining Questions

Beyond the nominal determinations of chromium content of the space food system, no other specific research is required given the current state of knowledge.

L. Other Trace Elements

No nutrition text would be complete without the acknowledgment that a handful of ultratrace elements have been studied and are proposed to play a required role in the human body. These include boron, vanadium, aluminum, and others [469]. While we do not dispute these findings, at this point their potential for having an impact on space missions would be extremely speculative.

IX. NUTRITIONAL ISSUES FOR EXTRAVEHICULAR ACTIVITY

Extravehicular activity (EVA), or spacewalking, is a unique situation from a nutritional perspective, because the EVA suit does not easily allow food consumption. On early Shuttle missions, a 165-kcal fruit bar was custom-made to fit in the EVA suit, but it was typically not consumed, and is no longer included. Crewmembers can go without food for as long as 8 to 10 hours while they are preparing for and performing EVA. Nutritional recommendations for EVA were designed to help maximize crew performance and efficiency. When nutrition for EVA was reviewed in 1991, the recommendation for EVA crewmembers was that they should consume an additional 500 kcal on days of EVA [457]. This was designed to account for the metabolic cost of EVA (~200 kcal/h).

In 2000, another review of this situation was requested by NASA's Flight Medicine Division. The resulting recommendation was to provide food items for consumption during EVA preparation (as close as possible to the donning of helmets). The food items should contain 300 to 500 kcal, with about 70 to 100 g of carbohydrate and a high content of soluble fiber. Candidate items are reviewed to ensure that in the attempt to meet the basic criteria, undesirable nutrients or additives are not included, and that crew preferences are accounted for. It was also recommended that crewmembers reconsider use of the in-suit food bar, or that alternatives be sought.

Fluid intake during EVA is also a topic of concern. Crewmembers lose 6 to 8 oz fluid/h (177 to 237 mL) during an EVA. The current EVA suit contains a 24- or 32-ounce drink bag (710 or 946 mL). Only water is used (early EVAs included flavored beverages, but a problem during a lunar EVA resulted in a programmatic decision to include only water). Provision of in-suit fluid is an important factor in suit design. For the current suit, use of the 32-ounce drink bag is recommended. The development of a larger, disposable drink bag is highly encouraged. The disposable drink bag should be designed so that a flavored drink (such as the current Shuttle food system beverages) could be used to increase palatability and intake, assuming that the technical concerns can be eliminated.

The issue of nutritional support during EVA was reviewed only briefly at the 2005 Standards and Operating Bands meeting, and no recommendations were made to change the 2000 guidelines. As suits are developed for exploration mission transit and planetary EVAs, following the suggestions above would alleviate problems deemed too complicated to solve by changing the existing suit used on the Shuttle and ISS.

Along with food and fluid issues associated with EVA, the hyperoxic environment of EVA has the potential for causing additional damage to the body. The pre-EVA protocol for

U.S. astronauts typically includes a 2.5-h "prebreathe" of 95% to 100% oxygen [422] to reduce the risk of decompression sickness. After the prebreathe, astronauts are typically exposed to hypobaric 100% oxygen for 6 to 10 hours during EVA. Studies from saturation dives show that oxidative damage occurs under conditions similar to those of EVA [608]. Judging by the results of numerous ground-based studies with hyperoxia, including data from a NASA Extreme Environment Mission Operations (NEEMO) 14-d saturation dive [608, 760], the potential exists for nutritional countermeasures to mitigate some of the oxidative damage [470, 658, 720].

REMAINING QUESTIONS

Because, according to proposed plans for lunar EVAs, they will be similar in duration (8 to 10 h) to current ISS EVAs but more frequent (2 to 3 times per week), there is a clear need for development of nutrition support during EVAs. A nutrition support system will need to fit the lunar suit design. The definition of the optimal nutrition support system will need to be based on the results of ground studies designed to optimize performance, minimize fatigue, and minimize oxidative damage from a high partial pressure of oxygen in the suit.

X. ANTIOXIDANTS

A. SOURCES OF OXIDATIVE STRESS

Space flight inevitably increases astronauts' likelihood of having cellular oxidative damage occur because the space environment is associated with numerous sources of oxidative stress. Some of these are hyperoxic (100% oxygen) conditions during EVA, exercise, high-linear energy transfer radiation exposure, and acute gravitational stress of reentry, all of which have been associated with initiating reactive oxygen species and oxidative damage in both human and animal ground-based studies [117, 329, 330, 534, 685].

