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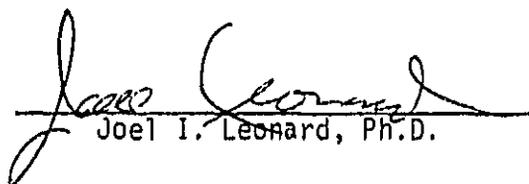
FROM Joel I. Leonard, Ph.D. TO N. Cintron, Ph.D./SD4

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SUBJECT Fluid-Electrolyte Responses During Prolonged Space Flight: A Review and Interpretation of Significant Findings

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RESPONSES DURING PROLONGED SPACE FLIGHT: A
REVIEW AND INTERPRETATION OF SIGNIFICANT
FINDINGS (Management and Technical Services Unclas
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This document contains a summary of the most important results of the Skylab studies related to fluid-electrolyte regulation. These data became the starting point of an extensive systems analysis to study adaptation to the weightlessness environment. A brief summary of the systems analysis study, including an interpretation of Skylab results, is also included.


Joel I. Leonard, Ph.D.

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Attachment

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FLUID-ELECTROLYTE RESPONSES DURING PROLONGED SPACE FLIGHT:
A REVIEW AND INTERPRETATION OF SIGNIFICANT FINDINGS

Prepared by

Joel I. Leonard, Ph.D.
Management and Technical Services Company
Houston, Texas

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Lyndon B. Johnson Space Center
Houston, Texas

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FLUID-ELECTROLYTE RESPONSES DURING PROLONGED SPACE FLIGHT:
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Joel I. Leonard, Ph.D.
Management and Technical Services Company
Houston, Texas

Throughout the manned space-flight program, there has been a continuous interest in the fluid regulating systems of the body. The cephalad redistribution of blood, the decrements in plasma volume, and negative water and electrolyte balances are believed to be common occurrences in weightlessness for all astronauts. Coupled with these well-known disturbances, are more complex and subtle changes in renal and circulatory dynamics, endocrine function, body biochemistry, and metabolism. The Skylab program provided the most comprehensive set of observations on these related systems during the most prolonged flights that the U.S. has undertaken. Interpretation of these data in terms of an integrated theory of space-flight adaptation has been a major goal of this author as well as other investigators. In contrast to experimental laboratory research or traditional statistical analysis, however, the primary tools of the current effort are mathematical models of physiological systems. Inasmuch as examination of the data must precede any detailed modeling analysis, and since the optimal use of mathematical models demands that data of a certain type and format be available, it was deemed appropriate that the derived data be collected and summarized. This report, therefore, represents a summary of the most important results of the Skylab studies related to fluid-electrolyte regulation and was the starting point of an extensive systems analysis which is available elsewhere (Ref. 1-22).

Most of the results contained herein have been previously published by the principal investigators, but in a different format (Ref. 20,23-33). New analyses of these data are presented here to permit a description of both the short and long-term responses to space flight. Obtaining a composite picture of these responses, based on the nine Skylab crewmen, was preferable in most instances to explaining the differences between flights. Thus, instead of presenting the individual crew data for day-by-day biochemical changes in

blood and urine (which have been previously reported), the same information has been computed as daily nine-man averages so that trends, if they exist, could be readily discerned. Also, water and electrolyte balance results are presented in a more complete form than has heretofore been available. Finally, questions concerning these observations were identified, categorized, and interpreted. These issues formed the basis of a subsequent simulation model analysis, as well as helping to design the next generation of space-flight experiments. A brief summary of the results of the model analyses concludes this document.

Pre-Skylab Results

Prior to Skylab, considerable information had been accumulated concerning the body's fluid and biochemical responses to space flight. These studies of the astronauts who participated in the Mercury, Gemini, and Apollo missions were designed to provide data relative to the maintenance of crew health and safety. The early flights entailed exceedingly complex technological constraints which made the design of valid physiological experiments nearly impossible. With the exception of two missions, only preflight and postflight measurements were permitted, and there was limited opportunity to provide experimental controls for diet and activity. Therefore, most of the information collected was in the form of observations based on urine and blood analyses and some whole-body measurements, most of which were obtained on the ground. From these data, only gross changes could be revealed, and inflight aberrations could only be inferred. The investigation and elucidation of the basic physiological mechanisms responsible for these changes were to be performed on future flights, such as Skylab.

