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Nutrition in the space station era

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Space flight is a new experience for man. Tension on the weight-bearing components of the musculo–skeletal system is greatly reduced, as is the work required for movement. The body responds by a reductive remodelling of the musculo–skeletal system. Protein is lost from muscles with anti-gravity functions. The rate of Ca loss from the weight-bearing bones is about 1 % per month. Voluntary dietary intake is reduced during space flight by about 20 %. These adaptations to weightlessness leave astronauts ill-equipped for life with gravity when they return to earth. Rates of energy expenditure are similar to that expected on the ground for comparable activities. Protein intake is adequate in flight but may be limiting after space flight due to substrate competition between repleting muscle and other anabolic processes. The most serious nutritional problem is the inability to maintain energy balance on missions with high exercise requirements. The poor dietary intake is probably a consequence of engineering-imposed environmental constraints. The low levels of lighting in the space vehicle may not be enough to promote vitamin D synthesis. Nevertheless, the evidence suggests that a normal well-balanced diet with plenty of fluids will be as healthy in space as on earth. The long-term goal of the manned space programme is to develop the means of sustaining human life beyond earth. This will involve the development of technologies to grow food, maintain a breathable atmosphere and recycle waste products with the only external input being energy.

Space flight: Protein: Energy: Vitamins: Calcium: Oxidative damage

Introduction

Space flight is a new experience for man. Lack of gravity removes the force that causes water to gravitate towards the lower body; hence there are fluid shifts from the lower body to the upper body and accompanying cardiovascular changes. Tension on the weight-bearing components of the musculo–skeletal system is greatly reduced, as is the work required for movement. The body responds by a reductive remodelling of the musculo–skeletal system. There is a mismatch

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Abbreviations: ISS, International Space Station; NASA, National Aeronautics and Space Administration; PTH, parathyroid hormone; RDA, recommended dietary allowance.

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between what is perceived by the eye and what is sensed by the gravity-sensing cells of the inner ear leading to a sensory–motor conflict in the brain. The result is space motion sickness. Finally, voluntary dietary intake is reduced during space flight by about 20 %. These adaptations to weightlessness leave astronauts ill-equipped for life with gravity when they return to earth.

In the short term, these are not serious problems; the motion sickness does not last beyond the first day or two in earth orbit and the small amount of muscle, bone and fat lost is rapidly regained after landing. After several months in space, however, the loss of muscle and bone is substantial and astronauts are in a debilitated state. The rate of bone loss has been estimated as being about 1 % per month; there is no apparent adaptation with time (Whedon *et al*. 1974; LeBlanc *et al*. 1996; Vico *et al*. 2000). Most of the muscle loss occurs early in flight but continues at a lower rate for the duration of the mission. Astronauts (and rats) returning from even short-duration space flights of 1–2 weeks often experience muscle fatigue, weakness, a lack of coordination in movement and for human subjects, muscle soreness (Stauber *et al.* 1990; Edgerton & Roy, 1994; Riley *et al*. 1995). Isometric, concentric and eccentric force development declines by as much as 30 %. The loss of muscle mass is responsible at least in part for the decrease in muscle strength and increased 'fatigability' observed after space flight (Leonard *et al.* 1983; Vorobyov *et al.* 1983, 1984; LeBlanc *et al.* 1992, 1996; Nicogossian *et al.* 1994; Grigor'ev *et al.* 1996). Nevertheless from the extensive Russian experience on the MIR space station, it is clear that man can survive for missions up to 1 year in duration.

Until recently, nutrition and metabolism have not been high priorities for space research. This perspective has changed; two recent National Aeronautics and Space Agency (NASA) reports identified nutrition as a high priority area for investigation (National Research Council, 1998; Vodovotz *et al.* 1999). As missions increase in duration, any nutritional deficiencies will become progressively more important. The ability of man to remain away from earth will be limited. The long-term goal of the International Space Station (ISS) programme is to prepare for the landing of man on Mars.

The next opportunities for Mars missions by man are in 2015 and 2021. Other than cost, NASA has concluded that the major problems in mounting a successful landing on Mars are physiological and behavioural rather than technical. A round trip to Mars will last about 30 months and there will be four transitions to different levels of gravity: from 1 $\boldsymbol{g}$ to 0 $\boldsymbol{g}$ for the outward journey, 0·3 $\boldsymbol{g}$ on Mars, from 0·3 $\boldsymbol{g}$ to 0 $\boldsymbol{g}$ for the return trip and from 0 $\boldsymbol{g}$ to 1 $\boldsymbol{g}$ after landing back on earth. The physiological issues include: (1) low dietary intake and the associated negative energy balance; (2) the potential for oxidative damage from the increased exposure to ionizing radiation, especially as astronauts venture beyond the earth's protective electromagnetic belts; (3) altered Fe metabolism secondary to a reduction in blood volume, which could increase free radical generation; (4) in-flight muscle and cardiovascular deconditioning, making emergency egress difficult: after landing, about half of the astronauts–cosmonauts require assistance in walking; (5) the full reversibility of the bone losses especially after more than one cycle, and the long time scale of recovery. Indeed NASA has likened space flight to ageing, on the basis of the similar responses of the musculo–skeletal system. If ageing is an appropriate model, this would be serious since prophylactic measures can slow down but not reverse age-related losses of muscle and bone; (6) behavioural factors are being given more emphasis as the various national space agencies contemplate the problems in having six people (men and women) of different cultural backgrounds living together in a small, isolated environment for 3 (SE 0·5) years.

Most of the data discussed in the present article is from the US programme which has had a greater interest in nutrition and metabolism than the Russian programme. The Russian view point was summarized by the former director General of the Soviet Space programme, Oleg Gazenko: ‘Man is endowed with sufficient plasticity to adapt fully to space conditions and feel at home there’ (Konovalov, 1987). Metabolic data from the Russian programme consists principally of post-flight measurements and until the recent Shuttle–MIR and Euro-MIR missions (1994–8) blood was not collected in flight. The Russian Life Sciences flight programme focused more on animal studies using the Bion satellites. In recent years, there has been an increase in European interest using either US (Space Shuttle) or Russian launch vehicles (MIR).

Even though blood has been quite frequently collected on US missions, much of the data is uninterpretable, because the blood samples were often collected under uncontrolled conditions and from only one or two subjects. The notable exceptions are the missions dedicated to the life sciences where facilities were provided for collecting biological specimens and the number of test subjects ranged between four and nine.

Interpretation of space flight data

One of the problems with space-flight research is to distinguish between the effects of microgravity and responses to the space-craft environment. The space-flight environment is not simply microgravity, but includes noise (about 90 dB), emotional excitement of a unique experience, close confinement, loss of privacy, reliance on processed foods, poor bathroom facilities, a totally conscribed lifestyle and the psychosocial stress of co-existing with fellow crew members. Psychosocial stress is a major concern (Bonde-Petersen, 1994; National Research Council, 1998). Future crews will have men and women and people of various ethnicities and cultural backgrounds. Personality conflicts in flight are not rare (Burrough, 1998). A further complication is that few missions are alike; they differ in space vehicle, work requirements, physical activity and duration. Nevertheless, comparing the results across different missions has proved to be useful in interpreting flight data. Also available for comparison are bed-rest studies with (Lee *et al.* 1997; Bamman *et al.* 1998; Ferrando *et al.* 1999) and without exercise (Gmunder *et al.* 1992; LeBlanc *et al.* 1992; Vernikos *et al.* 1993; Ferrando *et al.* 1996; Blanc *et al.* 1998).

Another major problem with evaluating space-flight data is that since opportunities to do quality science have been very limited, few repeat experiments in the life sciences have been done. This means that, in contrast to the usual need for replication of results as a criterion for publication, space-flight single observations are often disseminated and these can be misleading. Construction of the International Space Station (ISS) may change this since a significant proportion of the ISS programme will be focused on the life sciences.

Most ground-based experiments in the nutritional sciences involve four or more subjects. This minimal standard, and significant nutritional data, has only been attained on a few space flight missions (Table 1). Skylab was a prototype space station which consisted of three similar missions of 28, 56 and 84 d and was flown in 1973–4. The data from shuttle flights SLS1 and SLS2 are usually combined. Shuttle SLS1 was a 9 d mission. Shuttle SLS2 was a reflight of SLS1 but with measurements made up to day 12 of the 16 d mission. The 17 d LMS shuttle flight was flown in 1996 with about half of the resources being devoted to experiments in the life sciences. During the last decade NASA and European Space Agency have used the Russian Space Station MIR to obtain data on long-duration space flight. MIR could accommodate three crew-persons for missions up to 1 year.

Table 1. Principal space flight missions where nutritional data was obtained

Mission	Year(s) in which flown	Duration (d)	Crew (*n*)	Sex	Mission objectives
Apollo	1968–72	5–13	3	m	Moon landings
Soyuz	1970	17	2	m	Endurance
Skylab 2	1973	28	3	m	Life sciences
Skylab 3	1973	56	3	m	Life sciences
Skylab 4	1974	84	3	m	Life sciences
Shuttle, SLS1/2	1991, 1993	9, 16	6	m and f	Life sciences
Shuttle, Deutsche-2 (D-2)	1993	16	6	m	Varied, about 50 % life sciences
Shuttle, LMS	1996	17	4	m	Varied, about 50 % life sciences
MIR, Russia	1986–present	90–365	3	m	Varied about 25 % life sciences
NASA–MIR	1994–1998	90–250	3	m and f	Varied about 50 % life sciences
MIR–European Space Agency	1994–1999	90–250	3	m and f	Varied about 50 % life sciences

m, male; f, female; NASA, National Aeronautics and Space Administration.

