drainage pathways or drainage pathways that we can make using tissue engineering approaches.

However, a broader view of renal function offers more room for immediate optimism. Beyond the Homer Smith view of transport function of the kidney, the kidney does a lot more. For example, there are endocrine functions (e.g., renin production, vitamin D hydroxylation, erythropoietin secretion, and klotho production), metabolic functions (e.g., arginine production and fructose clearance), and detoxification roles. These do not require a drainage pathway. These additional functions are likely to be more readily reconstituted with organoid implants than transport functions, and they may, therefore, deserve priority.

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See related article, “Kidney Regeneration in Later-Stage Mouse Embryos via Transplanted Renal Progenitor Cells,” on pages 2293-2305.

Looking Back 50 Years at the Biology of Mankind in Space: The Renal-Cardiovascular Fluid Shift Conundrum

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In 1969, when the Apollo astronauts first set foot on the surface of the moon, the existence of man beyond the Earth’s environment as a distinct possibility became sealed in the public mind. If this was to be feasible, then an understanding of how human beings function in a zero-gravity (zero-g) situation became an important prerogative as much for biomedical scientists as for industrialists and politicians. Physiologic data had accumulated from space fights in the Mercury (1956–1963), Gemini (1961–1966), and Apollo (1969–1972) programs; from the 1969 moon landing; and from studies performed on the Skylab space station first launched by National Aeronautics and Space Administration (NASA) in 1973.1,2 This led the Space Science Board to solicit applications for biomedical experimention in the space shuttle. In 1976, NASA issued an Announcement of Opportunities for biomedical experimention in the space shuttle, to which it received over 1500 responses. It became apparent that an extensive effort would be needed to support this level of interest, particularly because a wide variety of disciplines wished to be involved.

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Accordingly, the Space Science Board asked Neal S. Bricker, a distinguished United States nephrologist, to constitute a study team and to convene a workshop on “Life beyond the earth’s environment: The biology of living organisms in space.” The meeting was held in Snowmass, Colorado, in 1977 and included 40 medical scientists, biologists, scientific consultants, and NASA consultants. A report with the above title was published by the National Academy of Sciences in 1979, naming the Space Sciences Board, the Assembly of Mathematical and Physical Sciences, and the National Research Council as sponsors.

In his introduction to the report, Bricker wrote: “It is unfortunate that some of the best minds in the biomedical sciences have failed to become involved in NASA’s research programs in the Life Sciences. . . . In the process of asking questions and designing experiments, expert scientists outside of NASA were too often not asked and not listened to, or in some instances, regarded as antagonists who criticized the activities or the data of the NASA scientists.”

This paper derives all of its information from this document. Meeting participants were grouped into six panels: (1) renal and electrolyte physiology, (2) cardiovascular, (3) endocrinology, (4) genetics and developmental biology, (5) vestibular research, and (6) ecology. This paper confines itself to the reports of the renal and electrolyte physiology panel and the cardiovascular panel. It aims to portray the thinking and level of knowledge of the time and does not indulge in examining information gathered beyond that period, which may have supported or refuted certain conclusions of the meeting’s participants.

(The members of the two panels are listed in the acknowledgments below. At the time, the author of this paper was a junior academic nephrologist working in the group of the meeting chairman, Neal S. Bricker, and served on the meeting staff, tasked with the role of collating the panel reports and summarizing the overview. Certain personal recollections of the author [identified as such] are mentioned where they serve to enlighten or provide insight into issues addressed by these panels. Quotations in the text are cited from ref. 3.)

**FLUID SHIFT AS THE CENTRAL FOCUS OF ATTENTION OF THE RENAL-ELECTROLYTE AND CARDIOVASCULAR PANELS**

The topic that captivated the fascination of both the renal-electrolyte and cardiovascular panels and one that occupied the vast majority of time in discussions was volume regulation and its effect on salt and water excretion and cardiovascular function during entry into the weightless environment. In essence, the issue was that translocation of approximately 2 L of fluid occurred from the lower limbs into the central vascular compartment during the first 24–48 hours of space flight. The causes and effects of this phenomenon required understanding. Ultimately, the two panels reached different conclusions.