Sufficient data were obtained, however, to demonstrate that space flight is associated with significant weight loss, substantial deficits in fluid and electrolyte balance, a variety of endocrine responses, demineralization of bone, and cardiovascular deconditioning (Ref. 34-39). Water losses were believed to occur principally on the first or second day of flight. On the basis of the rate of body weight recovery during the postflight phase, it was estimated that 50-85 percent of the total weight loss during space flights of about a week in duration could be attributed to water loss. The remaining

loss was taken to be due to catabolism of tissue components (fat and protein) which was a result of an inadequate diet (Ref. 40). In retrospect, it was suggested that a decrease in food consumption during the early period after launch might have been associated with low grade vestibular disturbances and space motion sickness symptoms (Ref. 41). Diminished urinary excretion in the immediate postflight period indicated efforts by the body to retain fluid and electrolytes lost inflight. Signs of musculoskeletal atrophy and loss of intracellular content was indicated by decreased total body potassium, a negative nitrogen balance, and reduced intracellular fluid volume. Preflight and postflight measurement of hormones related to fluid and electrolyte balance were also consistent with inflight loss and postflight retention. In particular, elevated levels were noted postflight for urinary anti-diuretic hormone (ADH), aldosterone, catecholamines, and plasma angiotensin. These hormones are usually secreted when retention of water and salt is required. Also noted were moderate losses of blood volume (both plasma and red cells). Cardiovascular alterations were indicated by a postflight decrease in orthostatic tolerance and a reduction in exercise capacity.

Following Apollo and before Skylab, a working hypothesis was proposed which presumably accounted for the adaptive changes in the fluids, electrolytes, and hormones (Ref. 27). Table 1 outlines those parts of the proposed hypothesis that describe factors influencing fluid shifts within the body. Upon initial entry into the weightless environment, the circulating blood volume shifts from the extremities and lower abdomen toward the central thoracic regions. This is interpreted by the body as an increase in total circulating blood volume (since "volume" receptors are located in the cardiopulmonary region), which the body attempts to reduce by a decrease in the production of ADH and aldosterone. The result is a loss of water, sodium, and potassium. The accompanying decrease in plasma volume may then produce a secondary aldosteronism. At this point, the body is believed to enter a phase of electrolyte and fluid imbalance, in which sodium retention increases, while potassium loss continues. The extracellular alkalosis which results from such a response may produce an intracellular exchange of potassium and hydrogen ions. At some point, it has been theorized, respiratory and renal compensation could halt the negative balance trend and produce a physiological system which is stabilized. This yields a new effective circulating blood volume and

TABLE 1

OVERVIEW OF PRE-SKYLAB HYPOTHESIS CONCERNING PROCESSES
INVOLVED IN MAN'S ADAPTATION IN ZERO GRAVITY*

EVENT	RESPONSE OF BODY
Entry into zero gravity. Redistrib- ution of circulating blood volume.	Body attempts to reduce volume. ADH decreases, aldosterone production decreases.
Loss of water, sodium, potassium (loss of body weight).	Decrease in plasma volume. Aldosterone increases (secondary aldosteronism).
Increased sodium retention. Potassium loss continues. Cell: acidotic — extracellular fluid: alkalotic	Intracellular exchange of potassium and hydrogen ions. Decrease in bone density, muscle cell potassium, and muscle mass; possibly including cardiac muscle.
Respiratory and renal compensa- tion. Halt to weight loss trend.	Stabilizes with new effective circulating blood volume. New body fluid and electrolyte balance.

* Taken from Berry (1973)

fluid and electrolyte balance. While some of the details of this hypothesis have not proved correct, the overall schema provides a means of explaining short-term fluid changes in space flight.