1. Hyperoxic Conditions

Currently astronauts are exposed to hypobaric hyperoxic conditions when they perform EVA (6 to 8 h). The pre-EVA protocol for U.S. astronauts typically includes a 2.5-h prebreathe of 95% to 100% oxygen [422] to reduce the risk of decompression sickness. After the prebreathe, astronauts are exposed to hypobaric 100% oxygen for 6 to 10 hours during EVA. Future lunar EVAs are expected to be longer in duration and more frequent than those performed now on the ISS.

The literature is replete with studies showing injury to virtually all organ systems after sufficient exposure to hyperoxia [109, 515]. A hyperoxic environment can induce oxidative damage and decrease antioxidant capacity, as demonstrated in numerous ground-based experiments using both normobaric and hypobaric hyperoxic conditions. Under physiological conditions (21% O_2), about 2% to 3% of the oxygen consumed by the body is converted into oxygen-derived reactive oxygen species [616]. Human antioxidant defenses are designed to protect against 21% oxygen, but these defenses are easily overwhelmed in hyperoxic environments.

It was first suggested in the 1950s that a hyperoxic environment may be toxic, because of eye damage among premature infants in incubators with high oxygen concentrations [87, 316, 500]. Evidence exists that acute exposure to > 95% oxygen is followed by increased lipid peroxidation. Increased lipid peroxidation (measured by urinary *n*-pentane) occurs in humans within 30 minutes of breathing 100% O_2 [449]. In another study, elevated plasma malondialdehyde (MDA) was reported in healthy humans after 125 min of normobaric exposure to 100% oxygen [398]. Animal studies support the human data [332, 681]. The

accuracy of *n*-pentane as a marker of lipid peroxidation is debated [83, 326], but this and increased MDA provide evidence that lipid peroxidation increases during hyperoxia. Hyperoxic conditions are also found to increase vasoconstriction in humans [418], deplete pulmonary extracellular superoxide dismutase (SOD) in mice [493], and increase apoptosis in PC12 cells [658], all of which indicate that hyperoxia can induce cellular oxidative damage.

2. Generation of Reactive Oxygen Species During Exercise

Exercise-induced fatigue and muscle atrophy are also mediated in part by reactive oxygen species (ROS). Electron spin resonance spectroscopy technology confirmed earlier findings from the 1950s suggesting that short-lived reactive intermediate molecules like ROS are present in skeletal muscle after exercise [534]. Since then, numerous studies support a role of ROS in skeletal muscle fatigue [483, 534, 686]. ROS denature proteins directly associated with the sarcoplasmic reticulum Ca^{2+} release mechanism [154], thus compromising tension development. Also, rat studies show that xanthine oxidase-induced ROS yields increased diaphragm fatigue, and that the elevated ROS during intense exercise is implicated in the onset of muscle fatigue [358]. Furthermore, decreased antioxidant status lowers exercise capacity and increases onset of fatigue in human and animal studies [483, 534].

Astronauts perform extensive upper-body exercise during EVA activity, and one of the limiting factors in completing EVA tasks is forearm and hand-muscle fatigue due to extensive tool operation. The fatigue often requires crewmembers to stop and rest, thereby prolonging the duration of EVA, and limits the number of tasks performed during each EVA.

3. Radiation Exposure

Astronauts are exposed to highly ionizing radiation, in addition to secondary radiations resulting from interactions with shielding materials or the human body. Biological effects of radiation include damage to DNA from a direct hit from an ion track, oxidative damage from generated ROS, and oxidative damage induced by a bystander effect [298, 306, 682]. A bystander effect occurs when cells damaged by radiation particles secrete cytokines or other proteins that can generate ROS in cells that are not destroyed [396].

B. Oxidative Damage Markers During Space Flight and in Ground Analogs

A number of studies show that astronauts have elevated levels of markers of oxidative damage after space flight. Plasma MDA, 8-iso-prostaglandin $F_{2\alpha}$, and urinary 8-hydroxy-2′-deoxyguanosine (8OHdG) have been measured during and after flight as indicators of lipid peroxidation (MDA and $PGF_{2\alpha}$) and DNA damage (8OHdG) [604, 633]. A significant elevation of urinary 8OHdG has been noted after long-duration missions (Mir and ISS) [610]. These data are supported by results from the ground-based analog, NEEMO, in which crewmembers underwent 10- to 14-day saturation dives [608, 760]. Similarly, urinary 8-iso-

prostaglandin $F_{2\alpha}$ was significantly decreased during flight but elevated about 2.5-fold after flight [633], and plasma MDA was increased both during and after flight [633]. In a Russian 120-day bed rest study, increased concentrations of markers of lipid peroxidation were found in subjects, and this increase was mitigated with vitamin E [752].