**VIEW OF THE RENAL AND ELECTROLYTE PANEL**

The view of this panel was that the fluid shift, initiated immediately on entry into zero-g, led to the excretion of an equivalent amount of salt and water by the kidneys. It was postulated that this diuresis begins shortly after the subject enters the weightless state and that there follows a reduction in body weight of about 2 kg with a rapid restitution of a new steady state with no further consequences. On the basis of information available at the time, the renal group argued that the fact that serum protein concentration and hematocrit tended to rise after the first 3 days pointed to the fact that the translocate fluid had been excreted. Furthermore, on re-entry to earth, fluid from the central compartment relocated to the legs, leading to a postflight period of salt and water retention.

The mechanisms underlying the natriuresis and diuresis were not clear, and the panel argued that hemodilution, vasopressin, aldosterone, and a putative natriuretic hormone (a subject of interest at the time) could be involved. Renin, aldosterone, and vasopressin levels rose by day 3 in space, but the magnitude of these changes was small and was not considered to be instrumental in the natriuresis and diuresis, with stress and antimotion sickness drugs being mentioned as possible additional stimuli.

Of interest was the fact that balance studies showed that the astronauts appeared to be in positive salt balance throughout the flight (i.e., less salt was collected in the urine than was ingested). There is a footnote in the report as follows: “Throughout the preflight period, during post-flight recovery and during flight, with the exception of the first few days, salt intake exceeded the increase output by considerable margin. Presumably this reflects significant but unmeasured salt loss in sweat. Such losses remain unaccounted for and make an interpretation of balance data difficult, except when there were major deviations from balance such as occurred in the first few days of flight and during recovery.” Clearly, the renal panel was of the opinion that the apparent positive sodium balance was an artifact of inaccurate output measurement.

(I recall a frustration expressed by the panel members related to the method of urine collection and the analysis of urinary electrolytes. NASA scientists had been using lithium as a urinary volume marker in its Skylab experiments and apparently were not aware of the fact that analyses of sodium and potassium had to be performed using a flame photometer, which required lithium to be used as the diluent of the urine samples loaded into the photometer. Hence, existing data on electrolyte excretion had to be questioned, but there is no allusion to this in the report.)

Supporting the contention of the renal panel that central volume expansion did not persist was the fact that there was weight loss following the diuresis and that there was no evidence of hemodilution, with hematocrit and plasma protein concentrations returning to baseline during subsequent observations.
Potassium and calcium balances were also reviewed by the renal panel, which summarized its conclusions as follows: “During the first 2 days of flight, there was a slight negative potassium balance associated with salt loss induced by expansion of central volume. Thereafter the loss was in proportion to the negative nitrogen balance, suggesting that it was consequent on the shrinkage of the muscle mass. In support of this view, increased excetration of creatinine provides evidence of loss of muscle, while the constancy of the plasma potassium concentration argues against potassium depletion.”

Of possibly greater long-term importance was the fact that urinary calcium excretion exceeded preflight urine plus fecal calcium loss. This area was covered in detail by the endocrinology panel (not discussed here), but it was also addressed by the renal panel given its relevance to the kidney. Continuous urinary calcium loss was considered to be due to bone demineralization. It was not responsive to exercise or any other maneuver. Of relevance to the kidneys was the fact that plasma calcium concentrations rose by about 0.5 g/dl (not fractionated). The hypercalcemia was considered to be due to suppression of tubular reabsorption, partially driven by the initial natriuresis but not sustained by it. Hormonal mechanisms were analyzed by the endocrine panel, but the implications for the kidney were obvious for long-term space flight (i.e., possible damage to the kidney either due to calcification of the parenchyma or formation of kidney stones).

**VIEW OF THE CARDIOVASCULAR PANEL**

In contrast to the view of the renal panel, this panel reached the conclusion that the fluid translocation during the early phase of space flight, alluded to above, could result in persistent engorgement of the central circulation rather than initiating a compensatory diuresis. If such engorgement were to persist for months, the panel believed that this could lead to a risk of cardiovascular and hemodynamic abnormalities comparable with those seen in patients with congestive heart failure. The positive sodium balance, which the renal panel chose to explain by inconsistent measurement of output, was viewed by the cardiovascular panel as being possibly relevant to such persistent volume expansion.

The panel members’ view was that, even in short-duration flights, the ensuing natriuresis and diuresis fail to restore central volume to normal and that central hypervolemia, pulmonary congestion, and an increase in heart size could persist. Acknowledging the list of possible humoral mediators mentioned by the renal panel, this panel expressed the need for an understanding of the afferent limb for release of these humoral factors (i.e., activation of mechanoreceptors in the heart and great vessels).