Prior to Skylab, little was known about the detailed nature and time course of these changes during weightlessness. Also, it was uncertain as to whether the changes represented a new adaptive steady-state, or whether they would progress to the point of adaptive failure somewhere beyond the two to three weeks exposure to weightlessness studied in previous flights (Ref. 42). Missing from the data collected on these early missions was a reliable baseline for quantitation of inflight urine excretion and inflight biochemical analysis of urine and blood, and sufficient postflight sampling to document the crew's return to normal. The Skylab experiments were designed to study, in greater detail, the aspects of biochemical and fluid regulation that had previously shown the most significant changes. The experiments were also designed to complete, where possible, the incomplete observations of the prior flight programs. Accordingly, the studies were designed to investigate the mechanisms involved in weight loss, demineralization, and altered endocrinological status. More specifically, evaluation of the endocrinological adaptation and other homeostatic mechanisms which control the volume and composition of the body fluids was needed. These objectives were accomplished under the Bioassay of Body Fluids Experiment by establishing controlled dietary conditions, collecting metabolic excreta and blood samples inflight, and taking whole-body measurements of fluid and electrolyte compartments prior to and after flights. Supporting this study were other related and overlapping experiments in which mineral balances, daily body mass, blood volumes, and leg volume measurements were performed.

Major Skylab Findings

Fluid-electrolyte status was characterized during Skylab by a number of physiological quantities which can be divided into the following categories: body weight losses (total body water, lean body mass); body fluid volumes within the major compartments (blood, extracellular, intracellular, upper body, lower body); and major body electrolytes and their plasma concentrations (sodium and potassium). Other groups included hormone levels which control

fluid-electrolyte balance (angiotensin, aldosterone, ADH, cortisol); renal excretion of water and electrolytes (rates and concentrations); and water and electrolyte balances (intake, excretion, sweat). Changes in these quantities, as measured on the Skylab crew, will be described below.

a) Weight Loss:

Weight loss has been one of the most commonly observed findings in astronauts returning from space flight, regardless of flight duration. Figure 1 shows the percentage weight loss compared to mission duration for all U.S. space crewmen (Ref. 23). The average measured weight loss has been 2.8 kg, or 3.8 percent of preflight body weight. Although Figure 1 suggests that weight loss may diminish for the longest flights, this is presumably not caused by any adaptive effects. Rather, it is caused by the fact that the dietary intake was increased on those flights; hence, fat loss was negligible.

Skylab permitted the first inflight measurements of body mass. The analysis of the components of this weight loss was based both on direct whole-body measurements and on indirect metabolic balance data. One of the conclusions from that analysis was that more than half of the weight loss was derived from lean body mass and the remainder from fat stores (Ref. 3 and 11). Inasmuch as lean body mass contains the most significant amounts of water and electrolytes, the losses of this tissue component are of crucial interest in understanding the fluid-electrolyte disturbances which occur in space flight. Some of the major components of the lean body mass loss in the Skylab crew are summarized in Table 2.

About half the total weight loss occurred within the first two days of flight, and it was due to water loss. The remaining loss occurred more gradually over the duration of the missions and was attributed to both fat and protein depletion. As demonstrated by inflight metabolic balances of nitrogen and potassium, the most significant losses of protein stores occurred during the first several weeks.