Amino acids and protein

The reductive remodelling of muscle mass with space flight is similar to that found with bed rest. Muscle mass is dependent on the load and so protein is lost from muscles with anti-gravity functions. The limited data (from Skylab) suggests that most of the muscle losses occur during the first month of flight (Rambaut *et al.* 1977*b*; Whedon *et al.* 1977; Leonard *et al.* 1983).

On most missions (US and Russian) where protein intake has been measured or estimated, protein intake has been at least 50 % greater than the US recommended dietary allowances (RDA) (Table 2; National Research Council, 1989; Lane *et al.* 1994). An exception was the 1996 LMS shuttle mission where protein intake was at the level of the RDA (Stein *et al.* 1999*c*). Overall, there is no evidence to suggest that the in-flight protein intake is inadequate. Plasma amino acids are either unchanged or are increased in flight because of the release of amino acids from muscle. On the SLS2 shuttle flight, plasma levels of the essential amino acids and the branched-chain amino acids in particular were increased. This increase occurred in spite of a 20 % reduction in protein intake (Stein & Schluter, 1998).

Repletion from malnutrition is probably not an appropriate model for rehabilitation after space flight (or bed rest). The loss of body fat after space flight is not so severe that energy stores are significantly depleted. Rather they are still substantial. However, the protein loss is substantial because the reductive remodelling of skeletal muscle and for space flight, there are the additive effects of undernutrition. During bed rest it is protein that is lost, energy stores usually remain intact.

Amino acids may be limiting after space flight. Russian investigators found plasma amino acids to be reduced after some long-duration flights (Popov & Latskevich, 1984; Vlasova *et al.* 1985). The most consistent findings have been with methionine. There appears to be a consensus across many missions that the plasma methionine levels are reduced in the immediate post-flight phase and that this decrease persists for at least 1 week after landing and possibly longer (Popov & Latskevich, 1984; Vlasova *et al.* 1985; Stein & Schluter, 1998). The database is too small and fragmented to permit detailed analysis. However, this observation is consistent with increased removal of amino acids from the plasma to support increased protein synthesis in the

Table 2. Dietary intake and energy expenditure for space flight and related ground models

Mission	Flight–model duration (d)	Energy intake, control period (kJ/kg per d)		Energy intake, flight–test period (kJ/kg per d)		Protein intake, flight–test period (g protein/kg per d)		Energy expenditure, flight–test period (kJ/kg per d)		Energy expenditure, method	Energy intake, recovery (kJ/kg per d)		Reference
		Mean	SE	Mean	SE	Mean	SE	Mean	SE		Mean	SE	
Apollo	5–13			104	4	1·09	0·05						Smith *et al.* (1971)
Soyuz								140		$LiOH–CO_2$,			Chirkov (1973)
Skylab 2*	28	175	5	164	3	1·37	0·02	190		Intake–bal.	179	7	Rambaut *et al.* (1977*a*), Leonard *et al.* (1983)
Skylab 3*	59	186	25	181	20	1·49	0·12	198		Intake–bal.	196	25	Rambaut *et al.* (1977*a*), Leonard *et al.* (1983)
Skylab 4*	84	191	10	182	3	1·62	0·02	191		Intake–bal.	186	6	Rambaut *et al.* (1977*a*), Leonard *et al.* (1983)
Shuttle, various†	5–17			113	8	1·01	0·10	151	7	DLW			Lane *et al.* (1997)
Shuttle, SLS1/2†	9–12	163	10	144	13	1·11	0·06	140		Intake–bal. DLW	165	8	Stein *et al.* (1996)
Shuttle, LMS†	17	155	9	102	10	0·81	0·08	171	3	DLW	151	13	Stein *et al.* (1999*a*)
Shuttle, D-2	16			105	8	0·92	0·10						Heer *et al.* (2000)
MIR†	90–190	145	14	109	10	1·13	0·19				137	9	Stein *et al.* (1999*b*)
Bedrest*								101	3	DLW			Gretebeck *et al.* (1995)
Bedrest*	42	144	2	129	2.4	1·45	0·02			DLW			Blanc *et al.* (1998)
Bedrest + exercise*	17	145	9	133	5	1·07	0·03	129	5	DLW	146	8	Stein *et al.* (1999*c*)
Isolation‡				117	10			131	8	DLW			Goran et al. (1994)

bal., balance; DLW, doubly-labelled water.

* Intake controlled during measurement period.

† Intake measured but not controlled.

‡ Isolation in a room sitting in a chair with minimal movement.

regenerating muscles. The Russians interpreted the decreases in plasma protein levels at 7 d post-flight as indicative of a deficit in hepatic protein synthesis (Vorobyov *et al.* 1983).

There is some supporting rodent data for amino acids being limiting in the post-flight period. A rat hindlimb-suspension study by Tucker *et al.* (1981) found that after suspension, protein synthesis in the gastrocnemius muscle returned to the pre-suspension baseline within 6 h, remained unchanged for the next 2 d and then on the fourth day doubled (Fig. 1). The lag period may have been nutritional in origin due to a shortage of amino acids.

It is possible that some of the essential amino acids may be a limiting factor for supporting optimal protein synthesis in the period immediately following landing. A competition for scarce resources may occur between needs for increased muscle protein synthesis and needs of another system such as an acute-phase protein response. Thus, there may be some advantage to amino acid supplementation before landing and after long-duration missions.

The dynamics of protein metabolism shows the expected responses to space flight. Fig. 2 gives the combined results for SLS1, SLS2, space shuttle mission (eleven subjects) and MIR (six subjects) using the [^{15}N]glycine method with NH_3 as the end product (Stein *et al.* 1996). The shuttle data were collected between flight days 2 and 12. A similar study on two subjects on the German D-2 shuttle mission showed one increase and one decrease on flight day 5 (Fern *et al.* 1994). There is an initial increase reflecting a metabolic stress response as the body responds to the abrupt change in environment. The increase is accompanied by increases in acute-phase protein synthesis, cortisol and proinflammatory cytokine activity.

Numerous bed-rest studies have shown that the whole-body protein turnover rate is decreased with bed rest due to reduced protein synthesis in the inactive muscles (Gibson *et al.* 1987; Ferrando *et al.* 1996). After >4 months in space, the expected reduction in protein synthesis is found.

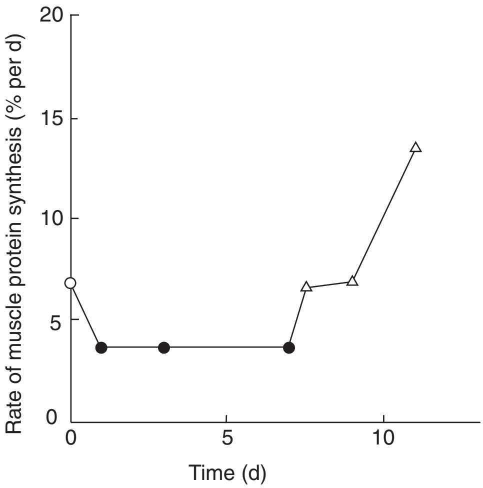

Fig. 1. Rat hindlimb protein synthesis during hindlimb suspension and recovery (Tucker *et al.* 1981). (○), Control (pre-suspension); (●), suspension; (△), recovery.

Energy

Energy intake

The most serious nutritional problem is the inability to maintain energy balance on missions with high exercise requirements. Voluntary dietary intake is always less during space flight than on the ground (Table 2). The variation is between missions rather than between subjects (Fig. 3). Within a given mission, all astronauts appear to eat about the same amount of food, suggesting that the decrease is mission-specific rather than microgravity-specific.

Dietary intake was controlled for the Skylab missions by having the astronauts eat all of a pre-defined meal. For the later shuttle and MIR missions, dietary intake was accurately logged using prepackaged foods and a bar-coding system. After the shuttle missions, NASA personnel went through the wet rubbish after the flight to recover, identify, and weigh any unconsumed food items to make sure that intake was indeed recorded accurately.

If intake is regulated and mandated, as was the situation on the 1973 Skylab missions, the reduction in intake can be prevented. The Skylab astronauts were taking part in a metabolic balance study and so were required to eat predefined meals. Energy intake was much higher on Skylab than on any other mission (Table 2). Post-flight comments by the Skylab astronauts on this requirement were so negative that NASA does not intend to repeat the experience. When intake is *ad libitum*, energy intake is much less than before flight (Table 2). This is true early and late in flight. After >3 months in space on MIR, dietary intake was only 110 (SE 10) kJ/kg per d (Stein *et al.* 1999*b*). The mean value is about the same as mean energy expenditure during bed rest (101 (SE 3) kJ/kg per d; Table 3; Gretebeck *et al.* 1995, and it is less than observed when physical activity was limited to personal grooming and excretory functions (117 (SE 10) kJ/kg per d; Goran *et al.* 1994).