The apparent increases in oxidative damage observed during and after flight could be caused by a number of factors, including altered DNA repair mechanisms, decreased antioxidant defense systems, or simply increased oxidative stress. Microgravity does not affect the repair of double-strand chromosome breaks [314, 521], but evidence exists that downregulation of antioxidant defense systems occurs during space flight [264]. Along with increases in markers of oxidative damage and decreases in antioxidant defense systems, a decrease in total antioxidant capacity also occurs.

XI. SUPPLEMENTS

The issue of supplement use arises with discussion of nutrient requirements for space travelers and the use of nutrients as countermeasures to the negative effects of space flight, especially oxidative damage and radiation-induced cancer risk. It is generally agreed that nutrients should be provided to astronauts in standard foods, as opposed to supplements [350, 457, 458, 460, 599]. This is essential, as natural foods also provide non-nutritive substances such as fiber, carotenoids, and flavonoids, as well as a sense of palatability and psychological well-being that will be important during long missions. The need for more detailed information about the "psychophysiology of hunger and eating" was noted decades ago during the early space programs [596], but this topic has yet to be studied in detail. It is clear from astronauts' experience on the Mir that when humans are in an isolated environment far from home, food becomes a very supportive psychological factor.

NASA currently does not recommend that astronauts take general nutritional supplements during flight, for several reasons. Experience to date indicates that crewmembers do not consume the recommended amount of energy intake, and accordingly, intake of many individual nutrients is therefore also inadequate. Unfortunately, the concept of a vitamin and mineral supplement to remedy this is unwarranted, as the primary problem—inadequate intake of food/energy—will not be resolved by a supplement. This situation may even be worsened if crewmembers believe that taking the supplement reduces the need for adequate food consumption, and thus eat even less. Furthermore, when many nutrients are provided as oral supplements, they are not metabolized by the body as they are when in foods [15]. Changes in bioavailability and metabolism of nutrients can increase the risk of malnutrition.

Vitamin or mineral supplements should be used only when the nutrient content of the nominal food system does not meet the requirements for a given nutrient, or when data show that the efficacy of single (or multiple) nutrient supplementation is advantageous. To date, 1 supplement has met this standard, and that is vitamin D. Vitamin D supplements have been provided to all U.S. crewmembers on the ISS. Early crews received 400 IU vitamin D_3 per day [610], but recently this was raised to 800 IU per day of supplementation [460].

REMAINING QUESTIONS

Before a supplement is recommended, a clear deficit of that nutrient in the space food system must be identified, as was the case with vitamin D. Stability of nutrients in the form of supplements would also need to be addressed; shelf lives for exploration travel must be

particularly long. Supplements, if they are recommended, would need to be tested in ground models for their efficacy in maintaining nutrient status, their stability over a long duration (3 to 5 y), and their potential interaction with pharmaceuticals. Most importantly, supplements will need rigorous testing to demonstrate that the level used is not toxic to other body systems, and will need close monitoring during flight to ensure that their interactions with the space flight environment do not prevent them from being effective or safe. For example, ground-based studies have shown that high doses of antioxidants, when provided in situations where oxidant stressors are present (such as cigarette smoking), can actually have a detrimental effect [205].

XII. NUTRIENT-DRUG INTERACTIONS

An understanding of interactions between nutrients and drugs used in medical care is necessary to implement safe and effective medical care and clinical intervention operations for astronauts on long-duration missions. The most common studies of nutrient-drug interactions concern their effects on a nutrient or drug's absorption, distribution, biotransformation, and excretion.

Normally, drugs must undergo biotransformation to allow their activation or excretion. For the activity of a drug to be terminated by excretion, the compound must be made water-soluble by biotransformation. For most drugs, this process yields a water-soluble compound that is less active than the original compound. Biotransformation occurs in 2 phases. Phase I is an oxidation or hydrolysis reaction to expose, add, or cleave a functional group. Cytochrome P450 enzymes are involved in this process. Humans have 12 families of cytochrome P450 enzymes, but CYP1, CYP2, and CYP3 are the forms most commonly used in drug metabolism [225]. Cytochrome P450 enzymes are unique in their ability to use a wide range of substrates [222]. Phase II biotransformation involves the conjugation of the parent compound to a polar group (acetate, glucuronides, sulfates, amino acids, glutathione), which inactivates most drugs. Biotransformation of drugs is influenced by several factors that could be affected by space flight and the space food system: dietary factors, nutrient metabolism, monoamine oxidase inhibitors, and antacids and proton pump inhibitors.

