Regulatory Physiology

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Chapter Overview

This chapter addresses some of the most important physiological functions regulating human adaptation to and survival in the space flight environment. A sizable amount of information has been accumulated since the flight of Gemini 7, which heralded the beginning of U.S. systematic collection of data revealing the medical consequences of human space flight. Specially developed technologies allowed NASA investigators to collect, preserve, and return biological samples for subsequent analysis on Earth. By the time of the Skylab missions, the laboratory technologies developed by NASA were mature enough to allow some investigations to be performed during flight. Spacelab and International Space Station missions have made additional capabilities available for in-flight sample collection and analysis. Among the first measurements performed during all phases of each space mission were those that pertained to body fluids and changes in their contents. Body fluids, electrolytes, and the endocrine system respond rapidly to space flight conditions and play a critical role in regulating the "milieu interior" and homeostasis in long-duration missions. The study of the beneficial effects of proper nutrition and neuro-endocrine system function on the regulation of fluids and renal function contributed to the simple but elegant countermeasures against the risk of renal stone formation in long-duration missions. A major risk for developing a potential "metabolic syndrome" and susceptibility to infections has not been fully resolved. This is especially true if combined with the increased and sustained radiation exposure levels during extended duration space missions).

Learning Objectives

1. Address the health implications of space flight impacts on the endocrine, fluid, electrolyte, and hematological systems.
2. Address the potential health risks of space flight and medical interventions to minimize risks.

Introduction

Weightlessness produces several changes in fluid and electrolyte balance. The cephalad shift of fluids initiates a series of compensatory mechanisms. Reduction of plasma and extracellular fluid volume is accompanied by decreased fluid intake and decreased circulating total protein. Glomerular filtration rate increases during short space flights. The renal stone-forming potentials of calcium oxalate and uric acid were found to be elevated immediately after space flights of 4–10 days, indicating a need to develop either dietary or pharmacological countermeasures (such as potassium citrate) to minimize these alterations. Some of the hormones involved in fluid and electrolyte regulation (Box 10.1) also are affected by physical and emotional stresses present during space flight, and the effects

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Box 10.1
Loss of electrolytes persists throughout flight, but restoration of fluid and electrolytes seems to begin immediately upon return to Earth's gravity.

of these and other factors may mask some of the predicted homeostatic responses. Weightlessness-induced changes in levels of hormones such as thyroxine, insulin, catecholamines, and cortisol may affect metabolism of protein, carbohydrates, and fats, thus helping to bring about loss of body mass.

Results from several investigations have suggested that space flight affects human hematologic function. This chapter describes changes observed before and after space flight in plasma volume and red blood cell mass, along with some of the implications of the resulting in-flight changes in iron stores.

Endocrine and Biochemical Functions

Exposure to the space flight environment produces a wide range of effects on body tissues and fluids (Table 10.1) [1–34]. Many of the changes observed in space crews during and after space flight are thought to be caused by the cephalad shift of fluids accompanying weightlessness, or by removal of the load from weight-bearing tissues. However,

Table 10.1 Summary of the metabolic and regulatory changes in short- and long-duration missions [1–34]

Parameter	Space flight changes	Clinical implications	Reference	Strength of evidence
Fluid and electrolyte	1. Reduced body fluid volume 2. Loss of electrolytes 3. Loss of sodium and water 4. Decreased total body mass (as a result of water loss)	Dehydration and orthostatic intolerance upon return from space missions	[1–12]	Robust
Plasma	1. Reduced plasma volume 2. Reduced plasma osmolality, sodium and chloride 3. Reduced plasma aldosterone 4. Changes in plasma angiotensim I 5. Decreased plasma cortisol	Post-flight orthostatic intolerance	[2, 6, 8, 11, 13–16]	Robust
Red cell mass	1. Decreased proportionally to plasma fluid reduction	Can produce an increase in body iron stores and increase the risk for hemosiderosis	[17–20]	Robust
Renal function	1. Risk	Incidence of bladder dystonia requiring catheterization None unless predisposition for renal calculi and possible infections	[21–23]	Good
Calcium regulation	1. Calcium loss 2. Increased bone resorption 3. Decreased bone formation	Risk of renal parenchymal and other soft tissue calcifications	[7, 24–28]	Robust
Renal stone risk	1. Elevated urinary calcium 2. Decreased urinary pH 3. Decreased urinary citrate level 4. Decreases in total urine volume and magnesium 5. Increases in urinary sulfate	In-flight renal calculus and UTI, can be incapacitating. One suspected episode in a long-duration mission. Mission was aborted after the renal colic subsided	[6, 11, 29–32]	Robust
Environmental stress and hormones	1. Elevated antidiuretic hormone 2. Reduced plasma aldosterone 3. Changes in plasma angiotensin I 4. Decreased plasma cortisol 5. Insulin-like growth factor I is unchanged 6. Decreased total cholesterol, HDL-C and LDL-C 7. No changes in testosterone or other reproductive hormones	Post flight orthostatic intolerance, dehydration. Long-term flights unlikely to increase the risks of dyslipidemia, cardiovascular and metabolic disorders. Use of oral contraceptives to suppress menstruation based on individual preferences. No evidence of reproductive disorders	[6, 14, 23, 24, 33, 34]	Good

Box 10.2
Measurement of endocrine and biochemical analytes typically requires collection and analysis of blood and urine samples. In space, lack of rapid laboratory equipment makes it imperative to freeze and store samples for further analysis on Earth. Two such simple systems are deployed on the ISS: the iSTAT (NASA) and the Reflotron developed by Roche (Russia). Only a few hematological and biochemical analyses are possible, and the shelf life of the reagent cartridges is limited to 6 months. These instruments provide useful information on time trends of Hbg, glucose, Ca, and electrolytes values.

Box 10.3
Many of the endocrine and biochemical changes observed in conjunction with space missions fit a consistent picture of homeostatic adjustments of circulatory dynamics, renal function, and endocrine response, probably initiated by fluid shifts and associated environmental stresses.

some of these changes, particularly hormonal ones, may be related to stress and other variables associated with space flight.

In most early space programs, samples were not acquired during space flight, but were obtained and studied before flight and as soon as possible (often within a few hours) after landing (Box 10.2). However, in-flight samples were obtained on one Gemini and one Apollo flight, the Skylab missions, and some Space Shuttle, Soyuz, Salyut, *Mir*, and International Space Station (ISS) flights.

Fluid and Electrolyte Regulation

Among the most significant changes accompanying space flight are those in body fluid volumes and regulation of electrolytes (Box 10.3) [1, 2, 33, 35]. The cephalad shift of fluids is thought to produce a transient increase in central blood volume that is detected by stretch receptors in the heart and interpreted as an increase in total blood volume [3, 4, 21]. A compensatory loss of water and sodium from the renal tubules is thought to be effected through a series of neural, humoral, and direct hydraulic mechanisms.

Physiologic mass measurements on Skylab documented rapid weight loss within the first few days in-flight, indicating that the weight loss was primarily fluid [5]. Most of this weight loss was regained rapidly after landing (Box 10.4) [6].

Box 10.4
The seven subjects on the Spacelab Life Sciences missions (SLS-1 and SLS-2) did not lose significant amounts of body mass or total body water [6]; the small changes that were observed were similar, again suggesting that weight loss on short-duration flights represents primarily fluid and not lean tissue.

Box 10.5
In the first days of flight, the decrease in plasma volume is proportionally larger than the decrease in extracellular fluid volume.

Small decreases in total body water have been measured during Space Shuttle flights. A decrease of 3.4 % occurred after 1–3 days of flight on STS-61C and STS-26 [36]. Data from ISS missions document similar changes in body mass (e.g., 3–4 % loss of body mass relative to pre-flight) [7], and also that crew members can consume enough energy to maintain mass on these long-duration missions [7, 37].

Extracellular fluid volume, which was reduced 2 % after the 28- to 84-day Skylab missions [8], had decreased 10 % after 24 h and 14 % after 8 days of flight on the SLS missions [6]. For the 3 SLS-2 crew members, extracellular fluid volume was reduced almost 18 % by flight day 12 [6]. At landing, extracellular fluid volume had returned to pre-flight levels. Similar effects were seen during and after 115 days of flight aboard *Mir* [9], and after long-duration Salyut missions [10].

Plasma volume, which normally is about one-fifth of extracellular fluid volume, was 17 % below its pre-flight level after 24 h of flight on the SLS missions and was restored slightly (to 10 % below pre-flight levels) on the eighth day of space flight (Box 10.5) [6]. At landing, the plasma volume was reduced, and by 6 days after landing plasma volume was at pre-flight levels [6]. In-flight plasma volume measurements have always been lower than pre-flight values, and post-flight measurements have generally been reduced as well [33].

This suggests that interstitial fluid volume (the other four-fifths of extracellular fluid) is initially conserved proportionally more than plasma volume, a situation that would be consistent with observed decreases in circulating total protein, specifically albumin [6]. This shift of protein, and associated oncotic pressure, from the intravascular to the extravascular space would facilitate the initial changes in plasma volume. After this initial adaptation, extracellular fluid volume decreases between the first days of flight and 8–12 days of flight, and plasma volume is partially restored in this same period. We hypothesize that excess extravascular albumin is metabolized in this period, and that the resulting

loss of oncotic forces results in these fluid volume changes (that is, decreased extracellular fluid volume, increased plasma volume). This loss of extracellular fluid protein (either intra- or extravascular), and associated decreased oncotic potential, probably plays a role in post-flight orthostatic intolerance. Reduced plasma volume upon landing has been thought to be a cause of post-flight orthostatic intolerance [13]. This loss of protein may explain why fluid loading alone does not restore circulatory volume, as there is no solute load to maintain the fluid volume.