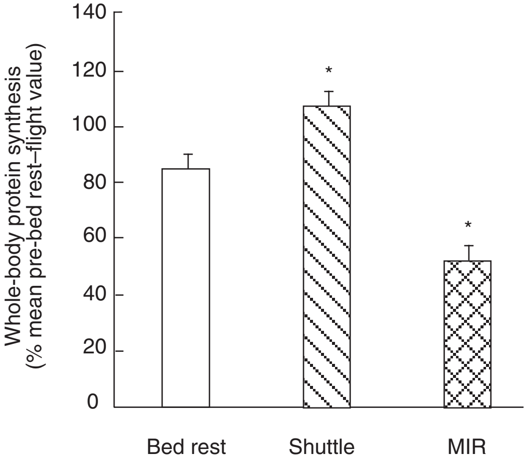

Fig. 2. Comparison of whole-body protein synthesis rates during bed rest, 2 weeks on the shuttle (n 11) and >4 months on MIR (n 6) (Stein *et al.* 1996, 1999*a,c*). Values are means with their standard errors shown by vertical bars. Mean values were significantly different from value during bed rest: $^{*}P < 0{\cdot}05$.

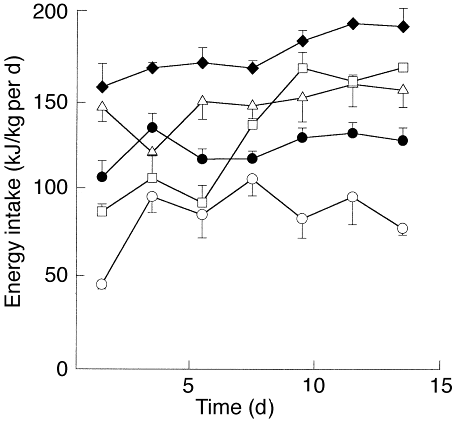

Fig. 3. Comparison of energy intake during the first 2 weeks of space flight for the three Skylab missions (Whedon *et al.* 1977), SLS1/2 (Stein *et al.* 1996) and the LMS shuttle mission (Stein *et al.* 1999). (△), Skylab 2; (□), Skylab 3; (◆), Skylab 4; (●), SLS1/2; (○), LMS. Values are means with their standard errors shown by vertical bars.

Table 3. Relationship between disease and the excretion of the products of DNA and lipid oxidation

	Increase (%)	Reference
8-OH dG		
After space flight on MIR	150	Stein & Leskiw (2000)
Smoking, 1 pack/d	200	Suzuki *et al.* (1995)
Environmental cigarette smoke	60	Howard *et al.* (1998)
Cancer	150	Loft & Poulsen (1998)
Radiotherapy	400	Loft & Poulsen (1998)
Isoprostanes		
After space flight on MIR	200	Stein & Leskiw (2000)
Smoking	200	Morrow *et al.* (1995)
Diabetes	350	Gopaul *et al.* (1995)
Liver disease	500	Awad *et al.* (1996)
Hepatorenal syndrome	900	Roberts & Morrow (1997)

8-OH dG, 8-oxo-7,8 dihydro-2 deoxyguanosine.

Energy expenditure

The total energy costs of living and working in space are unlikely to be comparable with costs on the ground because of the different energy costs of exercise, including movement around the cabin. Although the BMR has been measured on a number of missions by gas exchange–MS, none of the data have been published. It is reasonable to assume that had there been any significant differences the data would have been published. There is no evidence to suspect that there might be an effect of microgravity on BMR on short-term missions. For long-term missions, particularly where there is serious undernutrition there may well be a reduction in the BMR (see p. 95).

Energy expenditure during space flight was first estimated from metabolic CO_2 absorbed by $Li(OH)_2$ scrubbers (Kas'yan & Makarov, 1984) on a Soyuz mission in 1970 (Chirkov, 1973). Subsequently, energy expenditure has been measured by the intake balance method (Skylab, LMS, SLS1/2) and the doubly-labelled water method (various shuttle missions, Table 2). Not surprisingly, given the wide range of activities required from astronauts, energy expenditure rates during space flight are highly variable. Table 2 gives the energy intakes and expenditures for several missions, together with some reference data from ground studies. While the range is large, it is comparable with what would be expected on the ground.

Lane *et al.* (1997) measured the energy expenditure of thirteen random astronauts on several different missions which had varying activity requirements. The mean value corresponded well with the value predicted by the WHO equation for moderate activity, but the individual values did not correlate at all with the value estimated from the WHO equation (1·7 × resting energy expenditure for males and 1·6 × resting energy expenditure for females, r^2 0·02; Lane *et al.* 1997). It will therefore not be possible to devise a single recommendation for energy requirements to suit all subjects on all missions. Dietary recommendations for energy intake will have to be customized to meet individual needs. Astronauts do not have to be in precise energy balance, but they need to be close to it.

Energy balance

Energy balance is the real variable of interest. Energy balance data is available for Skylab, Shuttle LMS, Shuttle SLS1/2 and the heterogeneous group of astronauts studied by Lane (Rambaut *et al.* 1977*a*,*b*; Leonard *et al.* 1983; Lane *et al.* 1997; Stein *et al.* 1996, 1999*c*). The Skylab astronauts were required to eat predefined meals. For the first Skylab mission, it was assumed that energy requirements in-flight would be about 10 % less than on the ground. For the subsequent two Skylab missions, energy intake was progressively increased, but because the exercise requirement was also increased, detailed interpretation of the data is problematic. Energy expenditure was measured by the intake–change in body composition method. Overall the Skylab astronauts were in negative energy balance and lost 1·2 (SE 0·3) kg fat (Leonard *et al.* 1983). On all shuttle missions except SLS1/2 astronauts were in negative energy balance (Table 2).

N balance was also measured on Skylab, shuttle SLS1/2 and shuttle LMS. Urine collection in space is not a simple matter because in microgravity air and urine are mixed and do not separate into two phases. With the exception of the shuttle missions SLS1, SLS2 and LMS, urine was collected in plastic bags. For the three shuttle missions, urine was collected using a specially designed unisex system that collected, measured and recorded mass and time, and saved a 20 ml portion of each urine void. A similar system is planned for the ISS.

Fig. 4 shows a comparison of energy intake, expenditure, balance and N balance for the two very similar shuttle missions, SLS1/2 and LMS. The periods of comparison are the first 9–12 d on SLS1/2 (Stein *et al.* 1996) and the first 12 d for LMS (Stein *et al.* 1999*c*). The same orbiter (Columbia) in the same configuration (with the Space Lab module) was used for both missions. Both missions were very busy missions with science as the primary mission objective. Crew members were very active moving about the cabin throughout the day doing investigator originated experiments. The principal difference was that LMS had extensive exercise requirements as part of the scientific programme (LeBlanc *et al.* 1995; Stein *et al.* 1996). Dietary intake was not regulated on either mission.

The SLS1/2 astronauts who did not exercise, ate more and were in approximate energy balance (Stein *et al.* 1996). On LMS, energy intake failed to meet energy needs of the exercise programme and the protein loss was much greater (Fig. 4). Astronauts lost 1·0 (SE 0·4) kg body

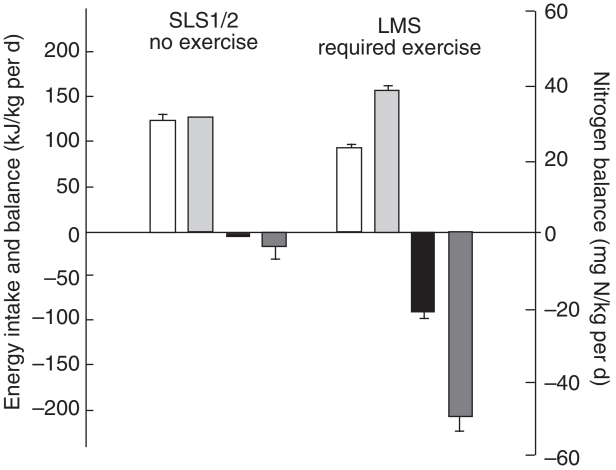

Fig. 4. Comparison of energy intake, expenditure and balance and nitrogen balance during space flight on SLS1/2 and LMS (Stein *et al.* 1996, 1999*c*). Values are means with their standard errors shown by vertical bars. (□), Energy intake; (▨), energy expenditure; (■), energy balance; (▩), nitrogen balance. Mean values for the differences in energy intake, expenditure and nitrogen balance were statistically significant: $P < 0.05$.

weight on SLS1/2 and 2·6 (SE 0·4) kg (1·5 (SE 0·6) kg fat) on LMS. The loss of body fat on the LMS mission was confirmed by three independent methods, dual-energy X-ray absorptiometry, ^{18}O isotope dilution and from the difference between energy intake and energy expenditure (Stein *et al.* 1996). A high rate of aerobic exercising is extremely costly in energy needs (Convertino, 1990). The energy costs of the two daily in-flight exercise periods on the Russian Salyut-7 mission were estimated as about 84 kJ/kg per d (Bychko *et al.* 1982; Vorobyov *et al.* 1983; Gazenko *et al.* 1990). SLS1/2 was the only mission without a mandatory exercise requirement. On all other shuttle missions where dietary intake was uncontrolled, energy intake was uniformly low, about 110 kJ/kg per d (Table 3).

This inability to match intake to expenditure on missions with high exercise requirements is not just an acute effect. On the long-duration high-exercise-requirement Shuttle–MIR missions, after >3 months in space on MIR, dietary intake was only 110 kJ/kg per d, with an average weight loss of 4·3 (SE 1·2) kg (Stein *et al.* 1999*b*). Even on Skylab with its prescribed intake, subjects lost body fat and were in negative energy balance (Rambaut *et al.* 1977*a*; Leonard *et al.* 1983). For all of these missions except LMS where protein intake was at the level of the RDA (Stein *et al.* 1999*c*), protein intake was substantially above the RDA (Rambaut *et al.* 1977*b*; Lane & Rambaut, 1994; Stein *et al.* 1996, 1999*b*) indicating that the shortfall is in energy intake rather than protein intake.