A. DIETARY FACTORS

Dietary factors (either an excess or deficiency) can influence both phases of drug biotransformation. In phase I, 3 factors are required: a sufficient energy source (because of the high energy demands of this system), a protein source for enzyme formation, and iron for cytochrome formation [690]. Phase II requires glucose, sulfur-containing amino acids, and glutathione [690].

The effects of nutrients on drug metabolism have been well studied in animal models; however, relatively few dietary factors have been studied in humans [221, 690]. Results from animal studies must be carefully weighed because of some differences between the cytochrome P450 enzymes of animals and humans.

One of the most well-documented food-drug interactions is between grapefruit juice and a number of medications [29, 301]. Flavonoid compounds such as naringin, naringenin, limonin, and obacunone, which are present in grapefruit juice, act as substrates for particular

intestinal cytochrome P450 enzymes (CYP3A4 and CYP1A2). Within hours of ingestion, grapefruit juice decreases CYP3A4 protein expression for up to 24 hours [401, 404]. The decrease in CYP3A4 is associated with a decreased capability for drug metabolism, and therefore increased drug bioavailability.

Other foods, nutrients, or supplements known to affect phase I and II biotransformations and cytochrome P450 enzymes include protein, carbohydrates, lipids, certain vitamins, minerals, char-broiled foods, red wine, monosodium glutamate and aspartate, and herbs such as St. John's wort [93, 192, 221, 513, 547, 690]. Generally, high-protein diets increase drug metabolism, and low-protein diets decrease drug metabolism. For instance, antipyrine and theophylline are metabolized more rapidly when subjects are on a high-protein diet [221]. Other macronutrients, including carbohydrates, can affect phase I and phase II biotransformation reactions when intakes are very high or low. Theophylline (for asthma) is particularly sensitive to dietary protein:carbohydrate ratios; increasing the ratio can decrease effectiveness of the drug, and decreasing the ratio may lead to toxicity of the drug [157]. Fatty acids in the diet can also affect cytochrome P450 enzymes because they can be metabolized by these enzymes. Specifically, CYP2E1 is responsible for lipid peroxidation, and activity of this enzyme is enhanced in the presence of highly polyunsaturated fatty acids such as fish oils.

B. NUTRIENT METABOLISM

Some nutrients are metabolized by cytochrome P450 enzymes; therefore, drugs or other nutrients that alter the activity of these enzymes can alter nutrient metabolism. Vitamin D and vitamin A are 2 examples of nutrients whose metabolism involves cytochrome P450 enzymes.

Exposure of 7-dehydrocholesterol to sunlight converts this substrate to previtamin D_3. Previtamin D_3 undergoes an isomerization to form vitamin D_3, a biologically inactive compound. CYP27A is a mitochondrial mixed-function oxidase that is responsible for hydroxylating vitamin D_3 to form 25-hydroxyvitamin D_3 [552]. CYP3A4 has been found to be a 25-hydroxylase as well [223]. CYP27B converts 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3. CYP24 is a 24-hydroxylase that hydroxylates the vitamin D side chain and ultimately terminates hormonal activity. Inhibition of CYP24 has recently been targeted in the development of novel anti-cancer drugs. Because 1,25-dihydroxyvitamin D_3 exerts antiproliferative and differentiating effects on many cell types including cancer, preventing its inactivation by inhibiting CYP24 activity may prove to be beneficial in treating cancer [566]. Certain drugs are known to activate CYP24 activity, including rifampin, isoniazid, and phenobarbital [499, 572]. Several studies show a relationship between the use of these drugs and osteomalacia [206, 579], which is caused by a deficiency of vitamin D. The discovery of the involvement of CYP3A4 in the metabolism of vitamin D may explain the effects on vitamin D metabolism of numerous drugs, including inducers or inhibitors of this enzyme (for example, grapefruit juice, erythromycin, omeprazole, carbamazepine, and dexamethasone), or implicate them in unexplained effects on vitamin D metabolism.

Vitamin A metabolism involves the actions of CYP1A2 and CYP4A4 in the conversion of retinol to retinoic acid [98, 545]. Inducers of CYP1A2 (cigarette smoke, cruciferous vegetables, broiled beef, rifampin) may affect vitamin A metabolism.