The percentage of body mass represented by total body water remained about the same before, during, and after the SLS flights [6]. However, on a volume basis, the change in extracellular fluid volume was greater than the change (or lack of change) in total body water. Thus, by difference, intracellular fluid volume increased during space flight [6]. This had been previously hypothesized from ground-based studies [38]. The mechanism by which it occurs is unknown, and detailed study of the phenomenon has not been possible.

Usually, water intake is markedly reduced during the first few days of weightlessness [39], partly because of motion sickness symptoms and pharmacologic agents taken to prevent or ameliorate the symptoms [33]. The 9 Skylab crew members decreased their water intake by about 700 mL/day during their first 6 days in-flight [11]. Since their urine volume decreased by only 400 mL/day during the same period, a net loss of water occurred. Fluid intake during both SLS missions was about 1 L less than pre-flight intake, although this difference was not statistically significant [6].

Diuresis, which has been observed in weightlessness simulation studies [40], might be expected to contribute to fluid loss during space flight, especially in the first few days. Yet it has not usually been measured during space flight [1, 15, 41–48], probably for several reasons. Operational constraints have made accurate documentation of urine volumes difficult on the first day of space flight. In an experiment performed on a Shuttle flight during which urine was collected from one crew member for 5 to 26 h (with an in-flight average of 11 h), the rate of urinary fluid excretion was found to increase on the second day of the flight [12]. On two short-term Russian missions, urine volume decreased during flight [49, 50]. On the SLS missions, urine volume was significantly lower on the first 3 days of flight and tended to be lower than pre-flight volume throughout the flights [6]. On the 59- and 84-day Skylab flights [11], urine volume decreased during the first week and was unchanged from pre-flight levels for the remainder of each mission.

Plasma osmolality, sodium, and chloride were reduced at almost all measurement times during the Skylab flights (Box 10.6) [11]. The mean amounts of reduction were as great as 4% for osmolality and 6% for sodium. Serum sodium was reduced by as much as 4% in crew members on Spacelab flights lasting up to 10 days [2, 6, 51]. Studies of venous blood serum or plasma samples [6, 33] or finger-stick blood samples [52] showed no change in sodium concentrations. Blood potassium concentrations were more variable but generally increased [1, 6, 11, 14]. Blood potassium concentrations were increased during flight when measured in finger-stick samples [52], but this was thought to be a collection artifact. In the same study, blood potassium concentrations were reduced at landing and 3 days thereafter.

Box 10.6
A decrease in the amount of any body fluid must be accompanied by losses of electrolytes from the affected fluid compartment or compartments. Such losses often have reached the point at which blood concentrations of electrolytes have been diminished during flight.

Electrolytes are lost mainly through renal excretion. Increases in urinary output of sodium, potassium, and chloride were observed during the Skylab flights [11], and increased rates of potassium and calcium excretion occurred early in the Shuttle mission on which urine was collected during flight [12] (see Fig. 10.1). Urinary electrolytes were variable during the two SLS flights. Sodium, potassium, and chloride excretion tended to be increased during the SLS-2 flight, whereas sodium and chloride were unchanged on SLS-1, with decreased urinary potassium excretion [6]. In the second and third months of long-term missions on Salyut-7, however, urinary excretion of total osmotically active substances and most electrolytes decreased (Box 10.7) [53, 54]. Drummer, Heer, and others have also documented similar changes in fluid and sodium metabolism during space flight [15, 42, 45, 55], and have proposed that storage of sodium non-osmotically may contribute to the adaptive responses to space flight [56].

Return to gravity induces many changes that must be distinguished from remnants of the effects of weightlessness. Moreover, the ingestion of saline solutions by astronauts [57] and cosmonauts [58] before landing to reduce orthostatic intolerance complicates interpretation of data from samples obtained after landing. Results of analysis of post-flight samples from Space Shuttle astronauts include increases in urine osmolality and decreases in urine volume, sodium, potassium, and chloride [6, 12, 59, 60]. The findings were not significantly different for crew members who used the saline ingestion countermeasure [60]. These results and those of Skylab studies [11] led to the conclusion that fluid and electrolyte retention begins very soon after return to gravity [59]. Fluid and sodium retention also were consistent findings in cosmonauts for the first 24 h after flights lasting from 2 to 366 days, but excretion of potassium and calcium was sometimes found to increase [1, 61]. Urine volume and urinary sodium, potassium, and chloride were below

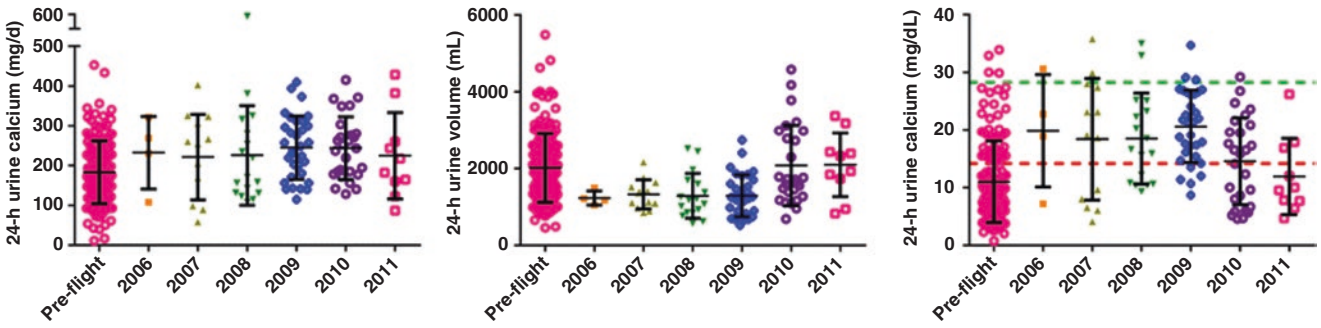

Fig. 10.1 Urinary calcium excretion (*left*), urine volume (*middle*), and urinary calcium concentration (*right*) before and during flight, by year of collection on the ISS. Each symbol represents a 24-h urine collection; 23 crew members may have each provided up to five 24-h collections during flight, and at least four before flight. Within data sets, the *horizontal lines* represent the mean ± 1 SD. The *green dashed line* in the *right panel* represents a calcium concentration of 28.3 mg/dL, the expected calcium precipitation point for Urine Processor Assembly (UPA) water recovery at 70 %, and the *red dashed line* represents calcium concentrations of 14.2 mg/dL, the expected calcium precipitation point for UPA water recovery at 85 %. A subset of these data, in a different form, have been published, along with details of urine collection procedures [37]. Reprinted under Creative Commons license from Smith SM, McCoy T, Gazda D, Morgan JLL, Heer M, Zwart SR. Space flight calcium: implications for astronaut health, spacecraft operations, and Earth. Nutrients. 2012;4:2047–68. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3546622/, Creative Commons license http://creativecommons.org/licenses/by/3.0/

Box 10.7
In the eighth month of a 237-day flight, results for urinary excretion of fluid, electrolytes, and osmotically active substances obtained from two cosmonauts were very different from each other [54].

Box 10.8
The best way to examine the state of the endocrine system during a period of rapid change would be to obtain many blood samples each day, but this is generally not possible under space flight conditions.

pre-flight levels for 3–5 days after *Mir* flights lasting up to 366 days [1, 58, 62].

Results for different flights have varied considerably for some hormones. Urinalysis has the advantage of being noninvasive and covering longer periods than blood samples, but urinary concentrations may not reflect the secretion rates or circulating levels of a hormone (Box 10.8). Other factors specific to a mission or program also may make interpretation difficult.

During the Spacelab flights, plasma concentrations of antidiuretic hormone (ADH) increased between 5 and 24 h after launch, and plasma ADH remained at least 100 % above pre-flight levels until more than 5 days after launch [6, 14]. The plasma ADH of SLS crew members was slightly lower than pre-flight values 7 days after launch [6, 33]. On the 25-day Aragatz flight on the *Mir* space station, plasma ADH in one subject was elevated more than fivefold after 9 days and almost tenfold after 20 days of flight, but these large increases were attributed to the high ambient temperature on the spacecraft [33, 50]. Plasma ADH was above pre-flight levels near the end of a 241-day *Mir* flight [1] but was below pre-flight levels in 3 cosmonauts on days 217–219 of the 237-day Salyut-7 mission [63]. Plasma ADH was decreased in 3 subjects near the end of a 115-day *Mir* flight [9]. Because plasma volume has almost always been reduced after space flights of up to 84 days, elevated circulating concentrations of ADH apparently do not produce their usual (1-*g*) effect of increasing plasma volume to its normal value [1]; however, if diuresis does not occur, this hormone may effectively contribute to fluid retention.

Urinary ADH decreased during the Skylab missions [11], the Salyut-7 flight [64], and the 115-day *Mir*-18 mission [9], but it increased at least 100 % toward the end of the 237-day flight [63]. The latter finding was attributed to decreased sensitivity of ADH receptors in the kidney. During Space Shuttle flights, the rate of ADH excretion increased during the first 24 h of flight and then returned to pre-flight levels [6, 12]. Because stimulation of the emetic reflex as a result of space motion sickness may cause a centrally induced increase in ADH secretion, caution is necessary in interpreting this finding as a peripheral effect of fluid transfer.