Importance of maintaining energy balance

On the ground, short-term periods of negative energy balance are buffered by the body's fat stores. In contrast, chronic energy deficit results in progressive weight loss, decreased physical performance, increased 'fatigability' (Edgerton *et al.* 1995; Riley *et al.* 1995) and a progressively increasing susceptibility to infection (Askanazi *et al.* 1982; Keusch & Farthing, 1986; Chandra, 1991). There is no reason to suspect that the physiological consequences of undernutrition differ in space. Decreased immunocompetence during space flight has been reported (Gmunder *et al.* 1994; Taylor *et al.* 1997; Tuschl *et al.* 1997; Levine & Greenleaf, 1998). Wound healing is also compromised with chronic undernutrition, which may be a problem if injury ever occurs during space flight (Kinney & Elwyn, 1983; Kirkpatrick *et al.* 1997).

Man exhibits both metabolic and discretionary adaptations to chronic energy deficits. An example of the former is the reduction in macronutrient substrate cycling (about 7 %) of which the major component is the reduction in protein turnover (Stein *et al.* 1991) and of the latter, a reduction in voluntary activity (Waterlow, 1986). The MIR crews probably adapted by reducing the amount of exercise done. Compliance with the prescribed exercise regimens on the recent Shuttle–MIR programme was variable (Burrough, 1998). Nevertheless, even with accommodation to the reduced intake at some point, metabolic processes will become compromised and the well-known consequences of severe undernutrition would occur.

One consequence is the major fall in protein synthesis. Numerous bed-rest studies have shown that the whole-body protein synthesis rate is reduced by about 15 % (Fig. 2; Schonhydr *et al.* 1954; Ferrando *et al.* 1996; Stein *et al.* 1999*a*), mainly accounted for by the approximately 50 % decrease in muscle protein synthesis (Gibson *et al.* 1987; Ferrando *et al.* 1996). However, the reduction on MIR was 46 (SE 5) %. The likely cause of this was the shortfall in energy intake (Stein *et al.* 1999*b*), as indicated by direct relationship between protein synthesis and estimated energy deficit (Fig. 5).

A second consequence of metabolic compromise on MIR was a decrease in endogenous antioxidant defences. The principal source of free radicals in the body is from free radical leakage (3–5 % of the electron flux) from the electron transport chain (Halliwell, 1997). Other sources of free radicals are phagocytes, arachidonate pathways, reactions involving transition metals, inflammatory processes, etc. An imbalance between free radical production and antioxidant defence results in oxidative damage. Oxidative damage to lipids can be detected by measuring the urinary excretion of isoprostanes (8-iso-prostaglandin $F_{2\alpha}$). Isoprostanes are derived from arachidonic acid in membrane-bound phospholipids by auto-oxidation leading to a series of prostaglandin F_2-like compounds, the isoprostanes. Like lipids, DNA is also susceptible to oxidative damage (Ames, 1989; Fraga *et al.* 1990; Pryor & Stone, 1993). The most abundant of the DNA nucleoside oxidation products is 8-oxo-7,8 dihydro-2 deoxyguanosine, which is also

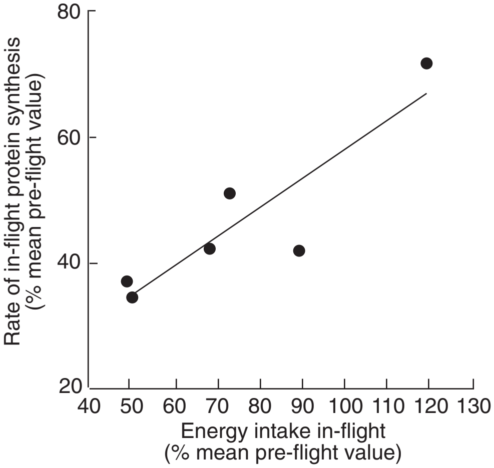

Fig. 5. Relationship between energy intake and whole-body protein synthesis rate during space flight on MIR (Stein *et al.* 1999*b*).

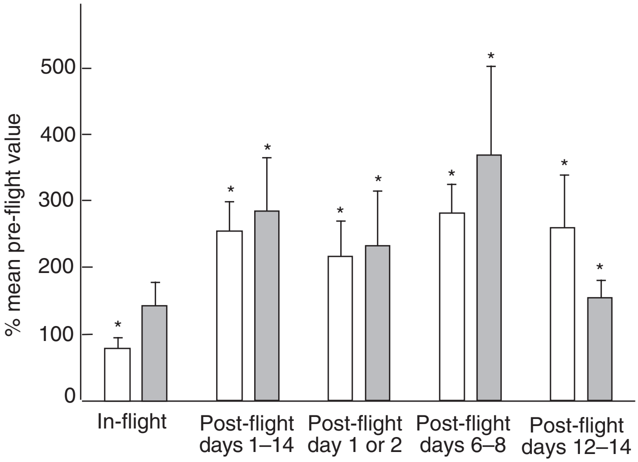

Fig. 6. Excretion of 8-oxo-7,8 dihydro-2 deoxyguanosine (8-OH dG) and isoprostane (8-iso-PGF$_{2\alpha}$) during and after flight on MIR (Stein & Leskiw, 2000). ■, 8-OH dG; □, 8-iso-PGF$_{2\alpha}$. Values are means with their standard errors shown by vertical bars. Mean values were significantly different from pre-flight values: *P < 0·05.

quantitatively excreted in the urine. Both 8-iso-prostaglandin F$_{2\alpha}$ and 8-oxo-7,8 dihydro-2 deoxyguanosine were measured on and after the MIR space flight.

During the flight on MIR, isoprostane excretion was depressed while after space flight it was increased by about 200 % (Stein & Leskiw, 2000; Fig. 6). A similar reduction was found during the LMS mission where energy intake was also very low (Stein & Leskiw, 2000), suggesting that the decrease in isoprostane production was due to a down-regulation of intermediary metabolism and a decreased electron transport system flux in response to the energy deficiency.

Both isoprostane and 8-oxo-7,8 dihydro-2 deoxyguanosine excretion were increased by about 200 % for the 2 weeks of the post-flight measurement period, indicating an increase in free radical-induced damage. This could be due to either increased free radical production or decreased host defences. An increase in free radical production could result from an increase in the flux though the electron transport chain or from damage as load is reimposed on the weakened anti-gravity muscles. Neither is likely. Energy intake was unchanged over preflight (145 (SE 12) *v*. 135 (SE 7) kJ/kg per d). On the ground, when there is increased oxidative damage after exercise (Cannon *et al.* 1991; Meydani *et al.* 1993), there is a parallel increase in 3-methylhistidine excretion (Evans *et al.* 1986; Fielding *et al.* 1991). 3-Methylhistidine excretion was not increased post-flight on MIR and neither was it increased after flight on Skylab (Leach *et al.* 1979; Fig. 7).

Interestingly, increased 3-methylhistidine excretion indicating increased muscle breakdown did occur in flight on Skylab (Leach *et al.* 1979; Stein & Schluter, 1997), but not on MIR (Stein, 2000*b*) (Fig. 7) or on the shuttle missions SLS1/2 (Stein & Schluter, 1997), and the magnitude of the increase on Skylab declined with time in orbit (Fig. 8). The probable reason was that on Skylab exercise, like diet, was mandated. In contrast on MIR, the crew had some freedom to choose when and how much to exercise and their musculo–skeletal systems were better able to adapt to space flight than the Skylab astronauts forced to follow a predetermined exercise programme. The result provides further support for the argument that an inappropriate in-flight exercise regimen is counter-productive.

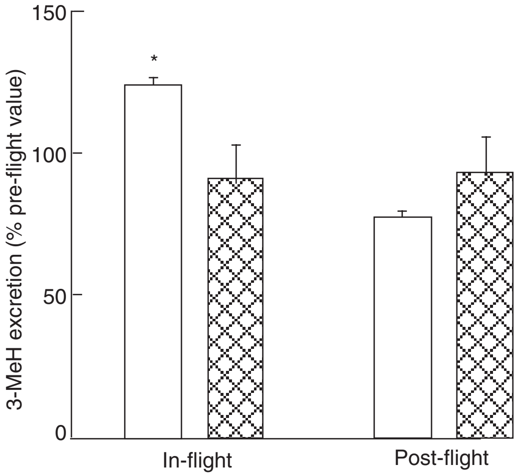

Fig. 7. Urinary 3-methylhistidine (3-MeH) excretion on MIR (▨; Stein, 2000) or Skylab (□; Leach *et al.* 1979). Values are means with their standard errors shown by vertical bars. Mean value was significantly different from preflight values: $*P < 0{\cdot}05$.

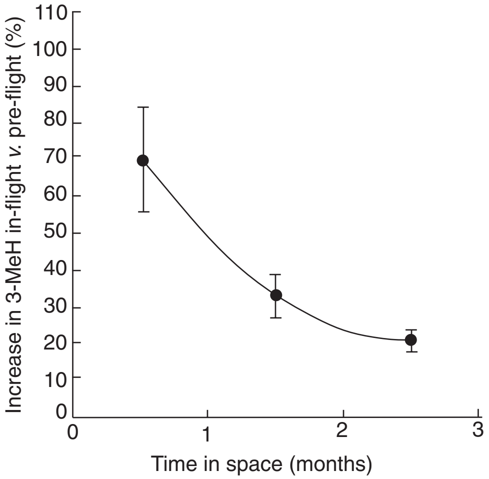

Fig. 8. Change in urinary 3-methylhistidine (3-MeH) excretion with time in orbit on Skylab (adapted from Leach *et al.* 1979). Values are means with their standard errors shown by vertical bars.