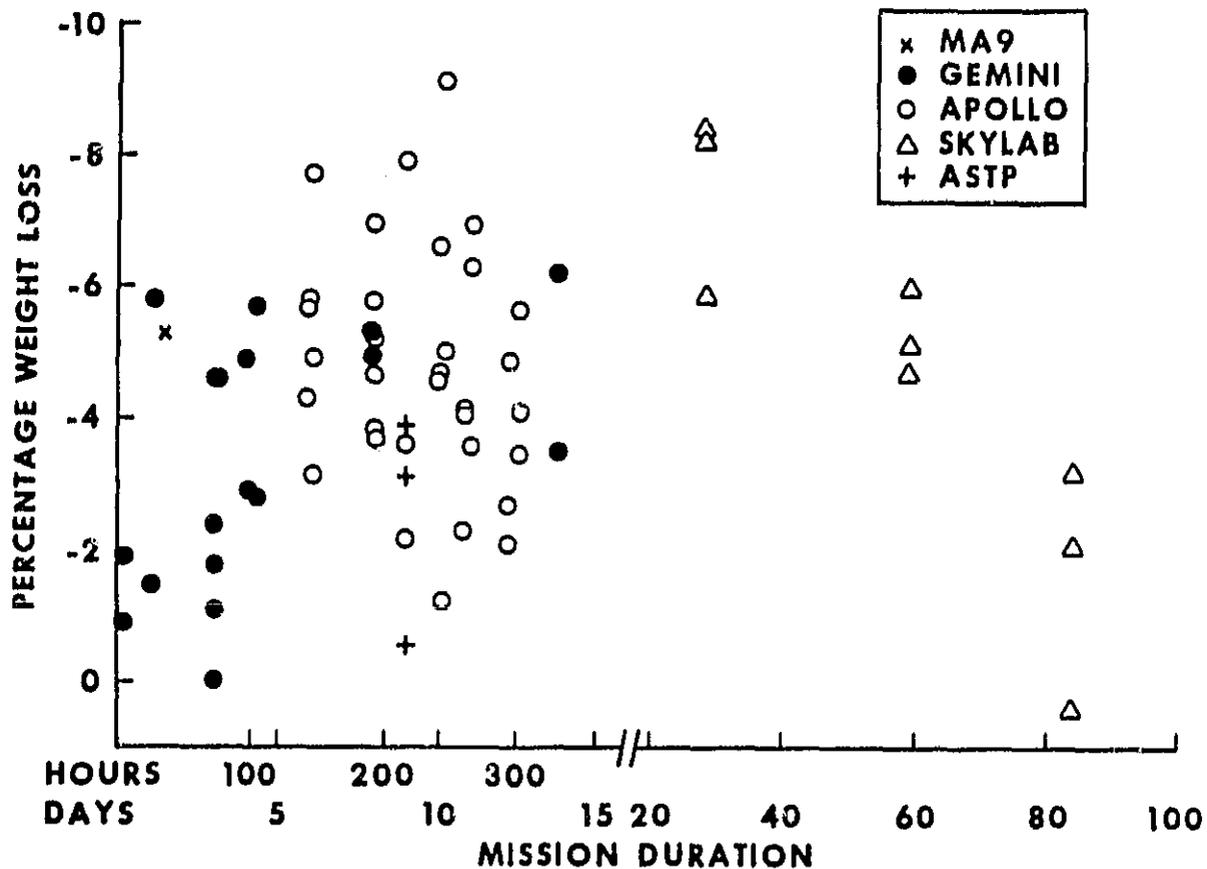


FIGURE 1

Percentage weight loss of U.S. space crewmen as a function of mission duration, based on preflight (usually the mean of multiple values) and immediate postflight weights. No correlation exists between weight loss and mission length for flights up to two weeks. On the Skylab missions weight loss diminished with flight duration but this was likely caused by increased dietary intake.

TABLE 2

CHANGES IN FLUID AND ELECTROLYTE COMPARTMENTS IN SKYLAB CREW (N=9)

<u>QUANTITY</u>	<u>INFLIGHT LOSSES*</u>	<u>POSTFLIGHT GAINS**</u>
Leg Volume (ml)	- 1500	+ 1500
Blood Volume (ml) [†]	- 590	+ 590
Red Cell Mass (ml)	- 230	+ 240
Plasma Volume (ml)	- 360	+ 550
Intracellular Water (ml) [†]	- 480	+ 530
Extracellular Water (ml) [†]	- 330	+ 590
Interstitial Water (ml) [†]	+ 30	+ 50
Total Body Water (ml)	- 820	+ 1120
Exchangeable Body K ⁺ (meq)	- 240	+ 164
Extracellular NA ⁺ (meq) [†]	- 90	+ 100
Body Mass (gm)	- 2630	+ 1840