Plasma aldosterone in Space Shuttle astronauts was reduced 20 % or more at most sampling times during flight [6, 14]. On the Skylab missions, a great deal of individual variation occurred at some measurement points [11]. During the first month of flight, aldosterone usually was elevated, but from 30 to 48 days it was reduced, and after that seemed to stabilize around its pre-flight level. This was also seen on short-duration *Mir* flights [15]. These data seem to reflect dynamic changes that are initiated within hours of the onset

of weightlessness and continue for 30 days. The changes in aldosterone probably represent the response of the body to sodium loss. Plasma aldosterone had decreased 33 % near the end of a 115-day *Mir* flight [65]. In the eighth month of the 237-day Salyut-7 flight, plasma aldosterone increased in two cosmonauts and decreased in another [1, 54]. Urine was collected by two of these cosmonauts during the same period, and urinary excretion of aldosterone was above pre-flight levels on the first 2 days of collection and below pre-flight levels on the third day. The increases in urinary aldosterone were thought to have been related to increased salt consumption. A decrease in the rate of 11-desoxycorticosterone excretion and increase in plasma renin activity [33, 53] were considered to indicate that secretion of aldosterone had increased. Urinary excretion of aldosterone has generally increased during space flight [11, 64, 66].

Plasma renin activity, an indicator of angiotensin I levels, decreased during the first 48 h of Space Shuttle flights and then increased to above pre-flight levels [6, 14]. During Skylab flights, it was elevated at most measurement times, with the greatest variability occurring in the first 30 days [11]. After that time, plasma angiotensin I was elevated at all sampling times on the Skylab missions. It also was elevated during the eighth month of the 237-day Salyut 7 mission [16], and on *Mir* missions [15].

Plasma atrial natriuretic peptide was reduced at most sampling times in the first 190 h of two Spacelab flights, but mean values were above pre-flight levels between 30 and 40 h [67]. Throughout the SLS missions [6], STS-60 [68], and short (15-day) [15] and long (115-day) *Mir* flights [65], levels of atrial natriuretic peptide were lower than pre-flight levels. The decrease in atrial natriuretic peptide [6] may be associated with the decrease in central venous pressure observed on Spacelab [69] and SLS [70] missions.

During Skylab [11], Shuttle [6, 14, 67, 68, 71], and ISS flights [34], plasma cortisol levels were usually, but not always, higher than pre-flight levels. In the eighth month of the 237-day Salyut-7 mission, plasma cortisol was elevated [54]; near the end of a 241-day *Mir* mission, though, plasma cortisol was no different from pre-flight levels [1]. Adrenocorticotropic hormone (ACTH) decreased at various times during Skylab flights [11], but on Spacelab and SLS flights it either increased or remained at pre-flight levels [6, 14, 71]. Urinary cortisol increased during Skylab missions [11] and was generally increased on Shuttle missions [33]. On some flights, the rate of cortisol excretion returned to pre-flight levels after the first day [6, 12]. Near the end of the 237-day Salyut mission, urinary cortisol was generally below pre-flight levels for two cosmonauts [54].

Post-flight hormone levels often differ from those measured during flight, and many seem to be associated with fluid and electrolyte retention in response to the return of gravity-induced hydrostatic pressure gradients (Box 10.9). These hormone measurements are often confounded by varying amounts of time, crew activity, and use of fluid-altering countermeasures before sample collection.

Box 10.9
Elevated plasma and urinary cortisol during space flight have been considered an indication of stress, but cortisol, like aldosterone, promotes sodium retention and potassium excretion.

After long-term Salyut-7 [54] and *Mir* [1, 61, 63] missions, plasma ADH was elevated. Urinary ADH did not change significantly after the Skylab missions; this observation was considered to demonstrate that the decrease in water clearance indicated by decreased urine volume at landing was a result of decreased renal blood flow rather than a need for water conservation [11]. However, when the change in urinary ADH from pre-flight to landing day was compared for Space Shuttle astronauts who did or did not use the fluid and salt loading countermeasure before landing, ADH of four crew members who did not use the countermeasure decreased 16 % and ADH of 25 crew members who did use it increased 44 % [60]. Urine volume was reduced more for crew members who used the countermeasure than for those who did not.

Plasma levels of aldosterone increased after Skylab [11] and Space Shuttle [6, 59, 72] flights and after short [73] and some long [54] Russian flights. After most long-term Salyut flights, however, plasma aldosterone decreased [74]. After long-term flight on *Mir*, plasma aldosterone was elevated, but sometimes not until a week after landing [1, 62]. Post-flight increases in urinary aldosterone have been consistent, indicating a need for sodium conservation [1, 10, 11, 59, 75]. Post-flight changes in plasma renin have varied considerably; angiotensin I was elevated after the Apollo-Soyuz Test Project and Space Shuttle and short Salyut flights [6, 59, 72, 73, 75], but it was reduced after longer? (as opposed to short in the line above) Salyut flights [10] and remained stable after Skylab flights on which G suits were worn to maintain blood pressure while the astronauts were in the upright position. Plasma cortisol levels increased after short-term Soyuz flights [76] but decreased 3 % after 2- to 11-day Shuttle flights [72] and 27 % after Apollo flights [77], and did not change after the Apollo-Soyuz Test Project [75], Skylab [11], or long-term Salyut flights [10]. Urinary cortisol levels, like those of aldosterone, generally have been found to increase after landing [6, 11, 60, 63, 64, 77] in response to the return to gravity. Plasma atrial natriuretic peptide is reduced after flight [6, 9, 67], as might be expected when blood volume is reduced [19]. Blood levels of pressor prostaglandins are decreased after landing whereas those of depressor prostaglandins are increased [1, 19, 62, 78].

Some of the endocrine changes observed during and after space flight are not the responses that might be expected. For example, concentrations of aldosterone and angiotensin I

often did not change in the same direction during flight [1, 11, 33]. ADH concentrations were elevated greatly in plasma at many sampling times during short flights [1, 11, 33]. The immediate elevation of plasma ADH at landing along with a sometimes delayed rise in blood aldosterone has been considered to indicate that body fluid is replenished more rapidly than blood sodium [62]. In certain patients with hyponatremia, a reduction in effective arterial blood volume was considered to cause nonosmotic stimulation of ADH secretion [79], and such a reduction may occur at landing after space flight (Box 10.10). Maintenance of fluid volume in the circulatory system is a necessity. Aldosterone's function as a sodium-retaining hormone may have been subordinated to its function as a regulator of serum potassium. Although potassium was being lost from tissue on the long-term Skylab flights, as indicated by significant increases in urinary potassium, blood potassium levels were usually slightly elevated [11].

In general, the body fluid and endocrine alterations during space flight are thought to represent adaptive responses to weightlessness [80]. Adaptation may require different amounts of time for different systems; the first 4–6 weeks seems to be a time of particularly dynamic change.

Water and electrolyte replenishment has been useful as a countermeasure against the loss of fluid and electrolytes induced by space flight [13, 81]. Lower body negative pressure also has been used successfully by cosmonauts before deorbit to relieve problems caused by fluid redistribution [82] (Box 10.11) [6, 42–45, 55, 83].

Box 10.10
The tendency of blood sodium and osmolality to be reduced at these times indicates that reduced plasma volume rather than elevated blood osmotic concentration is the effective stimulus for ADH secretion.

Renal Function

Creatinine clearance has been used as an estimate of glomerular filtration rate during space flight. Measurement of creatinine clearance from in-flight Skylab and ISS samples indicated that glomerular filtration rate increased slightly during flight [21, 22] (Fig. 10.2). Free water clearance, which indicates the responsiveness of the kidney collecting-duct epithelium to ADH, was slightly decreased during flight relative to pre-flight clearance [21]. Together with the Skylab astronauts' decreased ADH excretion, this finding may reflect increased sensitivity of the renal tubule to ADH [84]. Increased reabsorption of water might be related to increased glomerular filtration rate.

Renal function was investigated directly before, during, and after space flight for the first time on the SLS missions

Box 10.11
Because space flight also is associated with events such as emotional stress, space motion sickness, variable medication usage, gravity loads (launch and landing), and altered work/rest cycles, the simultaneous adjustment of many physiological variables may mask or negate certain predicted homeostatic responses to fluid shifts and electrolyte loss. The space flight data to date clearly document that bed rest is not a good model for changes in fluid and electrolyte homeostasis [6, 42–45, 55, 83].

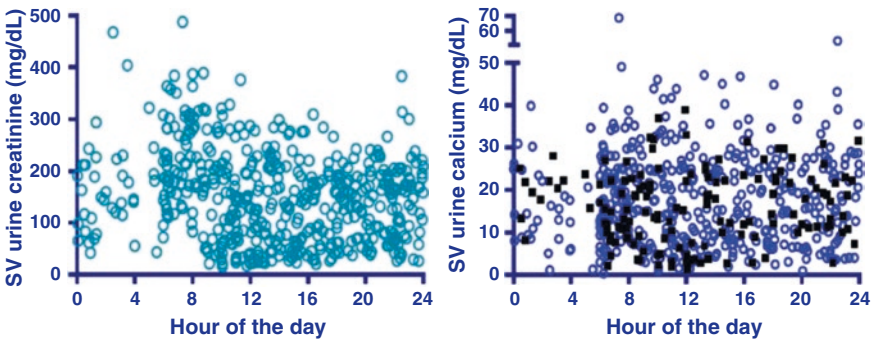

Fig. 10.2 Creatinine (*left panel*) and calcium (*right panel*) concentration in single-void (SV) urine samples, by time of day when samples were collected. Some ISS crew members were participating in an experiment on bisphosphonate (alendronate) use as a bone loss countermeasure. These data are shown with *filled symbols*, but did not have a significant effect on calcium concentration. Reprinted under Creative Commons license from Smith SM, McCoy T, Gazda D, Morgan JLL, Heer M, Zwart SR. Space flight calcium: implications for astronaut health, spacecraft operations, and Earth. Nutrients. 2012;4:2047–68. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3546622/, Creative Commons license http://creativecommons.org/licenses/by/3.0/

Box 10.12
Results of water and salt loading tests of cosmonauts have indicated that renal function is altered by space flight and undergoes a period of readaptation after return to 1 *g*.