The increased oxidative damage post-flight could reflect impaired endogenous antioxidant defences. The down-regulation of protein metabolism that occurred on MIR could cause some loss of protein-based antioxidant systems. Astronauts land with down-regulated protein metabolism which may involve compromised production of protein-related antioxidant defences, especially if there is competition post flight for amino acids between synthesis of such defences and repleting muscle and other tissues (Ushakov & Vlasova, 1976; Tucker *et al.* 1981; Vorobyov *et al.* 1983; Stein *et al.* 1999*b*). Whatever the mechanism, the greater amounts of the products of free radical damage to both lipids and DNA recovered in the urine indicate a more extensive and persistent (<2 weeks) free radical propagation post-flight.

The level of oxidative damage post-flight is physiologically significant. Table 3 shows a comparison of the astronaut data against some well-known clinical conditions. Long-duration space flight appears to rank with cigarette smoking. Problems of nutritional origin are often treatable. In this case, the potential remedies would involve preventing an energy deficit in flight along with the use of dietary antioxidant supplements. Millions of Americans and Europeans take vitamins and other dietary antioxidants in the hope of decreasing oxidative damage.

Possible reasons for the poor intake

Food for space missions is processed and some of the hedonistic aspects are lost. Gastrointestinal transit times may also be slower, satiety may be altered by food not sedimenting in the stomach and eating time may sometimes have been inadequate on some missions. However, poor intake is unlikely to reflect the type of food. Humans are omnivores who survive very well on a wide variety of different foods that vary in digestibility and physico-chemical properties.

The foods provided on the space craft (US and Russian) are a combination of commercially available foods that are thermally stable, foods that can be rehydrated (freeze-dried and powders for soups and drinks) and some dry snack items (candies, cookies, nuts). Before flight, astronauts chose their menu items. Time to eat may have been a factor on some missions, but not on MIR (Stein *et al.* 1999*b*) where crews worked regular scheduled days and time was specifically set aside for eating and for personal use. Nevertheless, intake remained very low (Table 2).

The inability to adjust intake to match needs is not an individual effect with some subjects on a given mission eating enough and others failing to do so. On the contrary, on a given mission, as Fig. 3 shows, all of the astronauts ate about the same amount of food. Astronauts appear to synchronize their energy intakes.

A number of observations suggest that the inverse relationship between exercise and energy intake may be due to problems in disposing of the metabolic by-products from exercise, namely heat and CO_2. Thermo-regulatory mechanisms are less efficient during space flight and this persists into the immediate post-flight period (Leach *et al.* 1978; Greenleaf & Reese, 1980; Convertino, 1996*b*; Fortney *et al.* 1998). The two primary avenues of heat loss that are affected by microgravity are convection and evaporation. At low air-flow rates, body heat loss occurs primarily by natural convection; heat exchange occurs when the air nearest the skin surface becomes warmer and lighter than the surrounding air (Newburg, 1949). In a 1 ***g*** environment this warm air rises away from the skin removing body heat. In microgravity the warm air does not rise and the absence of free convection limits the rate of heat loss.

In animals food intake drops precipitously as the environmental temperature increases from 18°C to 36°C (Brobeck, 1948; Ray, 1989; Llamas-Lamas & Combs, 1990; MacLeod & Dabutha, 1997). At 40°C rats stop feeding, and if force fed by intubation suffer heat stress and even die (Hamilton & Brobeck, 1966). Probably the most relevant studies are those on soldiers performing strenuous military duties in hot climates. Edholm found a 25 % decrease in food intake by British soldiers in Aden as compared with the UK (Edholm *et al.* 1964). The US army has developed a predictive equation for how much intake is reduced as the local temperature increases (Buskirk, 1993). Russian investigators found reduced intake by Russian miners during periods of heavy exercise under thermally stressed conditions (Peftiev, 1990).

Another factor that could contribute to the poor intake is high ambient CO_2 levels. CO_2 levels are generally high in the cabins of both the US and Russian space vehicles and this has been a long-term concern. The mean CO_2 concentration is about 0·3 %, ten times the concentration in ambient air; there have been prolonged periods where the level was above 0·7 % (Malkin, 1994; Wenzel *et al.* 1998; Wang & Wade, 2000). CO_2 is removed by $Li(OH)_2$ scrubbers on MIR and the shuttle. Decreasing the ambient CO_2 concentration by 10 % would require a significant improvement in the air-purification system and this would increase the weight of the system. By itself, increased air CO_2 is not a problem, but when superimposed on another metabolic stress (e.g. the space flight-induced adaptive remodelling) it may well be. A recent study with CO_2 levels at the 0·7 % level depressed voluntary food intake by rats under conditions where the hindlimbs were unloaded (Wang & Wade, 2000).

Exercise increases the amount of CO_2 that has to be removed. Whether the depressed food intake is secondary to the heat generated or the CO_2 produced, the cause is exercise-generated waste products (heat or CO_2) that cannot be disposed of rapidly. Either hypothesis explains the adverse effects of exercise and the observation that the effect is mission dependent rather than subject dependent and not a consequence of living without gravity. The cause is environmental and is related to air flow and purification. In the absence of gravitational-induced convection currents, air flow is totally dependent on mechanical means.

Iron metabolism

Gravity causes blood to drain from the upper body and to pool in the lower body, particularly the legs. In the absence of gravity this no longer occurs. The change is perceived as fluid migrating to the head (cephalic shift). The space available for blood in the upper body is constrained by the rib cage and skull so the net effect is less space for blood. This necessitates a reduction in blood volume by about 10–15 %. In order to maintain a constant packed cell volume the erythrocyte volume is reduced correspondingly. The decrease in the circulating erythrocytes corresponds to the loss of about 300 mg Fe from the intravascular space. As a consequence serum ferritin and body Fe stores, particularly in the reticuloendothelial cells, are increased (Alfrey *et al.* 1996).

After landing, the plasma volume rapidly returns to the preflight volume. But the in-flight reduction in erythrocyte number results in a decreased packed cell volume and a mild anaemia. In addition, gravity pulls the blood back from the upper part of the body back to the lower body (Gazenko *et al.* 1981; Charles & Lathers, 1991; Convertino, 1996*a*). The combination of decreased blood volume and fluid shifting away from the head to the lower body causes orthostatic hypotension after landing. Orthostatic hypotension contributes to the inability of astronauts to walk unassisted after space flight. A decrease in cardiac output also contributes to the orthostatic hypotension. Maximal heart rates and blood pressure are unchanged compared with preflight, but there is a one-third decrease in stroke volume which leads to proportionate decreases in cardiac output and O_2 delivery to the muscles (Levine *et al.* 1996; Shykoff *et al.* 1996).

The reduction in circulating erythrocytes is accomplished by the preferential removal of newly produced erythrocytes rather than the random removal of blood cells from the aggregate pool (Alfrey *et al.* 1996). Erythropoeitin, which regulates erythrocyte synthesis in bone marrow, is reduced during space flight. A reduction in erythropoetin increases the capture of circulating erythrocytes by splenic phagocytic cells. The reductive adaptation in erythrocyte mass is over by the end of the first week but recovery takes longer, i.e. 6–8 weeks for the production of new erythrocytes to replace the lost erythrocytes after landing (Alfrey *et al.* 1996). The role of Fe in blood volume regulation is minor and does not seem to warrant either decreasing Fe intake in flight or increasing Fe intake after space flight.

Calcium

Bone loss and the potential for radiation damage are believed to be the greatest impediments to long-term space flight. In the absence of gravity, load is decreased on the bones with anti-gravity functions. These are located principally in the back and legs (Table 4). The bone loss is a regional phenomenon; there is no bone loss from the upper body (Thornton & Rummel, 1977; LeBlanc *et al.* 1995, 1996). Videos of astronauts and cosmonauts in orbit show that they use their arms rather than their legs to move around the cabin. The legs are largely passive. The exercise from movement is apparently enough to prevent any bone loss from the upper body whereas exercise with devices (treadmill, bicycle, bungee cords) is inadequate to prevent bone loss in the legs and back.

The rate of bone loss from the weight-bearing bones is about 0·5–1·0 % per month (Rambaut *et al.* 1979; Tilton *et al.* 1980; Stupakov *et al.* 1984; Morey-Holton *et al.* 1996; Vico *et al.* 2000). For comparison, the rate of bone loss in some women in early menopause is 2–4 % per year. The space flight database is too small to evaluate whether this rate is constant or whether equilibrium is reached. On Skylab the rate of Ca loss did not appear to diminish with time in orbit (up to 84 d, Fig. 9; Rambaut & Johnson, 1979; Schneider *et al.* 1994). A recent Franco–Russian collaborative study on cosmonauts who spent from 1 to 6 months on MIR failed to find any convincing evidence for equilibration (Vico *et al.* 2000).

Like muscle, bone exhibits plasticity, changing its mass and architecture to adapt to the forces exerted upon it. Because the turnover rate of bone is very slow, adaptive remodelling to an altered gravitational load (decrease or increase) takes much longer than muscle. It would seem likely that a new equilibrium state will eventually be reached, but there is not enough data from long-duration space flights to either estimate the position of the equilibrium or how long equilibration will take.