One of the arguments made by the panel in support of persistent central hypervolemia was the puffiness and eyelid swelling of the faces of the astronauts seen in pictures taken in space. It argued that the interstitial pressure in the head region is apparently insufficient to oppose the outward flow of fluid from the capillaries. They pointed out that, in space, “a pressure close to central venous pressure prevails throughout the post-capillary circulation.” They also pointed to reports from some crew members that pretibial edema may have persisted for 2–3 weeks, supporting the notion. (The renal panel, in contrast, argued that “the puffiness of the face and distended neck veins reported by Skylab crew members throughout each flight, raises the question of persistent expansion of central volumes, but these findings might be explained by changes other than overexpansion of vascular volume for example by loss of gravitational molding of the face or increased venous tone.”)

The panel devoted time to considering experimental models that could best simulate zero-g and pointed to two ground-based techniques that simulate zero-g, albeit only partially, and that could inform an understanding of processes activated under zero-g conditions. These were prolonged bed rest and head-out water immersion.

In prolonged bed rest, the gravitational force on the legs is minimized, and central fluid translocation occurs gradually and is excreted. When the erect posture is assumed, it thereby reduces the pool of blood required to achieve proper filling of the heart. The converse is true on recumbency, when there is a reflex reduction in heart rate and peripheral vasodilatation. This intervention results in alterations in both cardiac and pulmonary function, which could be relevant to prolonged space flights. Approximately 400–500 ml of fluid is lost to achieve a steady state during bed rest over a number of days.

In head-out water immersion to the neck, with a subject seated in a temperature-controlled tank of water, the hydrostatic pressure, determined by the depth of the water during immersion, induces translocation of roughly 700–800 ml of blood into the central compartment. This blood is translocated into the thorax, central veins, and pulmonary vasculature, pressures increase, and natriuresis and diuresis ensue. (It was pointed out this maneuver does not induce central engorgement, because the central venous pressure [CVP] is determined by the water level in the tank.) This approach may simulate the early hours of fluid translocation, but it does not simulate weightlessness. The rise in central venous and pulmonary pressure (15–18 mm Hg) during immersion aroused a concern about the same effect occurring during space flight.

Relevant ventricular pressures had not been made. The concern of the panel members was that, if elevated left ventricular pressures do persist, “it is conceivable that long term exposure to zero-g environment could induce major deterioration of cardiac function.”

The panel ended its report with recommendations for ongoing studies in humans and animals on space flights. These included measurements of cardiac dimensions, plasma volume, vasomotor hormones, CVP, pulmonary and
systemic pressures, stroke volume and cardiac output, lung volumes, and lung function. On extended flights, they believed that sequential measurements were needed and that the effects of physical exercise programs and muscle biopsies would be informative about muscle wasting on long-term flights.

OUTCOMES

The renal panel, expressing uncertainty about the future and the absence of solutions to the problems addressed, particularly for bone and muscle wasting, argued that an attempt should be made to eliminate the weightless state in situations in which prolonged stay was planned in “any structure maintained for long-term human habitation” (e.g., a space station) and that every effort should be made to provide a simulated gravitational field. Panel members indicated that they were not sufficiently informed to know whether a fraction of one-g (gravity of the Earth’s surface) would suffice. Although not stated as such, what they had in mind was a centrifuge for humans. They were less concerned about salt, water, and cardiovascular issues, because they were “not certain that they exist!” If they did exist, they believed that manipulation of salt intake with drugs that increase salt excretion was adequate to bring pressures down to satisfactory levels.

Agreeing to disagree, the cardiovascular research panel members acknowledged that the initial period of fluid translocation “accommodated in the intrathoracic compartment, distending its vascular structures and presumably inducing significant changes in central hemodynamics,” elicits compensatory mechanisms for reducing such volume via renal excretion, but they were not sure that the compensation was complete. They acknowledged that this phenomenon did not impair any aspect of work activity in flight, but on re-entry into normal gravity, the compensatory contraction of blood volume became a problem where postflight circulatory studies had shown impaired work capacity, orthostatic hypotension, and lowered exercise stroke volume and cardiac output in the sitting position.

In a way, the disagreement about the importance of a physiologic finding was probably more valuable in the long term than agreement, because it would go on to stimulate research by the “disciples” of panel members in each discipline, each wishing to enlarge the relevant datasets on which they were called to opine.