(Box 10.12). Glomerular filtration rate, as measured by clearance of Inutest, had increased by 17 % after 1–2 days of flight and by 19 % after 8 days of flight (n = 6) [6]. On landing day, it had returned to near pre-flight levels. Para-aminohippurate clearance, used to measure effective renal plasma flow, was highly variable on the first day of flight but was above pre-flight levels on flight day 8. Renal plasma flow remained above pre-flight levels through 6 days after the flight. Because angiotensin I was elevated 120 % on flight day 8, when glomerular filtration rate was greatest, constriction of efferent arterioles in the renal cortex was thought to be a possible cause of the increase in glomerular filtration rate at that time [6]. Angiotensin I and aldosterone were at their highest measured concentrations on landing day, when effective renal plasma flow was greatest. Serum uric acid decreased and blood urea nitrogen increased after Apollo, Skylab, and Shuttle flights [11, 59, 85]; these findings may indicate a change in renal function as well as changes in tissue. Despite evidence documenting increased glomerular filtration rate, urinary albumin concentrations have been shown to be decreased during flight [86], and thus there is not simply an increased flux of constituents into the urine.

Reduction in the urinary excretion of water during water loading tests was considered to suggest that reabsorption of water by the kidney tubules increases after space flights of up to 30 days duration [87, 88]. After long-term flights, the ability of the kidney to concentrate urine [89] and to reabsorb sodium [90], calcium, and magnesium [89] seemed to be impaired. Results of potassium loading tests indicated that after exposure to weightlessness for 13 days or more, tissues do not retain potassium normally [89].

Regulation of Blood Calcium

Loss of bone and increases in urinary calcium have been observed after most long duration space flights (i.e., those lasting more than 30 days) [91–97]. These findings appear related to increased bone resorption [7, 24–27] and unchanged or decreased bone formation [24–27, 98] (Fig. 10.3). Many reviews have been written on this topic [32, 96, 99–109].

Calcium balance studies showed that at least 200 mg of calcium was lost per day of flight by Skylab astronauts [28]. Tracer

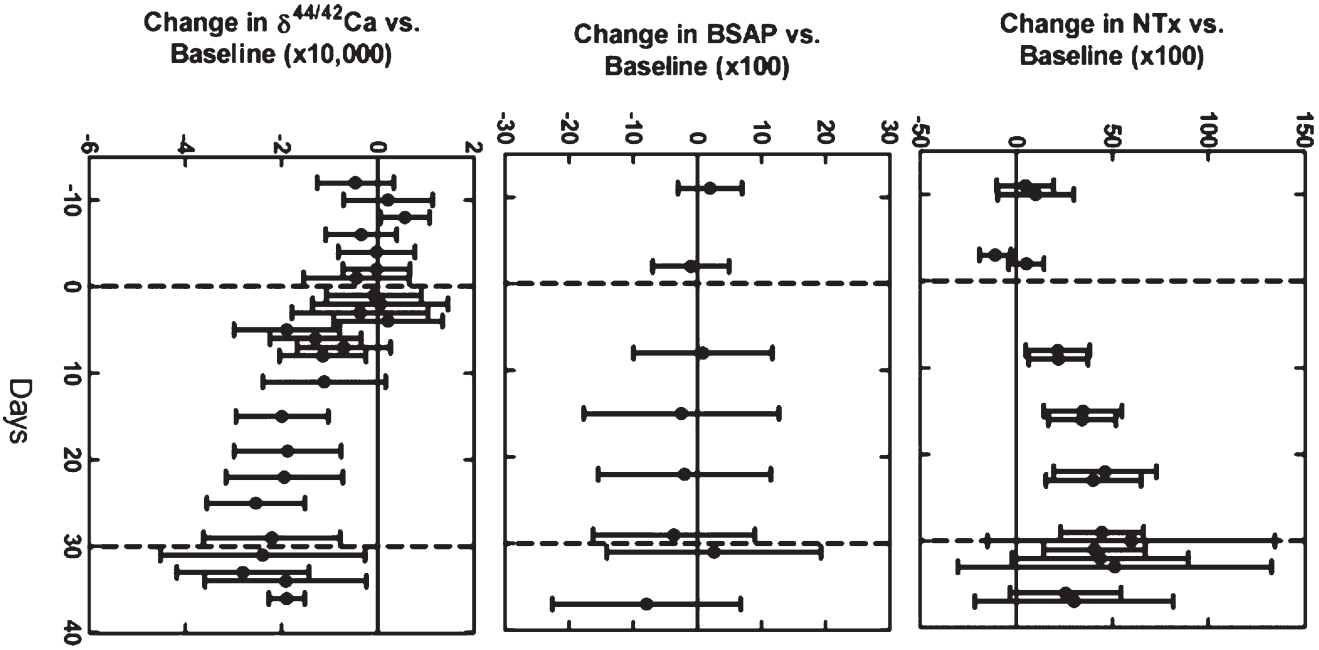

Fig. 10.3 Variations in bone biochemical markers *N*-telopeptide (NTX, *right panel*) and bone-specific alkaline phosphatase (BSAP, *middle panel*), along with calcium isotopes (*left panel*), before, during and after bed rest (days 0–40). Percent changes were calculated as the difference between the measured value at each time point and the average of the pre-bed rest values (baseline, days above day 0) for that individual. All values are mean ± SD. The calcium isotopes shift in a direction consistent with bone loss after just 7 days of bed rest and track the signal observed in NTX while BSAP remains unchanged. Original data are from 12 subjects [98]. Reprinted under Creative Commons license from Smith SM, McCoy T, Gazda D, Morgan JLL, Heer M, Zwart SR. Space flight calcium: implications for astronaut health, spacecraft operations, and Earth. Nutrients. 2012;4:2047–68. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3546622/, Creative Commons license http://creativecommons.org/licenses/by/3.0/

Box 10.13
The precise cause of bone mineral loss during weightlessness is not known, but several hormones known to influence bone remodeling have been found to change at different times during weightlessness.

Box 10.14
During head-down bed rest, plasma proteins showed a decreased ability to bind ionized calcium; and in cosmonauts, calcium absorption in the intestines and reabsorption in the kidneys decreased.

kinetic studies in 6 subjects aboard *Mir* also demonstrated bone calcium losses exceeding 200 mg/day [27, 110]. Since urinary calcium and collagen cross-link excretion continued to increase during the first 30 days of Skylab flights, and fecal calcium excretion increased throughout the missions despite constant dietary intake of calcium, calcium losses were thought to result from losses of bone mineral [24, 111]. Phosphorus balance also was consistent with increased bone resorption [111].

An increase in serum calcium and decrease in plasma albumin throughout the Skylab flights indicated that ionized calcium increased but bound calcium decreased in the blood [21]. During the first week of flight, ionized calcium concentrations were lower than pre-flight levels in 21 Shuttle crew members [52]; ionized calcium was increased 5–10 % above pre-flight levels on long flights [110]. Pre-flight and post-flight total serum calcium values for 133 astronauts on Shuttle flights of 2–11 days (average duration, about 6 days) were not different [72]. Blood collections during space flight revealed no differences in serum calcium concentrations relative to before flight (Box 10.13) [37].

No change in plasma levels of parathyroid hormone (PTH), which stimulates bone calcium resorption, was found during or after Skylab missions [11] or after 7-day flights [112]. Spacelab studies did show a significant (34 %) decrease [113] during flight, as did studies of one [26] and six [27, 110] subjects on *Mir* flights. PTH concentrations decreased during flight for ISS crews, but not in those who were well nourished (i.e., adequate energy intake and vitamin D status) and had access to an advanced resistance exercise device [37].

Post-flight findings suggest that the readaptation to 1 *g* begins quite rapidly. On the day after landing of 150-, 211-, and 237-day Russian flights, however, PTH was elevated more than 2-fold [112]. Serum PTH concentrations were above pre-flight levels within hours of landing after a 115-day *Mir* mission [110]. Calcitonin had increased 45 % by the day after landing of 7-day Shuttle flights but decreased (for some cosmonauts, to undetectable levels) after three long-term flights. Gastrin was elevated 44 % after 7-day Shuttle flights and threefold after the long-term flights. During and after *Mir* and early ISS missions, 25-hydroxyvitamin D concentrations decreased [7, 27, 110], probably as a result of decreased exposure to ultraviolet light [109]. Concentrations of 1,25-dihydroxyvitamin D also decreased during the *Mir* and ISS missions, likely because of decreased PTH-stimulated hydroxylation in the kidney [27, 37, 110, 114]. High levels of cortisol, which was increased in plasma and urine during Skylab [11] and Space Shuttle [6] missions, have been reported to cause bone mineral loss and negative calcium balance in humans [115] and may contribute to the changes in calcium regulation in space flight (Box 10.14) [1, 116].

Oganov [96] has proposed that changes in fluid and electrolyte regulation contribute to activation of bone resorption. Activity of the renin-angiotensin-aldosterone system, which participates in regulation of fluid and electrolytes, is inhibited in weightlessness [6, 14]. Rat hindlimb suspension studies have indicated that the rate of fluid movement in the endosteal canaliculi and the osteocytic lacunae of cortical femoral bone decreased during suspension [96]. The redistribution of body fluid may perturb tissue calcium flows in organs such as intestine, kidneys, and blood [96], and this perturbation may result in a decrease in the amount of calcium stored in the body. According to Oganov's hypothesis, these changes in calcium distribution are related to the redistribution of body fluid. Excessive excretion of calcium, resulting from lack of calcium absorption, may deplete blood calcium so that PTH secretion increases and calcium is mobilized from bone by the actions of osteoclasts and perhaps osteocytes and even osteoblasts to reabsorb bone mineral, stimulate the synthesis of collagenase, and perform other resorption-related functions. Ultrastructural analysis of bone from monkeys on the Bion II biosatellite provided evidence that resorption of bone by osteocytes was activated during space flight.