An attempt was made to study Ca kinetics on the recent shuttle–MIR missions. Unfortunately, interpretation of the results were confounded by the low dietary intakes with Ca intake only 580 (SE 108) mg/d (*n* 3), a 40 % reduction from preflight intakes (1065 (SE 71) mg/d). In spite of this great reduction (as with energy intake), urine Ca excretion was about the same as preflight (221 (SE 22) mg/d pre-flight, 335 (SE 79) mg/d in-flight). Even so, Ca resorption as measured with ^{43}Ca and ^{46}Ca was increased from 418 (SE 51) mg/d to 645 (SE 53) mg/d

Table 4. Bone loss during space flight on the MIR Space Station†
(Mean values with their standard errors)

	Mean loss (% per month)		
Variable	Mean	SE	*n*
Spine	1·07**	0·15	18
Neck of femur	1·16**	0·20	18
Trochanter	1·58**	0·23	18
Total body	0·35**	0·06	17
Pelvis	1·35**	0·13	17
Arm	0·04**	0·21	17
Leg	0·34**	0·08	16

† Data from LeBlanc *et al.* (1996) and the National Research Council (1998).

** $P < 0{\cdot}01$.

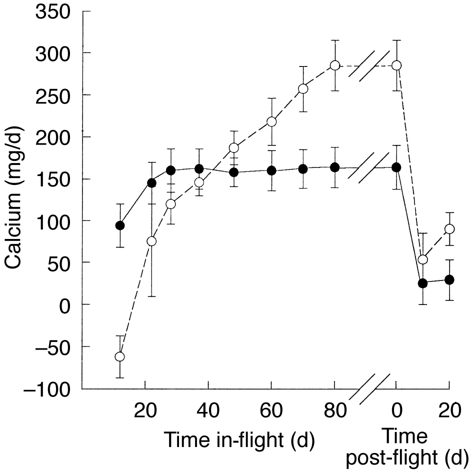

Fig. 9. Change in urine (●) and faecal (○) calcium excretion rates from preflight values during the 84 d Skylab 4 flight (Rambaut & Johnson, 1979). Values are means with their standard errors shown by vertical bars.

($P < 0.05$; Smith *et al.* 1999). This observation may not be in accord with ground-based findings. A recent review concluded that unloading of the skeleton leads to a decrease in bone formation with either a slight increase or no change in the resorption rate (Holick, 1999). A study on one astronaut on the 1997 German–MIR mission controlled the in-flight dietary Ca and vitamin D intakes at 1200 mg/d and 16 mg/d respectively (Heer *et al.* 1999). Intestinal Ca absorption as measured by the fractional Sr absorption method fell from 17 % preflight to 4 % in-flight. At the same time plasma parathyroid hormone (PTH) was decreased.

Eventually, chronic loss of Ca from bone will result in the low bone mass and micro-architectural deterioration of bone tissue characterizing osteoporosis resulting in increased bone fragility and susceptibility to fracture (Fortney *et al.* 1996; Morey-Holton *et al.* 1996). The space flight-induced osteoporosis reproduces the bone loss but has not yet proceeded far enough for there to be a measurable increase in risk of fracture (Oganov *et al.* 1991). Astronauts are healthy middle-aged subjects with strong bones who can afford to lose 5–10 % of their bone mass. However, for a 3-year mission if the bone loss continues at a rate of about 1 % per month, the losses could be as high as 30–50 %; this is unacceptable (Whedon *et al.* 1974; Holick, 2000).

A difference between the osteoporosis found with post-menopausal women and that of space flight is that the former is pathological whereas the latter is the normal physiological response to the loss of weight on some bones. Even so, the losses leave the astronaut vulnerable to fracture once gravity is reimposed. Women are at a greater risk because they start off with less bone.

On the ground, Ca intake is encouraged as a preventive and therapeutic measure. There is an added benefit if vitamin D intake is increased at the same time (Prince, 1997). It is essential that dietary Ca intake be adequate. Table 5 summarizes the Ca intakes for a number of missions. With the exception of the NASA–MIR missions studied by Smith *et al.* (1999) and the EuroMIR 1994 study (Heer *et al.* 1999) Ca intake has been about the same as the RDA for middle-aged adults.

Table 5. Dietary calcium intake before and during space flight
(Mean values with their standard errors)

	Calcium intake preflight (mg/d)		Calcium intake in-flight (mg/d)		
Mission	Mean	SE	Mean	SE	Reference
Skylab	725	18	729	42	Whedon *et al.* (1977)
Shuttle, SLS1/2	1340	270	1000	90	TP Stein (unpublished results)
Shuttle, LMS	1188	323	943	146	TP Stein (unpublished results)
NASA–MIR	1065	59	581	111	Smith *et al.* (1999)
Germany–MIR			740		Heer *et al.* (1999)
France–MIR			700–1200*		Vico *et al.* (2000)

* For comment, see text below.

On the recent Franco–Russian MIR missions it was claimed that Ca intake was in the range 700–1200 mg/d (Table 5). This seems unlikely, implying that the in-flight dietary intake was unchanged from preflight. The authors claimed that: ‘a balanced diet was given during flight’, but admitted that they were: ‘unable to check adherence with dietary and exercise constraints’, and: ‘we do not have precise information as to the exact nature of diet’. On the very similar NASA–MIR missions dietary intake in-flight was measured and was reduced by 45 % (Smith *et al.* 1999, Table 5).

Like the Skylab investigators, Vico *et al.* (2000) found a ‘surprisingly’ large variation between individuals. They attributed this to a lack of information on dietary intake, genetics, exercise done and other possible covariates. Since diet and exercise were controlled on Skylab, genetic factors may be the dominant covariate, as they are for bone loss on the ground (Arden & Spector, 1997).

Even with low Ca intake, on the two missions where Ca excretion has been measured, urinary excretion has been high (Whedon *et al.* 1974; Schneider *et al.* 1994; Smith *et al.* 1999). It is difficult to envisage how any counter-measure for bone loss can be effective when intake is so low. There have been no ground-based studies on the Ca balance and kinetics in subjects on hypocalcaemic diets undergoing either bed rest or a bed rest plus exercise regimen. At a minimum dietary Ca intake should be brought up to the RDA level.

Increasing dietary Ca intake in-flight above the RDA is contra-indicated because of the propensity of Ca to form renal stones (Whitson *et al.* 1993, 1997). The space-flight environment is already conducive to renal stone formation without imposing additional dietary Ca. The continuing loss of Ca from bone leads to hypercalciurea, which is one of the factors leading to renal stone formation. Other factors favouring renal stone formation are the high salt concentration of the diets and in particular the tendency of astronauts to reduce fluid intake during space flight. There have been at least four instances of kidney stone formation so far on the US and Russian programmes (Whitson *et al.* 1997). However, this does not mean that dietary Ca intake should be reduced below the RDA (800 mg/d; National Research Council, 1989).

Space-flight diets tend to be high in Na. The high Na content of the diet may also contribute in a small way to the Ca loss. High levels of NaCl promote urinary Ca loss (Dawson-Hughes *et al.* 1996). In a rodent hindlimb-suspension study Navidi *et al.* (1995) found increased Ca excretion on high-Na diets. Space-flight diets are high in Na because they are based on commercially-available prepared foods that tend to be high in Na. For reasons of cost, there are very few foods specifically prepared for either space programme. NASA and the Russian Space Agency assess stability at ambient temperature and then repackage the foods for space flight.

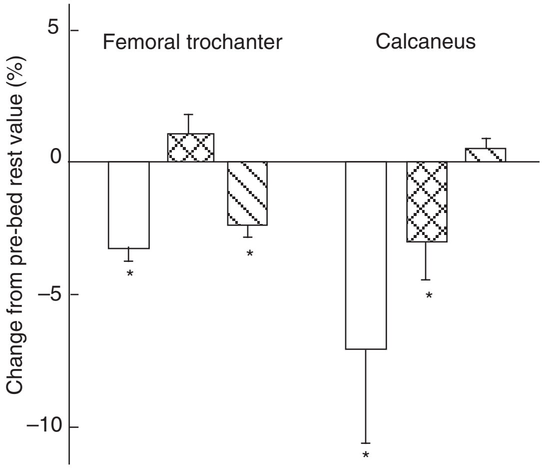

Fig. 10. Comparison of exercise and pharmacological intervention as counter-measures against disuse bone-loss. Adapted from LC Shackleford, AD LeBlanc, AH Feiveson, HJ Evans, TB Driscoll and NJ Rianon (unpublished results). (□), Control; (▩), Alendronate (Merck Inc, Rahway, NJ, USA); (▧), exercise. Values are means with their standard errors shown by vertical bars. Mean values were significantly different from pre-bed rest values: $^*P < 0{\cdot}05$.

The current emphasis of research programmes in counter-measures is principally on exercise with some interest in the use of bisphosphonates to counter osteoporosis. Even though exercise is a routine component of most space-flight missions, bone Ca loss invariably occurs. Nevertheless, there is good ground-based evidence from bed-rest experiments that have incorporated an exercise module to suggest that an appropriate exercise programme should decrease the bone loss (Lee *et al.* 1997; Bamman *et al.* 1998; Ferrando *et al.* 1999). Ground-based studies are currently exploring the use of bisphosphonates, a class of anti-osteoporosis drugs. Bisphosphonates decrease the loss of Ca from bone in the hindlimb-unloaded rat model (Grigoriev *et al.* 1998) and during bed rest (Lockwood *et al.* 1975; Chappard *et al.* 1989; Grigoriev *et al.* 1992; Ruml *et al.* 1995). However, the long-term consequences of taking bisphosphonates during long-duration space travel is not known and is likely to be difficult to evaluate. There is a reluctance to rely on a purely pharmacological approach in an exotic environment where the potential for ‘side effects’ is not known and cannot be easily determined (Dawson-Hughes *et al*. 1996; Bikle *et al.* 1997; Holick, 2000).