* Measured from preflight to recovery day
(average mission length = 57 days)

** Measured from recovery day to two weeks postflight

+ Measured indirectly

b) Body Fluids:

The loss of body water was studied in considerable detail (Ref. 2-8, 12, 17), since it provides major clues to understanding the headward shift of fluids, the fate of electrolytes, renal function, and endocrine regulation. The fluid compartments of the body were measured directly before and after flight the crewmen returned to Earth and this information is summarized in the composite analysis of Table 2. Interpretation of these results is confounded by the fact that fluid compartments are labile and probably subject to rapid changes, as a result of reentry forces. Therefore, these results may not truly reflect the magnitude of change incurred inflight. This was exemplified in the detailed water balance analysis (Ref. 14) which indicated that the inflight loss of water was probably closer to 1.1 liters rather than the 0.8 liter shown in Table 2. This discrepancy was explained by demonstrating partial replenishment of water from drinking prior to the isotope dilution studies.

In order to determine alterations of body water during the flight itself, it was necessary to develop special techniques to examine the water balance data. The dynamic behavior of body water was derived using these methods (Ref. 2-8, 12, 17) and is shown in Figure 2 for the first 28 days of flight. (This time period was chosen for analysis of most of the data presented here, because it is the longest continuous inflight period in which all crewmen from the three missions can be included in an averaging procedure.) A loss of between 1.0 and 1.4 liters occurred rapidly and then essentially stabilized at the reduced level after a day or so followed by a slight tendency toward partial recovery. A greater initial loss of water was associated with the crewmen who exhibited space motion sickness and drank less fluid.

Significant postflight decrements were found in blood volume (-600 ml), extracellular (-300 ml), and intracellular fluid (-300 ml). Interstitial fluid volume did not appear to change appreciably. Blood volume loss was caused by a combination of plasma volume and red cell loss. Hemoglobin concentration measurements, performed inflight, indicated that plasma volume losses of 10 to 15 percent occurred within the first few days and might have been rather stable thereafter. However, red cell mass was lost more gradually

BODY WATER AND ELECTROLYTE CHANGES DURING PROLONGED SPACEFLIGHT SKYLAB MEAN (N = 9)