Renal Stone Risk

Some of the physiological changes induced by space flight increase the potential for renal stone formation [8, 117–119]. Pre-flight and post-flight assessments of 86 crew members who participated in Space Shuttle flights lasting 4–10 days were compared to determine whether stone-forming potential was increased immediately after space flight [29] (Box 10.15).

For in-flight assessments of risk, six male astronauts collected urine early (flight days 2–4) and late (flight days 10–13) during Space Shuttle flights ranging from 11 to 16 days [30]. The effects of long (>100 days) flight on renal stone-forming potential were also examined during the Shuttle-*Mir* flights [31]. Metabolic risk factors that were

Box 10.15
Urinary risk factors have been assessed in astronauts and cosmonauts before, during, and after both short and long space flights.

Box 10.16
Uric acid crystals often act as a nidus for calcium stone formation. Hence, the decreased pH and the resulting diminished solubility of uric acid contribute to an increased risk of renal stone formation after space flight.

examined included urinary calcium, oxalate, uric acid, citrate, and pH, and environmental risk factors included total urine volume and urinary sodium, sulfate, phosphorus, and magnesium. From these data, the physicochemical risk of stone formation after space flight was calculated by using a computer program by Finlayson [120].

Urinary calcium was significantly higher on landing day (relative to before flight) immediately after short flights [29, 31]. Urinary calcium of all 6 crew members increased despite their lesser consumption of calcium during flight. Urinary calcium excretion after long flights was also greater than pre-flight values [31]. Hypercalciuria has been associated with calcium nephrolithiasis as early as 1939 [121]; hypercalciuria was noted during space flight and immediately after landing in Skylab astronauts [11, 28], as well as during and immediately after bed rest [122]. Thus, hypercalciuria is an important risk factor for the formation of renal stones by crew members during and immediately after space flight. A study of 30 *Mir* and ISS crew members documented the ability of potassium citrate to reduce urinary calcium, increase urine pH, and thus mitigate associated renal stone risk [123].

Urinary pH values were decreased after short space flights [29, 30] (Box 10.16). After long flights, urinary pH changes were varied, with some crew members having similar decreases [31]. The varied responses after the long flights may be related to readaptation effects after landing on either Space Shuttle (flights returning crew members from *Mir*) or Soyuz vehicles, or may also reflect differences in dietary habits between astronauts and cosmonauts. Potassium citrate has been shown to increase urine pH (and thus decrease renal stone risk) [123]. Dietary means to accomplish the same thing have been proposed on the basis of bed rest data [124–126], and in-flight testing is currently underway.

On landing day after short space flights, urinary citrate was significantly lower than pre-flight values [29]. During short Space Shuttle flights, urinary citrate levels tended to decrease early in-flight and remain lower than pre-flight levels throughout the flight and on landing day [30]. Preliminary results from nine crew members on long missions were similar to in-flight results from Space Shuttle crew members on short missions [31]. Urinary citrate tended to be lower during flight for seven of these nine crew members. The decrease in these crew members' urinary citrate further complicates the possible effects of the increase in urinary calcium, because citrate, an inhibitor of stone formation, acts by complexing with calcium, thereby decreasing the calcium available for crystal growth and aggregation [127].

Box 10.17
Magnesium acts as an inhibitor of stone formation by complexing with oxalate, decreasing the amount of oxalate available to form calcium oxalate stones.

An increase in the renal stone-forming potential was also indicated by decreases in total urine volume and magnesium (Box 10.17), and increases in urinary sulfate. The latter increases stone-forming potential by decreasing pH and reabsorption of calcium in the renal tubule.

Skylab crew members excreted more magnesium during flight than before, but these values dropped markedly upon return to Earth [11]. The Skylab data suggest that changes in magnesium probably do not contribute significantly to renal stone risk during flight. During short flights, magnesium did not increase significantly, but mean urinary levels were 24 % lower on landing day than before flight [30, 119]. At landing after long flights aboard *Mir* and ISS, urinary magnesium was significantly lower than it was before flight [7, 109, 128].

The most significant environmental factor in renal stone risk is urine volume. Earth-based studies of people with renal stones have shown that increasing the urine output to more than 2 L/day minimizes the risk of forming stones. The decreases in urine volume observed after Space Shuttle flights [6, 30] and during Skylab [11] and ISS missions [32] contributed to an increase in stone-forming risk by concentrating the precipitable salts. Average fluid intake on Space Shuttle flights and on long flights aboard *Mir* was significantly decreased, producing urine volumes that were about 47 and 30 % less, respectively, than before flight, despite instruction regarding the benefits of increasing fluid intake to increase urine volume. ISS crews also had less fluid intake and urine volume during flight, although since calcium precipitation was discovered to interfere with the urine processing (water reclamation) system [32], fluid intakes have tended to be greater (Fig. 10.4).

Reduced amounts of inhibitory compounds and the relative increase in amounts of stone-forming salts in pooled post-flight samples from Space Shuttle crew members combined to produce an increased physicochemical risk of forming calcium oxalate and uric acid stones immediately after space flight (Box 10.18). Although these data were

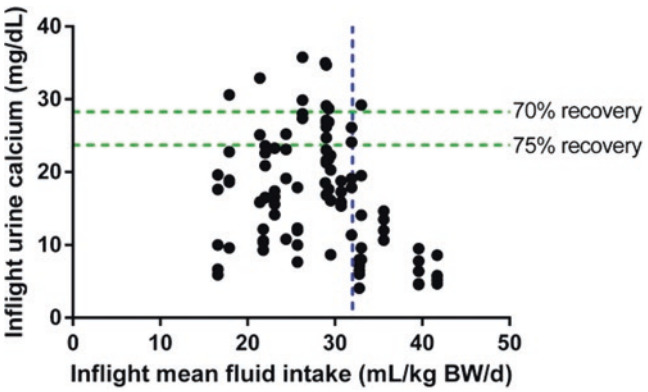

Fig. 10.4 In-flight fluid intake and associated in-flight urinary calcium concentration of crew members on the ISS. Each symbol represents a 24-h urine collection; individual crew members may have provided up to five 24-h collections during flight, and at least four before flight. *Dashed horizontal lines* reflect urinary calcium concentrations above which calcium precipitation would be expected for Urine Processor Assembly water recoveries at 70 and 75 %. Reprinted under Creative Commons license from Smith SM, McCoy T, Gazda D, Morgan JLL, Heer M, Zwart SR. Space flight calcium: implications for astronaut health, spacecraft operations, and Earth. Nutrients. 2012;4:2047–68. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3546622/, Creative Commons license http://creativecommons.org/licenses/by/3.0/

Box 10.18
The risk of calcium oxalate stone formation after long missions remained elevated for 2 weeks after landing; however, after short missions, this risk factor returned to pre-flight levels about 1 week after landing.

influenced by recovery from microgravity, data from a bed rest study [122] and from Skylab flights [11] suggested that stone-forming risk may be even greater during flight than at landing. The post-flight data from short Space Shuttle flights (4–10 days) suggested that flight duration may affect the risk of forming calcium oxalate stones [29]. In contrast to the study involving post-flight urine collection (in which brushite risk was not increased) [29], brushite supersaturation was significantly increased during both Space Shuttle and *Mir* space missions [31], indicating a significant increase in the risk of stone formation from calcium salts during space flight.

In summary, crew members exposed to the microgravity environment of space flight undergo many physiological changes that affect stone-forming potential. Increased urinary calcium and decreased urine volume and citrate levels favor the crystallization of stone-forming salts, increasing the risk of renal stone formation. The increased risk begins early and continues throughout the flight and after landing. Results from ground-based clinical studies and flight studies indicate that increasing fluid intake to increase urinary output may prove beneficial in reducing the risk of renal stone development (Box 10.19).

Box 10.19
However, increasing urine volume alone will not affect the elevated calcium excretion or alter the hypocitraturia observed in crew members exposed to microgravity.

Box 10.20
Possible in-flight stressors include launch, weightlessness itself, motion sickness, physical activity, lack of privacy, and noise.

Studies now underway include assessments of the risk of renal stone formation during long missions, the effects of space flight on inhibitors of renal stone urinary proteins (Tamm-Horsfall protein and uropontin), and whether ingesting potassium citrate will increase urinary citrate levels and normalize urinary pH values during and immediately after space flight.

Stress

Biochemical indicators of stress confirm what would be expected: that space flight is a stress-inducing condition and the body responds in some of the same ways as it does to other stressors (Box 10.20). It is important to distinguish between responses associated with weightlessness and those associated with landing. The variable *g* loads experienced during atmospheric entry and the physical stress of the return to a 1-*g* environment are probably the most important stressors at mission conclusion.

Concentrations of "stress hormones" measured during flight have been variable, seemingly depending on flight duration, physical activity, and undefined factors. Plasma levels of growth hormone were increased significantly in Skylab crew members after 3 or 4 days of flight but not at any other time, and plasma cortisol levels were increased significantly after 5, 58, and 82 days [11]. Bioassayable growth hormone levels were lower during flight, and the response to exercise was blunted during flight, in 4 astronauts on the STS-78 mission [129]. Plasma and urinary cortisol concentrations are usually elevated during space flight (see discussion under "Fluid and Electrolyte Regulation"). A peak of urinary cortisol excretion followed a peak of ADH excretion (possibly associated with motion sickness) for one Shuttle astronaut in the first 2 days of flight [12].