Not included in the meeting report was any allusion to social events, two of which come to mind. One guest appearance was by the eminent cultural anthropologist Margaret Mead,3 one of America’s most well known intellectuals of the 60s and 70s, who was asked to talk about what life would be like in a closed environment. When asked “who would want to live in space anyway?,” she responded: “Of course, people who want to live in space, the same way that some people want live in deserts and some in ice-bound places. There is enough variation in human beings to cater to all tastes.” The other guest was the after-dinner speaker Nichelle Nichols, who played a lead role on television as Communication Officer Lieutenant Uhura on the poplar sci-fi television show Star Trek.

Reflecting on the historical conundrum described above, it becomes clear that this situation pertains to all scientific differences of opinion, which are subsequently resolved by the provision of new and relevant information. In this case, the existence of CVP measurements would have been the irresistible fact that could have resolved the conundrum. Even more intriguing is the fact, not mentioned in the report, that CVP could have been measured in a peripheral vein under zero-g conditions, where pressures equilibrate across the entire venous system.

CLOSING THE CIRCLE IN LIGHT OF CURRENT UNDERSTANDINGS

It is of obvious current interest to know how the conundrum described above has been resolved in light of information gathered over the subsequent 40 years. The matters to be resolved from that time were as follows. (1) Is there a persistent increase of pressure in the central circulation in short-duration (10–11 days) and long-duration (up to 6 months) flights due to fluid shifts? (2) Is there any evidence that such fluid shifts lead to increased cardiovascular morbidity and mortality? This review allows for only a very selective allusion to recent information and on the basis of observations made on a sizeable number of human subjects involved in space flight over this time period.

Shen and Frishman6 address the question of central volume expansion in their review of the effect of space flight on cardiovascular physiology. They indicate that, in both short- and long-term flights, heart rate and mean arterial pressures have not been shown to be different from preflight supine values and that they are significantly lower (but not higher) in space flight compared with preflight standing values. They point out that arterial pressures at the level of the feet, heart, and head equilibrate to about 100 mm Hg and that this likely accounts for the “puffy” facial features observed in astronauts. These pressure changes activate mechanoreceptors that trigger an autonomic response to regulate volume, resulting in peripheral vasodilation and pooling of blood as well as renal fluid and salt loss. They further conclude that there is a decrease in cardiac filling pressures, which paradoxically coexist with increased cardiac chamber volumes. This is explained by the fact that chest wall expansion is induced by weightlessness, creating an even larger drop in intrathoracic pressure than the drop in CVP and resulting in an increase in cardiac transmural pressure and increase in atrial diameter.

Cardiac atrophy occurs after 10 days in space flight, which reveals itself as a reduction in stroke volume immediately after landing on earth.6 Almost all astronauts exhibit postural tachycardia after returning to earth, consistent with volume contraction occurring in space. A return to baseline takes about 2 weeks. In balance, therefore, there is no evidence for persistent central volume expansion in space. The opposite is the case.
To address the question of a possible increase in cardiovascular mortality, Ade et al. describe a study of 310 astronauts and 981 nonastronaut NASA employees that were matched for age, sex, and body mass index. Recruitment was conducted in two phases: historical and prospective. The study extended from 1992 to 2010. Primary outcomes were composites of clinical cardiovascular disease (myocardial infarction, congestive heart failure, stroke, and coronary artery bypass surgery) and coronary artery disease (myocardial infarction and coronary artery bypass surgery). The conclusion drawn was that the “findings suggest that being an astronaut is not associated with increased long-term risk of cardiovascular disease.” They further emphasize that there is no difference in risk of cardiovascular disease or coronary artery disease between astronauts with varying space flight experience.

These insights do not imply that longer-term flights or residence in deep space are risk free. The long-term effects of hypercalciuria may have damaging effects on the kidneys. The effects of radiation exposure on vascular endothelium may be significant. Only 24 astronauts have thus far existed in deep space (12 have walked on the moon), and limited information has indicated that such lunar astronauts may have a higher cardiovascular mortality than those who flew in low-earth orbits, possibly caused by radiation injury. If this finding holds up in a larger population of astronauts living in deep space, it will be a cause for major concern.

A future long-term flight to Mars is certain to raise many more issues and many more surprises.

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DISCLOSURES

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