Fig. 10 shows preliminary data from a 17-week bed-rest study (LC Shackleford, AD LeBlanc, AH Feiveson, HJ Evans, TB Driscoll and NJ Rianon, unpublished results). The objectives of the first phase of the study were to compare the efficacy of a second generation bisphosphonate (Alendronate; Merck Inc. Rahway, NJ, USA) against exercise and then to evaluate the combination. Fig. 10 shows that neither treatment is wholly effective, and that effectiveness differs. The objective of the second phase (in progress) is to evaluate the combination of exercise and bisphosphonates. Given that the benefits of the treatments differ, there is a reasonable probability that the combination of pharmacological intervention with bisphosphonates and exercise will be synergistic. The combined approach of using exercise to provide some load to the bones should shift the equilibrium to somewhere between the 1 ***g*** and 0 ***g*** states and the bisphosphonates will decrease the resorption step, thereby slowing down the rate of attainment of the new equilibrium position.

Vitamins

Vitamin supplementation is of interest for two reasons: as an adjunct in the treatment of the bone loss and to provide additional antioxidants. Even though any contribution from vitamins to lessening the bone loss is likely to be small, small effects can be additive. The three vitamins involved in bone metabolism are C, D and K. Vitamin C is an essential cofactor in the synthesis of hydroxyproline and so is involved in collagen formation. Epidemiological studies have suggested that there is a link between vitamin C intake and bone density, but as yet there have been no intervention studies assessing the role of vitamin C in bone remodelling (Weber, 1999). Most interest has focused on vitamins D and K.

Vitamin D

Cholecalciferol can be synthesized in skin from 7-dehydrocholesterol when exposed to about 20 min u.v. light between 290 and 315 nm. Cholecalciferol is converted to 25-hydroxycholecalciferol in the liver and this is converted to 1,25-dihydroxycholecalciferol in the kidneys. 1,25-dihydroxycholecalciferol facilitates the intestinal absorption of Ca, the synthesis of Ca-binding proteins and regulates the transcription of genes involved in Ca homeostasis (Morey-Holton *et al.* 1996; Lian *et al.* 1999). There has been some concern that the low levels of lighting in the space vehicle may not be not enough to promote synthesis of cholecalciferol (Belakovskii *et al.* 1992; Rettberg *et al.* 1998; Holick, 2000). The multi-vitamin capsule that is routinely taken by astronauts appears to be adequate for short-term missions (Morey-Holton *et al.* 1988) but may not be for long duration missions (Belakovskii *et al.* 1992; Rettberg *et al.* 1998). On the ground, vitamin D supplementation increases bone Ca content (Dawson-Hughes *et al.* 1997).

Another potential factor that could lead to decreased vitamin D activity is a decrease in PTH secretion. The release of Ca from bone leads to a rise in the serum Ca level which is recognized by Ca sensors in the parathyroid gland and causes a decrease in PTH secretion. PTH activity is reduced during bed rest (Arnaud *et al.* 1992). The decrease in PTH activity causes an increase in urinary Ca and decreases the efficiency of the conversion of 25-hydroxycholecalciferol to 1,25. This increases intestinal Ca absorption and reabsorption of Ca-dihydroxycholecalciferol by the kidney. A decrease in the renal production of 1,25-dihydroxycholecalciferol is likely therefore to lead to a decrease in the efficiency of Ca absorption (Morey-Holton *et al.* 1996; Holick, 2000). The net effect of this normal integrated physiological response is to smoothly effect a selective reduction in bone mass to adapt to the new situation. It is just unfortunate that the adapted state is undesirable and external measures to counteract it are needed.

Increasing PTH and vitamin D is another approach to decreasing resorption since both can have anabolic effects on bone (Holick, 2000). Space-flight measurements of PTH and vitamin D have been inconclusive (Morey-Holton *et al.* 1988; Tipton *et al.* 1996; Vermeer *et al.* 1998). Post-flight PTH is increased and calcitonin decreased (Grigor'ev *et al.* 1999). The quality and quantity of in-flight endocrine data on astronauts is poor and limited. A US National Research Council decennial review of NASA's research programme in the life sciences strongly recommended that obtaining a human hormonal profile of the endocrine response to space flight be given a very high priority once the ISS is available for scientific work (National Research Council, 1998).

Vitamin K

There are two forms of vitamin K, phylloquinone and menaquinone, which differ in the number of isoprene units attached. Vitamin K catalyses the post-translational carboxylation of a series of Ca-binding proteins, one of which is osteocalcin (Suttie, 1993; Lian *et al.* 1999). Osteocalcin is a non-collagenous protein produced by differentiated osteoblasts. If osteocalcin is not carboxylated it does not bind to bone hydroxyapatite (Price & Williamson, 1985; Koshihara *et al.* 1996). In hindlimb-unloaded rats, feeding menaquinone attenuates the bone loss (Yamaguchi *et al.* 1999), but as yet there is no data from the space programme.

Antioxidant vitamins

Although the use of antioxidant vitamins has been repeatedly proposed as a protective measure against radiation (Vorob'ev *et al.* 1981; Robbins & Yang, 1994; Bantseev *et al.* 1997; Joseph *et al.* 1998), there is no in-flight data or ground-based data on the protective effects of antioxidants from very high energy radiation. Whether antioxidant vitamins can provide any prophylactic benefit against radiation has been questioned on theoretical grounds. Free radical scavengers are less effective against high linear energy transfer radiation, because the ionization produced is the result of direct hits from high energy particles on random molecules rather than indirectly through the products of water radiolysis (National Research Council, 1996). A separate issue is whether there will be any benefit to giving supplemental doses of antioxidant vitamins post-flight once the in-flight negative energy balance problem has been solved.

Increases in the dietary intakes of vitamins C and E have been recommended as prophylaxis against chronic disease (National Research Council, 2000); however, chronic disease is an inappropriate model for the recovery from space flight. The appropriate ground-based analogies are recuperation after bed rest and exercise by deconditioned subjects. Free radical generation from exercise is increased in rodents and human subjects (Davies *et al.* 1982; Reid *et al.* 1992; Viguie *et al.* 1993; Borzone *et al.* 1994; Sen, 1995; O'Neill *et al.* 1996; Powers & Hamilton, 1999) with the threshold being lower for untrained and elderly subjects (Meydani *et al.* 1993; Viguie *et al.* 1993; Fielding & Evans, 1997).

Antioxidant intervention is not likely to prevent muscle injury resulting from physical damage, but it could decrease the ability of free radicals to attack other sites within the cell (Warren *et al.* 1992; Sen, 1995). Ground-based studies with exercise suggest that giving supplemental dietary antioxidants may be of benefit.

Vitamin supplementation during and after exercise with vitamin E (Meydani *et al.* 1993; O'Neill *et al.* 1996) and vitamin C (Alessio & Goldfarb, 1988; Jakeman & Maxwell, 1993) decreases the urinary excretion of markers for oxidative damage. Vitamin E supplementation for 48 d accelerated recovery from downhill running-induced muscle damage (Cannon *et al.* 1990). Supplementation with a mixture of β-carotene, vitamins C and E for 5 weeks resulted in decreased malondialdehyde and breath pentane after exercise (Kanter *et al.* 1993) as well as protecting erythrocytes and skeletal muscle from exercise-induced damage (Witt *et al.* 1992). Several supplementation studies have focused on whether antioxidant vitamin supplementation can improve performance and have used athletes as test subjects (Packer, 1997; Sharpe, 1999; Takanami *et al.* 2000). A minority of studies, principally in the physically fit, found no benefit (biochemical or performance related), possibly because endogenous antioxidant levels were already high enough (Maxwell, 1995; Sen, 1995; Sharpe, 1999).

The benefits from antioxidant supplementation appear to be to the less fit individuals (Meydani *et al.* 1993; Goldfarb, 1999; Sharpe, 1999). The combination of muscle atrophy and nutritional depletion would place astronauts in this category. The space-flight situation is different from the ground-based exercise studies. In the latter case, concerns are directed towards performance, whereas for the astronauts, the concern is the potential for long-term damage.

Space food systems

The history of food for space flight has been a progression from foods designed to meet engineering-imposed constraints to the ISS diets which are similar to a Western diet, albeit with a heavy emphasis on prepared foods (Bourland, 1999). The first foods eaten in space were packaged in aluminium tubes and the astronaut or cosmonaut squeezed the contents of the tube into his/her mouth. Such packaging was convenient, simple, efficient, easy to sterilize and prevented food from getting loose in the cabin. The Apollo missions relied heavily on dehydrated foods; water was available from the fuel cells. In the early days of manned space flight there was a need to minimize urine and faeces production. There were no toilet systems until after the Apollo moon-landing missions. Astronauts and cosmonauts used diapers. Diets were low in fibre to reduce faecal output.

The primary limitation has been, and still is, the high cost of getting food and associated equipment (e.g. refrigerators, freezers, facilities for food preparation) into orbit. Launching mass into space is very expensive and will continue to be so for the near future. The current estimates of the costs of delivery of 1 kg to Mars is $11 000 (Zasypkin & Lee, 1999). Table 6 summarizes one estimate of the amount of food, water and O_2 that an astronaut requires together with the amount of waste products generated (Nelson, 1997).