Cortisol exists in the body in an unbound form and in a form that is bound to corticosteroid-binding globulin (CBG)

[130]. Only the unbound form is biologically active. "Plasma cortisol" generally includes the unbound and bound fractions of cortisol, and urinary cortisol is generally unbound cortisol. Acute stressors suppress the binding of cortisol to CBG [130]. If the stress of space flight suppresses this binding, urinary cortisol could be increased after space missions while plasma (total) cortisol does not change, and the amount of stress, or perhaps an individual's response to stress, could affect the amount of bound cortisol.

Urinary norepinephrine excretion was decreased or unchanged during the two SLS flights [6]. Urinary epinephrine and norepinephrine were consistently decreased during all three Skylab flights [84]. Elevation of epinephrine and norepinephrine at different times during the 25-day Aragatz mission on *Mir* [131] and results of measurements of blood and urine samples from days 217–219 of a Salyut-7 flight [39] were considered to indicate that a "slight" activation of the sympathoadrenal system at these times was caused by physical activity and not by weightlessness. Microgravity, therefore, was said not to produce stress continually [53], similar to the conclusions from cortisol data. After landing, however, urinary epinephrine and norepinephrine are increased, with implications for immune and other systems [132].

It has been suggested [133] that the sympathoadrenal and adrenal glucocorticoid systems are activated during readaptation to gravity. After long-term flights, however, activation may be delayed. Angiotensin I, aldosterone, epinephrine, and norepinephrine seem to be most consistently elevated after landing (Box 10.21).

In-flight measurements during short-term flights have shown ACTH to be unchanged [6, 71]. After a 1-year *Mir* flight, plasma ACTH was elevated more than tenfold; it had not returned to its baseline value by 70 days after landing [1, 62]. The ratio of cyclic adenosine-3′,5′-monophosphate (cAMP) to cyclic guanosine-3′,5′-monophosphate (cGMP) increased in cosmonauts after long-term space flights [134] because of an increase in cAMP and a decrease in cGMP. These findings were taken as an indication that adrenergic mechanisms of regulation had been activated.

Kvetnansky et al. [135] investigated the activation of the adrenomedullary system in one astronaut and 15 bed rest subjects. Activation was induced by hypoglycemia produced by intravenous administration of insulin. Although activation of the adrenomedullary system (increased plasma epinephrine and norepinephrine) was produced before flight and bed rest, a reduced response of epinephrine was observed on the fifth day of space flight and the fifth day of head-down bed rest. The authors suggested that increased blood flow in the brain, which would have increased the glucose supply to nerve cells, might have caused the reduced epinephrine response.

As part of a study to determine why 20 % of astronauts experience presyncope when standing upright on landing day, Meck et al. [136] measured plasma norepinephrine, the norepinephrine intracellular metabolite dihydroxyphenylglycol (DHPG), norepinephrine release with tyramine injections, and norepinephrine release with upright tilt, in 23 astronauts before and after flight. The presyncopal astronauts had significantly smaller baseline norepinephrine but significantly larger DHPG levels on landing day than non-presyncopal astronauts. They had significantly greater norepinephrine release with tyramine on landing day, and they had significantly smaller norepinephrine release and greater epinephrine release with upright tilt on landing day. Meck et al. [136] interpreted their results to indicate that orthostatic hypotension and presyncope at landing are associated with low alpha-1 adrenergic receptor responsiveness before flight and remodeling of the central nervous system during space flight so that the sympathetic responses to baroreceptor input are impaired.

Christensen et al. [137] measured platelet epinephrine and norepinephrine as indexes of long-term changes in sympathoadrenal activity in 5 cosmonauts and 10 head-down bed rest subjects. During bed rest, platelet norepinephrine, which has a long half-life, decreased significantly and platelet epinephrine did not change. During space flight, however, both of these platelet catecholamines increased in four of the five cosmonauts. Christensen et al. [137] suggested that the mechanism of the sympathoadrenal response during space flight is related to the decrease in plasma volume.

Even after the very brief Mercury flights, urinary epinephrine and norepinephrine were elevated (Box 10.22) [138]. Resting plasma norepinephrine and epinephrine levels were elevated (relative to pre-flight levels) on landing day after Space Shuttle flights [139, 140], as was urinary norepinephrine [6]. In addition, the catecholamine response to standing after space flight was significantly increased on landing day for both norepinephrine and epinephrine [139] and remained increased for up to 3 days after landing. Increased urinary excretion of catecholamines was recorded

Box 10.21
The day after landing of a 1-year mission, plasma epinephrine and norepinephrine concentrations of two cosmonauts were greater than they were before flight.

Box 10.22
Although differences in epinephrine levels may be partially accounted for by circadian effects, norepinephrine response after space flight cannot be accounted for in this manner.

after Russian flights of 4–14 days, and this finding was interpreted as indicating stimulation of the sympathoadrenal system [133]. Stimulation of this system seemed to be even greater after flights of longer duration [133], but the response could be delayed for a week or more [141] and activation could continue for weeks [131]. After a 1-year mission on *Mir*, excretion of epinephrine was elevated on landing day and excretion of norepinephrine, dopamine, and catecholamine metabolites was reduced [1, 62].

Increased urinary excretion of stress hormones has been related to evidence of reactivation of latent viruses in astronauts, suggesting that stress promotes latent virus reactivation after space flight [142, 143]. For 27 of 28 Space Shuttle astronauts, urinary cortisol, epinephrine, and norepinephrine were significantly greater at landing than they were 10 days before launch. Eleven of the 28 astronauts—8 (35%) of 23 male astronauts and three (60%) of five female astronauts —had serological evidence of Epstein-Barr virus (EBV) reactivation [143]. After space flight their titer of immunoglobulin G antibodies to viral capsid antigen was at least 5120 and their titer of antibodies to EBV early antigen was at least 160—increases of 8- to 64-fold. The increase in antibodies to early antigen indicated acute lytic replication of the virus. When urinary stress hormones of this group of astronauts were compared with those of the other 16 astronauts, epinephrine and norepinephrine were significantly greater in the reactivating group of 11 [144].

Metabolism

Thyroxine is an important regulator of cellular energy production. It has not been measured in samples obtained during space flight, but was found to increase after Skylab [11], Salyut [74], and *Mir* [63] flights. A slight but statistically significant increase also was noted in a study of 133 Space Shuttle crew members [72]. In-flight [145] and postflight [11, 72] increases in thyroid-stimulating hormone also have been observed, although these changes were not statistically significant. Three days after landing of Skylab missions, thyroid-stimulating hormone was significantly elevated.

An increase in thyroxine would cause increased oxygen consumption, heat production, and metabolism of carbohydrates, protein, and fats. Oxygen consumption did in fact increase significantly during Skylab flights [61]. In the first few days of flight, blood glucose increased slightly, but it soon decreased below pre-flight levels and remained low for the rest of the flight [11]. Blood glucose was elevated after both Skylab [11] and Space Shuttle [72] flights. Changes in glucose observed after Russian flights were variable: after flights of 8–10 days, blood glucose was reduced [146], but after flights of 160–326 days it increased [53].

Thyroid hormone molecules contain iodide, which is obtained from dietary intake. Iodine intake on Space Shuttle missions was high because iodine was used as a bactericidal agent in the water system [147]. Some changes in thyroid status that were potentially related to iodine excess were observed in ground studies and in-flight crews [148–150]. As a result, in the late 1990s a system to remove iodine from water was deployed on most missions, and this was shown to correct the noted elevations in thyroid stimulating hormone at landing [151].

Exposure to microgravity reduces muscle mass, volume, and performance, especially in the legs, on both short [152–158] and long flights [152, 154, 159–163]. Some of the loss of lean body mass during space flight is believed to result from muscle atrophy and altered protein metabolism [164, 165]. Biochemical measurements provided evidence that this deconditioning is caused largely by increased degradation of muscle tissue. The six crew members of the first two Skylab flights had a negative in-flight nitrogen balance (–4.5 g/day) and decreases in total body potassium [28]. An increase in plasma amino acids has been observed in cosmonauts after flight [166]. Excretion of creatinine, sarcosine, and 3-methylhistidine increased during Skylab flights [167], an indication that the contractile proteins of skeletal muscle are degraded in weightlessness.

The rate of protein turnover in skeletal muscle is believed to be influenced by insulin, thyroxine, and growth hormone [168]. Plasma insulin levels were decreased at most sampling times during Skylab flights [11], and decreased insulin favors catabolism (Box 10.23). However, a slight increase in plasma insulin was noted during the 10-day Spacelab D-2 mission [169], during *Mir* missions [46, 170], and after Space Shuttle flights lasting 2–11 days [72]. Changes in thyroxine and growth hormone associated with space flight are discussed in the preceding paragraphs. A high correlation ($r=0.79$) between 3-methylhistidine (a marker for muscle degradation) and cortisol excretion during Skylab missions indicated that cortisol probably plays a role in muscle degradation during space flight [167].

Decreased blood cholesterol after Apollo [85] and Skylab [11] missions is consistent with an in-flight increase in

Box 10.23
Catecholamines are known to play an important role in metabolic regulation by increasing the rate of energy utilization and mobilizing stored fuels in metabolizing tissues. Because of the variability of alterations in plasma and urinary catecholamine concentrations during space flight, as discussed in the section "Stress," it is not clear whether changes in plasma catecholamines have significant effects on metabolism during flight.