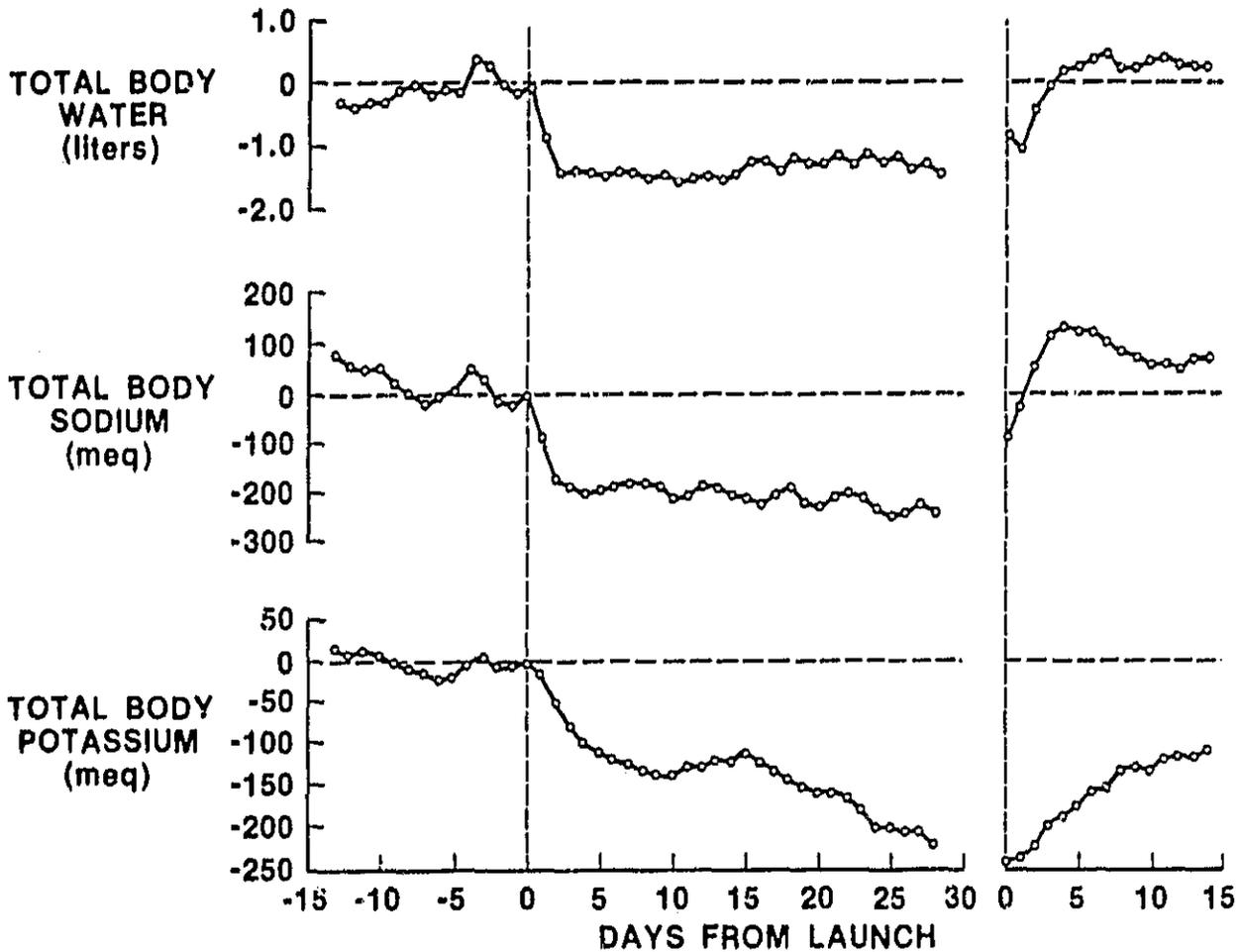


FIGURE 2

Changes in total body water, body sodium and body potassium for the entire Skylab crewmembers during preflight the first inflight month and recovery. Values shown are changes from morning of launch. Data was obtained by the indirect metabolic balance method.

(-11 percent) over the course of the entire mission (Ref. 24-26). During the two-week postflight period, blood volume and intracellular fluid volume recovered completely. Blood volume replenishment was primarily a result of overrecovery of plasma volume, since less than 20 percent of the red cells lost during space flight were regained during this time.

c) Fluid Redistribution:

Headward shifts of fluid in weightlessness were documented for the first time by leg volume measurements performed on the crew on the 84-day mission. Most, if not all, of the body fluid deficit could be accounted for by losses in the lower limbs. Postural change is usually associated with an acute fluid volume shift of 600 to 800 ml. The fluid volume that shifted from the legs after several days of weightlessness appears to be much greater (about 1.2 liters). This implies that there are greater reserves of mobilized fluid than previously recognized. A mean leg volume loss of 1.5 liters for all nine crewmembers was found just after reentry, and this was almost completely regained within the first postflight week.

There are two important questions that were not completely resolved from these studies. The contribution of each major leg compartment (blood, interstitial, intracellular) to the initial loss of leg volume is still undetermined. It was also not determined how much of the fluid shifted was not excreted from the body and in which compartments of the upper body it was stored. The puffy tissues of the face and distended head and neck veins of the crewmen suggested that these regions were involved as storage depots. An expanded fluid volume in the upper body, if sustained and not accommodated, could have long-term consequences on pulmonary function, cardiac function, and volume receptor pathways (Ref. 43).

d) Altered Water Balance:

Body fluid loss was expected to result from increased renal excretion. However, a diuresis was not recorded in the 24-hour pooled urine samples obtained from each crewmember early in the mission. As indicated in Figure 3, urinary excretion was diminished for the first ten days of the mission. The

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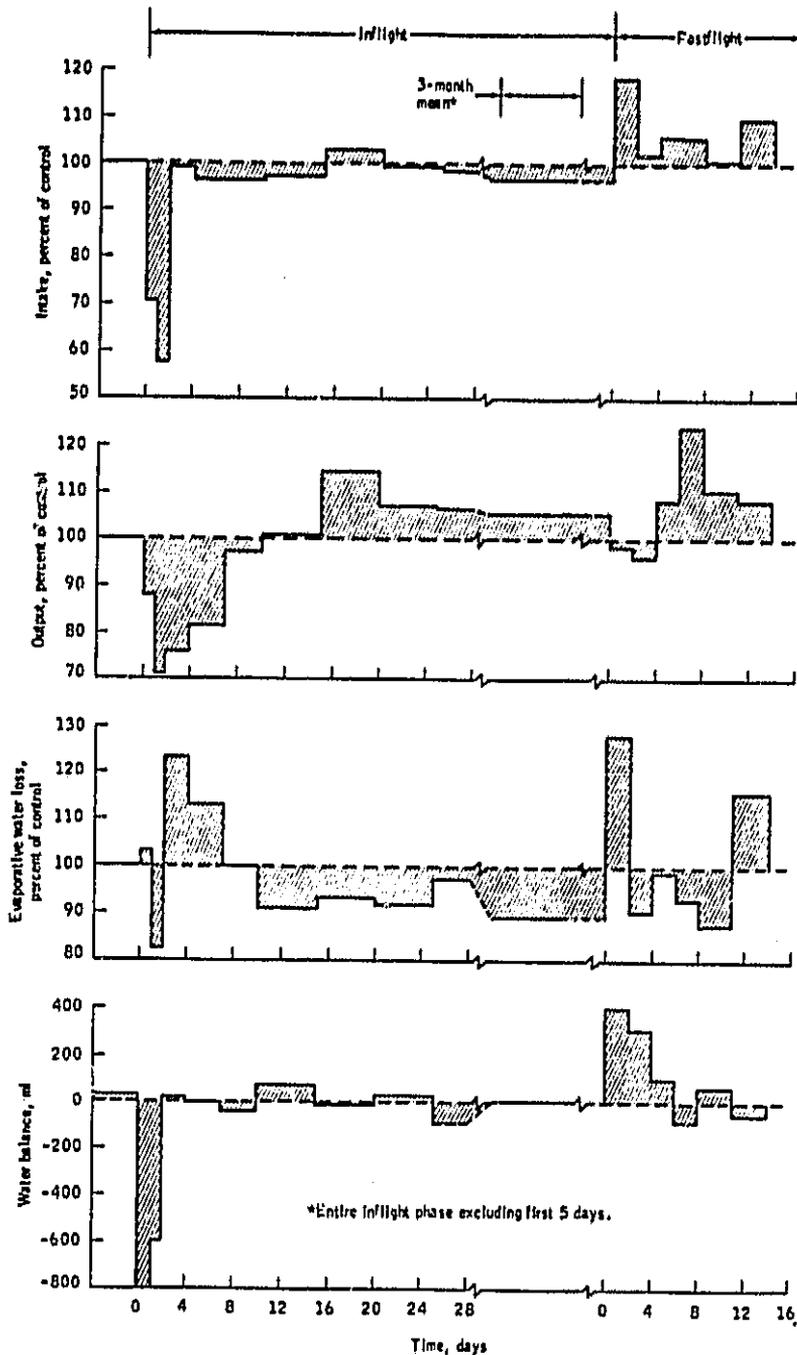


FIGURE 3

A composite water balance analysis of the Skylab crew (N=9). Percent changes from control are indicated for the first 28 days and the two weeks postflight. Also shown is the average three month mean that provides insight into long-term changes of intake, excreta and evaporative water loss during a time when the water balance is essentially zero. Intake includes drinking water, water in food and metabolically produced water. Output includes both urine and fecal water. Evaporative water loss was estimated indirectly, (Leonard, 1977).