C. MONOAMINE OXIDASE INHIBITORS

First-generation monoamine oxidase inhibitors include agents such as antidepressants (phenelzine, tranylcypromine, pargyline, and selegiline), chemotherapeutic drugs (procarbazine), antiprotozoal drugs (furazolidone), and analgesics (meperidine). Monoamine oxidase is responsible for metabolizing dietary phenylethylamines, including tyramine, in the gastrointestinal tract and in the liver. Inhibitors of monoamine oxidase prevent the breakdown of these compounds, and therefore the compounds are taken up in the brain. In the brain, tyramine displaces norepinephrine from storage vesicles, which results in release of a flood of norepinephrine at synapses. Acute hypertension and the potential for stroke or myocardial infarction could result from this process [690]. Fermented foods and protein-rich foods that have begun to spoil are rich in phenylethylamines [690].

D. ANTACIDS AND PROTON PUMP INHIBITORS

By altering the pH of the stomach, chronic antacid or proton pump medications can negatively affect the bioavailability of several nutrients, including phosphate, thiamin, folate, vitamin B_{12}, vitamin C, and vitamin A [182, 450, 690]. Antacids can precipitate folic acid at a pH greater than 4.0, thus rendering it insoluble and not available for absorption [551]. A high pH also affects thiamin bioavailability because the vitamin is not stable at high pH [690]. Similarly, at a neutral pH, the antioxidant action of vitamin C on dietary nitrites is hindered. Normally, dietary nitrite is quickly reduced to nitric oxide by ascorbic acid in the acidic gastric juice and it is then absorbed by the mucosa. However, at neutral pH, the nitrite does not react with ascorbic acid and accumulates in the stomach, which can increase the likelihood that potentially carcinogenic *N*-nitroso compounds will be formed [450]. These changes are observed mostly in subjects who are infected by *Helicobacter pylori* and are taking proton-pump inhibitors [450].

Vitamin B_{12} and vitamin A are also malabsorbed at higher pH because an acidic environment is essential for their release from dietary proteins. Because large stores of vitamin B_{12} exist in the body, malabsorption of this vitamin is unlikely to lead to deficiency unless a subject has been taking proton pump inhibitors chronically for at least 2 years [182]. This would be particularly harmful if vitamin B_{12} stores were low before initiation of therapy.

E. REMAINING QUESTIONS

Currently no data are available that pertain to specific drug-nutrient interactions during space flight. The main concerns for a long-duration mission involve use of pharmacological agents that are taken chronically. Side effects will be especially harmful if the status of all

nutrients is not adequate at the beginning of a long-duration mission. Addressing these concerns of drug-nutrient interactions will be especially crucial for crewmembers who embark on exploration-class missions lasting several years.

XIII. LOOKING FORWARD

NASA has undertaken an exploration initiative that will return humans to the Moon and eventually take them to Mars. Although the first missions to the Moon are projected to be short and will not require significant, if any, modifications to the food system, the initial round trip to Mars using current propulsion technology is projected to take 3 years. This will require a food system with items having even longer shelf lives than those currently available for the ISS missions [353, 504]. As NASA designs the vehicles for these missions, the challenges for the food system will be very similar to those met by all previous space food systems. Mass and volume of the food system and its associated packaging will need to be limited. Refrigerators and freezers will not be available. Acceptability of the food items will become even more important on a 3-year mission. New challenges for this exploration food system will include the need for a 3- to 5-year shelf life and the possibility that the increased radiation encountered on a trip to Mars might affect the nutritional content and quality of the food over time.

Long-term plans for exploration include the establishment of habitats on the Moon (Figure 68) and eventually on Mars (Figure 69) for long-duration stays [353, 504]. The lunar habitats will be used to test technologies needed for a mission to Mars. Most of the plans for habitats include the growing of plants to aid in the recycling of air and water within the habitat [36]. These crops will be available for use in the food system. The presence of partial gravity on both the Moon and Mars will allow crops to be processed into ingredients (for example, milling wheat into flour) and then used to prepare menu items for crew consumption [353].

The long-term missions, either months living on the Moon or years going to and from Mars, will require careful planning of nutrition. Understanding nutrient requirements and utilizing the food system to fulfill them will allow mitigation of some of the negative effects of microgravity on human physiology. In light of the duration of a Mars mission, a chronic deficiency, potentially even a marginal deficiency over a long enough period, could be devastating. After the requirements are defined and we have a detailed understanding of absorption, metabolism, and excretion of each nutrient, provision of these nutrients and understanding their stability in the space environment (for the months to years waiting to be consumed) will be critical. Just as for the sailors who left Europe in sailing ships, it is not enough to have food; one must have the right food.