One of the final steps in construction of the ISS (in about 2005) will be the addition of a habitat module that will contain a refrigerator and freezer for food as well as a microwave–convection oven for food preparation. There will be refrigerator–freezer capacity to support scientific research by early 2001. There has been no in-orbit freezer capacity for food since the Skylab missions, nearly 30 years ago. Until the addition of the habitat module, all food will be stored at ambient temperature. Table 7 shows the distribution of preservation processes that will be employed during the first few years of the space station (Bourland, 1999; Vodovotz *et al.* 1999).

The Russians pioneered the use of unmanned vehicles ('Progress') to resupply their MIR space station with fresh fruit and vegetables. This system will be used for the ISS. Fresh fruit,

Table 6. Estimated food and water requirements and waste generated by one astronaut*

	kg/d	kg/year
Inputs		
Food (dry)	0·6	219
Oxygen	0·9	329
Drinking water	1·8	657
Flush water	2·3	840
Subtotal	5·6	2045
Wash water	16·8	6135
Total	21·4	8180
By-products		
Water		
Urine in water, faeces	3·0	1095
Metabolic water	0·4	146
Perspiration	1·7	621
Wash–flush water	15·0	5843
Solids		
Faeces, urine, sweat solids	0·2	73
Gas		
CO_2	1·1	402
Total	21·4	8180

vegetables and other foods will be limited to what can be supplied by Russian Progress supply ships and visits from the space shuttle. Since it takes 2–3 d for either vehicle to reach the station, the choice of fruits and vegetables is limited to temperature-stable items such as apples, pears, oranges, lettuce, carrots etc.

Clearly the MIR–ISS model could not be used for a Mars mission. Two alternatives are under consideration. (1) Shipping a 3-year supply of food with the crew. The problems with this approach are the power costs for refrigeration, and, more importantly, the implications of failure for possible food loss. There is no such risk with foods that can be stored at ambient temperatures. (2) The crew only take enough food plus reserves for the outbound journey. The rest will be pre-positioned at the Mars landing site to await the arrival of the astronauts. Sending the food and other supplies separately in lighter unmanned vehicles is much cheaper.

Bioregenerative systems

On the shuttle, water is available as a by-product from the fuel cells. This is not a viable proposition for a long-term mission. The Russians have pioneered the recycling of urine and wash water using an evaporation system. The system on MIR recycles the water for washing but not drinking. Drinking water is brought up in the Progress supply vehicles. Initially a similar system will be used for the ISS. The water for food preparation and drinking will be supplied from the shuttle visits, all other water needs will be met from recycled water. Eventually this system will be replaced by a three-stage bioreactor using bacteria to breakdown the excreta, reverse osmosis to remove salts and a combination of photolysis and absorptive materials to remove the last traces of organics. Solid nitrogenous waste disposal is a problem since release into space would risk contamination of the optical equipment on the ISS. The current plan is to return it to earth on the shuttle.

At present and for the foreseeable future O_2 is not recycled; the CO_2 is trapped with alkali metal hydroxides and either brought back to earth or released into space, but there is some research on regenerating O_2 from CO_2 by Pt catalysis (with H_2 from water electrolysis to give CH_4 and O_2).

A short-term goal is to use recycled water to grow fresh salad vegetables hydroponically in space. The long-term goal, to develop the means of sustaining human life beyond earth, will require the ability to grow food, maintain a breathable atmosphere and recycle waste products with the only external input being energy, i.e. in ‘closed ecological life support systems’ (Fig. 11). Two useful resources are the reviews by NASA and Nelson (Nelson, 1997; National Aeronautics and Space Administration, 2000).

Table 7. Food preservation methods for the Space Station*

Process	Examples	% total food
Rehydratable	Freeze-dried (potatoes, shrimp)	25
Rehydratable beverages	All drinks (tea, coffee, fruit juice)	22
Thermostabilized	Pouches, canned foods	30
Radiation sterilized	Some meats	3
Natural state	Cookies, nuts, candies	10
Frozen–refrigerated†	Fruits, vegetables	20–25

* Data from Bourland (1999) and Vodovotz *et al.* (1999).

† Refrigerator–freezer capability will not be available until 2005–6.

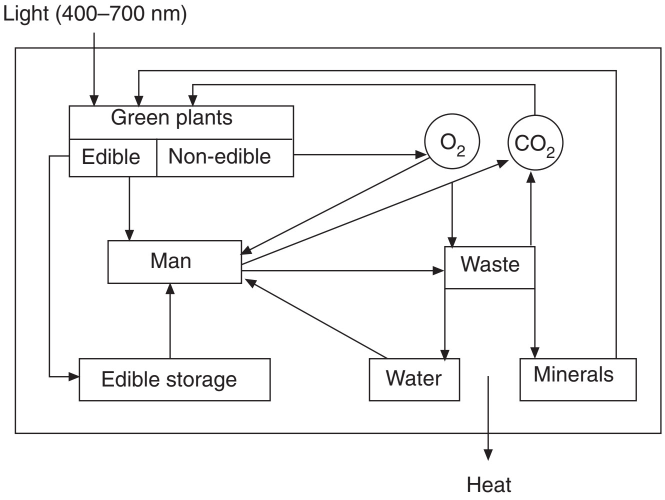

Fig. 11. Model of a bioregenerative life support system. Adapted from Mitchell (1994).

Both the Russians and NASA have invested heavily in developing methodologies to grow salads in space-like environments (Barta & Henninger, 1994; Nelson, 1997). However, current technology is limited to feasibility studies of growing ‘salad vegetables’, i.e. tomatoes, potatoes, carrots, lettuce, radishes, all of which grow well in hydroponic systems. The focus is on high crop density, rapid maturation, robustness and no requirement for processing (currently not feasible in a recycling environment).

Although the food energy contribution of salad vegetables to the diet is negligible, non-nutritive benefits are incurred, e.g. removal of CO_2 and generation of O_2 (Salisbury, 1999) and psychosocial benefits for the crew from growing edible crops.

The technology for bioregenerative facilities is currently not available and the ISS will not have any bioregenerative facilities. However, by the third mission to Mars, food production on the surface of Mars is planned: a simpler task than growing food in space without the constraint of weight and recycling and with construction of a climate-controlled greenhouse similar to that for human habitat. If the problem is solved for human habitation it will be a simple matter to adapt it for plant growth.

Concluding remarks

With the one notable exception of depressed food intake, all of the observed changes found with space flight are the expected normal physiological adaptations to the loss of gravity and not pathological. The problem is unusual, with no obvious physiological reason why absence of gravity should depress food intake and prevent energy balance and no obvious adaptive advantage. The most likely explanation is that of engineering-imposed environmental constraints. The low food intake is likely to have other adverse consequences, for example a low Ca intake. While the impact of reduced Ca intake in-flight on bone is uncertain, it is not likely to be benign given that on the ground poor Ca intake leads to accelerated bone loss in susceptible populations.

There is nothing unique about the nutritional requirements for space flight so that the healthy diet in space is a normal well-balanced diet with adequate fluids, as on earth. The main problem to solve is to get the astronauts to eat. There is no obvious solution to this as yet and neither the Americans nor the Russians have any intention of regulating dietary intake on the ISS.

The normal physiological adaptations to the new equilibrium state of space flight leave astronauts poorly adapted to respond to the reimposition of gravity, especially the musculo–skeletal system which has a slow response time and takes longer than expected (Tilton *et al.* 1980; Leblanc *et al.* 1990; Holick, 1999; Vico *et al.* 2000). Five years after spending 3 months in space, the Skylab astronauts still had not regained all of the bone lost in-flight (Tilton *et al.* 1980).

Countermeasures in space can either shift the equilibrium position away from adaptation to 0 ***g*** to an intermediate value (e.g. exercise for muscle), delay attainment of the equilibrium position (e.g. bisphosphonates for bone) or focus on accelerating the attainment of the new equilibrium position when shifting between gravitational levels (rehabilitation). All of these would decrease the time needed for recovery. Clearly, developing methods to hasten recovery from disuse atrophy would have great value within clinical medicine and the space-flight model provides the opportunity for such research, including nutritional support, possibly with antioxidants and amino acid supplementation.

A mystery is why after a period of environment-related nutritional depletion, voluntary food intake is not increased (Edholm, 1977; Stein *et al.* 1999*b*, 1999*c*). The phenomenon is not unique to space flight; it occurred after strenuous military activity in an environmentally stressful environment, for example the soldiers in Aden studied by Edholm (Table 8; Edholm *et al.* 1964; Edholm, 1977). The recovery process is not as glamorous as flight, but as space flights become progressively longer, the recovery process will increase in importance. A trip to Mars is impossible until full recovery can be assured.

Table 8. Voluntary energy intake drops during space flight or strenuous military activity in hot climate (Mean values with their standard errors)

Mission period	Intake control (kJ/kg per d)		Intake flight–stress (kJ/kg per d)		Intake recovery (kJ/kg per d)		Recovery of stress (%)		Recovery of control (%)		Reference
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Shuttle, SLS1/2*	163	10	144	13	165	8	88		101		Stein *et al.* (1996)
Shuttle, LMS*	155	9	102	10	151	13	66		97		Stein *et al.* (1999*c*)
MIR*	145	14	109	10	137	9	75		94		Stein *et al.* (1999*b*)
Military†	220‡	5	161§	6	210	7	73		95		Edholm (1977)
Mean							76	5	97	2	

* Space flight data.

† Strenuous military activity in cool and hot climates (Edholm, 1977).

‡ UK, cool.

§ Aden, hot.

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