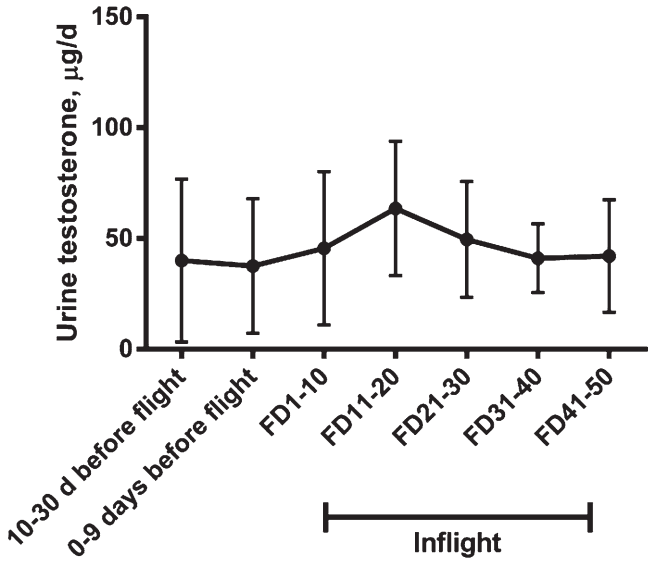

Fig. 10.5 Urinary testosterone levels during space flight

thyroxine, which is believed to increase the rate of metabolism of cholesterol to cholic acid [171]. Lipoprotein carriers of cholesterol were measured in astronaut blood samples for the first time during the Space Shuttle program [172]. Total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and very low density lipoprotein (VLDL) cholesterol levels of 47 astronauts were measured before flight and immediately after landing. Of these, only HDL cholesterol changed significantly, decreasing by 13 %. Analysis of 133 crew members revealed a statistically significant decrease of 8 % in HDL cholesterol, along with a 6 % increase in LDL and no change in total cholesterol [72]. In blood samples drawn 3–23 days after landing, HDL cholesterol was still significantly below pre-flight levels [172]. Studies of cosmonauts have shown slight decreases in HDL and increases in LDL during flight [173]. These levels of changes may not be thought to have clinical significance, but because of the association between cholesterol carriers and heart disease, and their role in lipid metabolism, further evaluation is warranted.

Testosterone has been proposed as a countermeasure for bone and muscle loss of space flight [174], on the basis of limited Shuttle astronaut data [71] and animal studies [174, 175] (see Fig. 10.5). Circulating testosterone is affected by stress and by restricted energy intake, and these factors among others may have confounded these initial reports. Data from ISS crews and bed rest studies has shown that circulating testosterone does not change during flight [33].

Hematologic Alterations

Plasma Volume

The most significant hematologic changes associated with space flight are reductions in plasma volume and red blood cell mass [20]. Decreases in plasma volume have been observed almost every time plasma volume was measured after U.S. space missions. The only exception was the 14-day Gemini-7 mission, after which plasma volume in both crew members had increased [176]. The first in-flight measurements of plasma volume in three crew members aboard the first Spacelab Life Sciences (SLS-1) mission indicated dramatic reductions on mission day 2 (23 %) and mission day 8 (14 %) [177]. Recovery of plasma volume after that 9-day mission was complete within 6 days of returning to Earth, a time span that was consistent with previous observations of recovery within 8 days after landing [178]. After the Skylab missions (28–84 days in duration), plasma volume was not measured between landing day and 14 days thereafter, when plasma volume had recovered [179]. In summary, plasma volume decreases soon after onset of microgravity and recovers to pre-flight levels within 2 weeks after crew members return to Earth.

Red Blood Cell Mass

Losses of red blood cell mass (recorded after U.S. missions) and hemoglobin mass (after Russian missions) have been documented (Box 10.24) [17–20, 180]. Results from both programs showed considerable variation in the hematologic responses of individual crew members.

With regard to recovery, red blood cell mass of the Spacelab-1 crew members had not returned to pre-flight levels 6 days after landing [178]. After the SLS-1 mission, red blood cell mass was measured once at landing and again 45 days thereafter. Red cell mass had recovered to pre-flight

Box 10.24
The decrease in red cell mass seems to begin within 4 days of launch and reaches a maximum after about 40–60 days of exposure to weightlessness [17–20]. In the Russian program, hemoglobin levels were measured using the carbon monoxide method, which involves spectroscopic measurement of blood carboxyhemoglobin after the subject breathes a mixture of air and carbon monoxide in a closed system [180].

values by the 45-day measurement [177]. The three Skylab missions lasted 28, 59, and 84 days. When the percentage change in red blood cell mass was plotted against time after launch (rather than landing), recovery of red cell mass seemed to begin between 40 and 60 days after launch, whether landing had occurred or not [181].

Red Blood Cell Count, Hematocrit, and Hemoglobin

Observed changes in red blood cell count have been even more variable than those noted for red cell or hemoglobin mass. Soviet scientists have reported that red cell counts remain constant on flights of 3 days or less [76] but vary greatly after flights of 4–18 days [182]. The greatest mean reduction in erythrocyte count (15 %) was observed after the 28-day Skylab mission [181].

Changes in hematocrit, like those in erythrocyte count, have varied considerably. The greatest increases in hematocrit (as great as 11 %) were observed after U.S. Space Shuttle flights [72] and after a 49-day Soviet flight [182]. The greatest decreases (as much as 15 %) occurred after 18- and 63-day Soviet flights and after the 28-day Skylab mission [181]. In a study of 16 cosmonauts on space flights lasting as long as a year, hematocrit was highly variable during the first 6–20 days of flight, but after that time it consistently decreased (4–14 %) from pre-flight levels [183]. Slight, but statistically significant, decreases in hematocrit and hemoglobin have been observed after ISS missions [184].

Changes in hemoglobin concentration have been comparable to those of hematocrit and erythrocyte count. Hemoglobin was elevated by 11 % after Space Shuttle flights [72] and by 5 and 3 % after the 59-day and 84-day Skylab missions. The greatest decrease (26 %) was noted after a 96-day Salyut-4 flight [182]. After a year-long flight aboard *Mir*, hemoglobin was reduced by 12 % [185]. Kimzey [181] noted that when hemoglobin was measured during the Skylab-3 and Skylab-4 missions, it decreased only after day 60, the approximate time at which recovery of red blood cell mass began. Kimzey suggested that a decrease in hemoglobin concentration might be involved in stimulating erythropoiesis. However, erythropoietin levels decline long before hemoglobin does during space flight (see later: Red Blood Cell Production and Destruction).

Cause of Red Cell Mass Loss

A space flight-related decrease in red cell mass has been observed since the early Gemini missions [176]. Initially, these losses were thought to be related to the 100 % oxygen atmosphere aboard early spacecraft, which may have produced mild and early oxygen toxicity. High oxygen, with reduced ambient pressure of 4 psi, was postulated to cause changes in red cell integrity (membrane) and premature intravascular hemolysis. However, subsequent hematologic data from Skylab [179] and the ground-based 59-day Skylab Medical Experiments Altitude Test (SMEAT) [186] did not support this hypothesis. Skylab and the SMEAT simulation chamber had normoxic, sea-level equivalent oxygen concentrations (70 % oxygen and 30 % nitrogen, at 0.34 atm), but only the Skylab astronauts showed decreases in red cell mass (Box 10.25) [187, 188]. Red cell mass also decreased in Space Shuttle Spacelab crew members, who were not exposed to hyperoxia [178].

Box 10.25
In an initial hypothesis, the hyperoxic environment of the spacecraft atmosphere and/or frequent phlebotomies for collecting blood samples were singled out for the observed decrease in red blood cell mass. However, ground-based simulations of space flight have shown that neither the removal of blood for analysis nor the higher percentage of the hypobaric atmosphere oxygen concentration results in red cell mass losses as great as those measured after flight [187, 188].

Loss of red blood cell mass now is thought to occur as the result of regulatory mechanisms that accompany the decrease in plasma volume [179]. A net loss of red blood cell mass could occur by several different mechanisms:

1. Permanent loss of erythrocytes by loss of blood, extravasation, or lysis;
2. Increased destruction of red blood cells by the reticuloendothelial system;
3. Temporary sequestration of erythrocytes in the reticuloendothelial system; and
4. Transient suppression of red blood cell production.

These possibilities are explored further below.

Red Blood Cell Production and Destruction

No evidence exists that erythrocytes are lost passively by hemorrhage or extravasation (escape of cells through the walls of blood vessels into the tissues). Several enzymes and metabolites involved in red cell metabolism were evaluated in Skylab crewmen to access the maintenance of erythrocyte integrity [189]. Levels of red cell components involved in peroxidation of lipids, enzymes of red cell metabolism, 2,3-diphosphoglyceric acid (DPG), and adenosine triphosphate (ATP) were analyzed. Although amounts of enzymes

and metabolites changed, they did so in no consistent pattern and with no evidence of lipid peroxidation, which is associated with irreversible damage to red blood cells (often seen following exposures to high oxygen concentrations). Amounts of DPG or ATP did not change during or after the Spacelab-1 flight [187]. If substantial hemolysis had occurred, then haptoglobin would be expected to decrease, which was not the case in Apollo [190], Skylab [181], or Space Shuttle [187] crew members.

Some evidence suggests that the rate at which red blood cells are destroyed by the reticuloendothelial system increases during space flight [18, 188]. Increased destruction or lack of production of erythrocytes, as measured by an increase in iron stores, without dietary iron, could be associated with an increase in serum ferritin. Subsequent investigations showed significant increased ferritin levels between 1 and 7 days after launch, returning to pre-flight levels between 1 and 8 days after landing [177, 187]. ISS findings corroborate these findings [184]. Red cell survival times after space flight generally remain normal [177, 188, 191]. Survival times usually are measured by labeling cells with ^{51}Cr and determining the percentage of ^{51}Cr that remains 8 days later. The cells are labeled almost randomly with respect to age, with some bias toward younger erythrocytes. A different method involving ^{14}C-glycine was used to determine erythrocyte survival time before and after the Skylab missions. No change in mean survival time was observed when all three Skylab missions were included [179]. On the 28-day mission, labeled cells exposed to microgravity were older than those on the other two flights because the glycine had been injected 50 days before launch instead of 20. A decrease in labeled erythrocytes was observed by the fourth day of flight, the first time that blood samples were obtained during the mission. Survival times of the relatively young erythrocytes on the other two flights did not change, suggesting that older cells—but not younger ones—are removed prematurely. Other findings dispute this conclusion, however; Alfrey and colleagues [18, 19, 192] proposed that the most plausible explanation for the combination of rapid fall in red cell mass, normal erythrocyte iron turnover and incorporation, and normal red cell survival is selective destruction of the youngest red cells [18].