Figure 68. Artist's image of the next-generation lunar landing. Credit: NASA.

Figure 69. Artist's concept of Martian habitat and exploration vehicles. Credit: NASA.

XIV. CONCLUSION

Nutrition is essential for health—on Earth and in space. Determining the nutritional requirements for travelers on short-, medium-, and long-duration exploration missions will be crucial for ensuring health. The ability of nutrients and nutrition to mitigate negative effects of space travel is far from being fully explored. Ground-based evidence is being amassed but is yet to be fully tested. In many ways, nutrition offers a suite of countermeasures that require no more crew time than that already allotted for meals. While care clearly needs to be taken to avoid excess amounts of any nutrient, the risks of using nutritional countermeasures compared to those of using pharmacological countermeasures are negligible.

This document details the evidence collected to date that shows why inadequate nutrition is a risk during long-term space travel. The evidence is substantial, and drives a significant ongoing effort to optimize nutrition for space travelers and to use nutrition as a tool to mitigate the health risks of microgravity exposure.

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Martina Heer is Senior Nutritionist and Director of Nutrition Health at Profil Institute for Metabolic Research, Neuss, Germany. Previously she headed the Space Physiology Division, Institute of Aerospace Medicine, at the German Aerospace Center (DLR) for 6 years. Her main research interest is to understand the interaction of nutrition (in particular the nutrients sodium and sodium chloride) with other physiological systems such as the musculoskeletal and cardiovascular systems. Her space flight studies started with Shuttle missions and missions to the Mir station, and they continue with experiments on the ISS. The space studies are combined with extended research in the form of space analog studies on the ground,

which take place in the Institute's clinical research facility. In addition to her position at Profil Institute for Metabolic Research, Dr. Heer is adjunct associate professor in Nutrition Physiology at the University of Bonn, Germany. She also represents the European Space Agency (ESA) in the Multilateral Medical Operations Panel's Nutrition Working Group for the International Space Station and is a member of the ESA Nutrition Expert Committee.

XVII. EDITOR

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XVIII. LIST OF FIGURES

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XX. ABBREVIATIONS

8OHdG	8-hydroxy-2'-deoxyguanosine
AI	adequate intake
AMP	adenosine monophosphate
ASTP	Apollo-Soyuz Test Project
BW	body weight
cal	calorie
CoA	coenzyme A
d	day
DFE	dietary folate equivalent
DLR	German Aerospace Center
DNA	deoxyribonucleic acid
DRI	dietary reference intake
EAR	estimated average requirement
EE	energy expenditure
EER	estimated energy requirement
EGR	erythrocyte glutathione reductase
Eq	equivalent
ESA	European Space Agency
EVA	extravehicular activity (space walk)
FAD	flavin-adenine dinucleotide
g	gram
G	acceleration, gravity; 1G = Earth gravity
GLA	gamma-carboxyglutamic acid
GPX	glutathione peroxidase
Gy	Gray
h, hr	hour
HDL	high-density lipoprotein
HRP	Human Research Program
ISS	International Space Station
IU	international unit
IVA	intravehicular activity
J	joule
k	kilo
L	liter

LBM	lean body mass
LDL	low-density lipoprotein
μ	micro
m	meter, milli
M	mega
MDA	malondialdehyde
mol	mole
MRI	magnetic resonance imaging
mRNA	messenger RNA
n	nano
n	number of subjects
NAD	nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
NADPH	reduced form of nicotinamide adenine dinucleotide phosphate
NASA	National Aeronautics and Space Administration
NDS-R	Nutrition Data System for Research
NE	niacin equivalent
NEEMO	NASA Extreme Environment Mission Operations
NLT	not less than
NTE	not to exceed
NTX	n-telopeptide
P	probability
PL	pyridoxal
PLP	pyridoxal 5'-phosphate
PM	pyridoxamine
PMP	pyridoxamine 5'-phosphate
PN	pyridoxine
PNP	pyridoxine 5'-phosphate
PTH	parathyroid hormone
RBC	red blood cell
RDA	recommended dietary allowance
RE	retinol equivalent
RNA	ribonucleic acid
ROS	reactive oxygen species
RSA	Russian Space Agency
SD	standard deviation
SEM	standard error of the mean
SLS	Spacelab Life Sciences
SOD	superoxide dismutase
TEE	total energy expenditure
THF	tetrahydrofolate
U	unit
UV-B	ultraviolet B light
WHO	World Health Organization
y	year

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