Changes in the distribution of red cell shapes might contribute to premature destruction of some cells by the spleen. Blood samples obtained before, during, and after the Skylab [181] and Spacelab-1 [187] missions were examined by light and scanning electron microscopy for alterations in the shape of red blood cells (Box 10.26). During flight a decline in the proportion of *discocytes* occurred, accompanied by increases in the proportions of other cell types, particularly *echinocytes* (crenated cells), and on occasion, a week after return from space, the proportion of *echinocytes* was elevated 210 %. Cosmonauts on Salyut-6 missions (96, 140, 175, and 185 days) showed post-flight decreases in the proportion of discoid red blood cells that were readily reversed after even the longest space missions, suggesting that space flight produced no permanent changes of the bone marrow function.

Box 10.26
Usually, 80–90 % of erythrocytes ("discocytes") have a biconcave discoid shape, and the rest have more or less flattened shapes. Nondiscoid shapes can be caused by changes in plasma or in the cells themselves.

Box 10.27
Soviet investigators reported increases in blood and urine levels of erythropoietin in Salyut-6 cosmonauts the day after landing, with the increase being greatest after the shorter flights (16–30 days) [45, 59]. Soviet investigators have considered their findings to indicate that readaptation to normal gravity after long flights stimulates erythropoiesis [193].

The mechanism considered most likely to account for most of the red blood cell mass deficit is suppression of red blood cell production [18, 177]. Decreases in *erythropoietin* concentration, iron incorporation, rate of hemoglobin labeling, and reticulocyte count constitute evidence for this hypothesis [18]. Twenty-four hours into space flight *erythropoietin* had decreased by 23 %, and it was still 18 % below pre-flight values after 7 days of flight [187]. Immediately after landing, erythropoietin was close to its pre-flight level, but the next day it was elevated and it increased further (to 31 % above pre-flight concentrations) in the 12–13 days after landing. Results from the SLS-1 mission are consistent with a reduction in in-flight erythropoietin levels, beginning within 24 h after launch, and with an increase in erythropoietin levels beginning the day after landing [18, 177]. The in-flight reduction was 30–40 %, and the highest concentration of erythropoietin was observed on the day after landing (Box 10.27) [45, 59, 193].

Iron incorporation by red blood cells has been found to be normal after space flight [177, 187, 191], but during the SLS-1 mission, ^{59}Fe incorporation decreased from 89 to 62 % [177]. A decrease in the rate of change in the specific activity of ^{51}Cr-hemoglobin during the SLS-1 mission indicates that the rate of release of new erythrocytes from bone marrow decreased [177] (Box 10.28).

In short-duration missions *reticulocyte* count, as a percentage of erythrocyte count, is usually decreased during and immediately after space flight but recovers at rates that seem

Box 10.28
The rapid onset (within 4 days) of the decrease in red cell mass during space flight indicates that this reduction is not caused solely by a decrease in erythrocyte production, but rather that the reticuloendothelial system may selectively destroy erythrocytes on an age-related basis. From the clinical perspective, this altered function of the bone marrow results in increases of body iron stores and the availability of committed *erythroid precursors* for rapid release from bone marrow soon after landing.

to depend on flight duration. Although *reticulocyte* count decreased by more than 50 % from pre-flight levels during and immediately after the 10-day Spacelab-1 mission, on the day after landing only a 6 % decrease was evident [187]. In long-duration missions such as Skylab and *Mir*, *reticulocyte* count was found to be as low as 44–69 % of the mean pre-flight values with post-flight increases persisting several months [10, 179, 185]. In summary, the complex mechanisms controlling red blood cell mass during and after weightlessness are beginning to be elucidated. The rapid recovery of reticulocyte count after return to Earth suggests that erythropoiesis is suspended at a late stage as well as an early stage (indicated by the reduction in circulating erythropoietin). A normal rate of intramedullary erythrocyte production is coupled with a decreased release of new red blood cells into the circulation during space flight. These findings are consistent with ineffective erythropoiesis or intramedullary destruction of red blood cell precursors accompanying the decrease in erythropoietin levels [18, 177]. Neocytolysis results in release of iron from the destroyed RBCs, which increases iron stores [20]. Data from ISS missions document that these increased iron stores are associated with increased oxidative stress and with bone loss [184]. Animal studies also document an intertwined relationship of oxidative stress, radiation, and iron stores, with health implications for bone, and likely other systems [184, 194–196]. Given the growing understanding of the role of excess iron in disease states [197–201], the implications of increased iron stores during space flight require further investigation before we embark on exploration-class missions. Low erythropoietin levels may permit the programmed cell death (or *apoptosis*) of *erythroid progenitors* in the marrow. This process, termed *neocytolysis* [192, 202–204], reflects the selective destruction of newly formed erythrocytes and thus provides a mechanism for the rapid reduction in red blood cells through regulating the ability to complete erythropoiesis already in progress. This mechanism is also consistent with the availability of committed *erythroid precursors* for rapid release from bone marrow soon after landing.

Conclusion

Exposure to microgravity and the associated cephalad shift of fluids result in a series of compensatory mechanisms. A rapid, significant reduction in plasma volume is followed by a decrease in erythropoietin levels and a subsequent reduction in red blood cell mass. The decrease in red blood cell mass results from a depression of erythropoiesis, which is caused primarily by low erythropoietin and the associated ineffective erythropoiesis or intramedullary destruction of red blood cell precursors. During long space flights, red blood cell mass apparently reaches an equilibrium that is optimal for the microgravity environment. Further investigation of fluid volumes, regulatory endocrinology, and relationships with other physiologic systems are planned for future ISS missions, where additional scientific measurements can be conducted during long-term orbital flight.

Case Studies

Case 1

Learning Objective: Clinical risk assessment and aeromedical disposition of past history of renal stone.

A 36-year-old man of the European Space Agency and former test pilot, is selected as an astronaut and assigned to a future short-duration space mission (less than 1 month in space). He reports to the flight clinic for his annual examination, which reveals a young athletic male in excellent physical condition. The examining medical certifying flight surgeon reviews his past records and laboratory test results. The astronaut had several combat tours of duty, and reports suffering an episode of renal colic while waiting several hours for a scramble command, inside the cockpit of his fighter plane on a hot desert runway. He was flown to a military hospital and diagnosed with a small right parenchymal renal calculi, and was treated successfully with a shock-wave lithotripsy procedure [23]. No further details on the calculi chemical composition are available. He has remained free of symptoms of renal stone formation for the past 10 years. His family history is negative for renal stone risk factors. Additional tests are requested. All return negative, for urine content and composition, anatomical or pathological changes of the urogenital system, and bladder urine voiding function. The examining physician approves the medical flight for duty certificate and recommends adequate hydration and administration of potassium citrate during the actual space flight. The medical certification is limited to short-duration missions (<1 month), with consideration of a medical waiver for long-duration missions in low Earth orbit, where rapid return and rescue is possible.

Case 2

Learning Objective: Aeromedical disposition of hypothyroidism in a female astronaut

A 52-year-old woman astronaut, with more than 3000 h of short- and long-duration space flights, presents at the medical clinic with a complaint of fatigue, hair loss, and modest weight gain despite daily exercises. She is diagnosed with Hashimoto disease and put on *oral levothyroxine sodium*. After 8 weeks of treatment she is euthyroid on a 50 μg daily dose of levothyroxine sulfate. She has been assigned for a short-duration mission to the ISS. The flight surgeon conducts additional tests, which include a 24-h Holter monitor for the presence of arrhythmias and a maximum heart rate stress test for cardiac function, which are normal. She is issued a medical certificate, limited to short-duration space flight (<1 month). She is also required to have periodic cardiovascular monitoring and cautioned not to take any oral medications such as hypnotics, vitamins containing iodine, and estrogen-containing preparations. Her thyroid function will be monitored for at least 2 months post flight.

Self-Study Questions

1. Review potential medical concerns in reproductive function, contraception, and family planning for missions beyond low Earth orbit (>3 years).
2. Is "space anemia," first described in 1962, an accurate characterization of the hematopoietic system response to microgravity?
3. Limiting iron intake and supplements in space missions to prevent hemosiderosis: Is it a necessary preventive measure for missions beyond low Earth orbit?
4. Can post-flight hemodilution following rehydration affect astronaut health?
5. Review how hormonal changes influence the adaptation process in extended-duration mission beyond low Earth orbit.
6. Review proper approaches to reduce the risk for kidney stones in space, upon landing on a planetary surface (such as Mars), and upon return to Earth.

Key Points to Remember

1. In space the RBC mass decreases proportionally to the reduction of the circulating plasma volume.
2. Fluid and electrolytes are decreased as a result of the decreased total body water content, but electrolyte concentrations remain within the normal physiological range.
3. Total plasma reduction can reach 13 % and, together with endocrine changes, contributes to orthostatic intolerance in the early post-flight period.
4. Increased urinary calcium and protein losses and reduced urinary volume and citrate increase the risk of renal stone formation, especially during the post-flight period.
5. Fluctuations of renin-angiotensin, adrenocortical, reproductive, and other hormones are within the physiological ranges during short- and long-duration space missions.

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