loss of body water during the first two days primarily resulted from a deficit intake of fluid. Evaporative water loss increased significantly for several days during the first week, mainly as a result of increased ambient temperatures in the orbital workshop when a heat shield malfunctioned on the first mission (Ref. 2). However, due to a corresponding increase in fluid intake and diminished excretion, this did not result in further body water losses. The three-month averages, as shown in Figure 3, indicate that an essentially zero water balance was achieved at new equilibrium levels for intake (slightly diminished compared to preflight), excretion (slightly increased), and evaporative water loss (decreased 10 percent). During the first few days of the postflight period, water was regained because of enhanced intake and diminished excretion, similar to results found in earlier flights.

e) Electrolyte Losses:

Of all physiological changes seen during and after space flight, probably the most reliable clues to the mechanisms involved are offered by an examination of the electrolyte response. Loss of extracellular fluid is always accompanied by its major cation, sodium. Potassium, nitrogen, and magnesium are located primarily in the intracellular spaces. Loss of these quantities is assumed to reflect muscle degradation, a process known to occur during gravity unloading. Calcium and phosphorus losses are useful indicators of bone demineralization.

Of these substances, sodium and potassium were subjected to a more careful analysis (Ref. 1,7). Exchangeable body potassium decreased about 240 meq (6.4 percent) from preflight levels, indicating a significant loss of cellular mass (see Table 2). A net loss of approximately 100 meq of sodium occurred from the extracellular space, and most of these changes were regained during the two-week postflight period as summarized in Figure 2. There was an expected correspondence between total body water and sodium dynamics, since these quantities are associated with extracellular fluids, especially during periods of rapid changes. While body water and sodium appeared to stabilize after the initial inflight disturbance, body tissue, as exemplified by potassium loss, continued to decline gradually. Potassium and nitrogen losses (not shown) were essentially parallel (Ref. 17) as might be expected for a

generalized degradation of cellular material. Two quantities that probably should have correlated, but which did not, were cell water loss and potassium loss; much more intracellular water than was measured should have accompanied potassium loss if their normal ratios had been maintained.

The changes in metabolic balance (intake minus excreta) for the major intracellular electrolytes, calcium, phosphorus, nitrogen, and magnesium are shown in Table 3. While the loss of electrolytes represent significant changes in the body's physiology, it does not significantly contribute to the overall loss in body weight.

f) Plasma and Urine Analysis:

Disturbances in the fluid-electrolyte system were also measured by analysis of weekly blood samples and daily urine collections. These represent the first systematic collection of inflight body fluid specimens under somewhat controlled conditions during the space program. Plasma electrolyte concentrations are very useful in interpreting metabolic and hormonal alterations. Elevations in plasma levels were noted for potassium, calcium, and phosphate, constituents which are normally associated with intracellular metabolism (see Table 4). The plasma concentration of the major extracellular salt, sodium chloride, was found to be reduced as was the plasma osmolarity. Elevated rates of renal excretion were found for all electrolytes (sodium, potassium, calcium phosphates, and magnesium) during the flight period (see Figure 4); all except calcium were reduced during the period following recovery. Loss of body protein was indicated by elevated levels of urine creatinine and total urinary nitrogen. Uric acid was one of the few metabolites showing a decreased rate of renal excretion. Taken as a whole, these findings suggest loss of lean body mass constituent and degradation of tissues (Ref. 30). However, unless all the routes of metabolism are examined, it is not possible to quantitatively estimate rates of loss by analyzing either plasma or urine composition alone.

TABLE 3

AVERAGE DAILY
NET METABOLIC BALANCES OF INTRACELLULAR MINERALS

	<u>PREFLIGHT</u>	<u>1ST INFLIGHT MONTH</u>	<u>2ND INFLIGHT MONTH</u>	<u>3RD INFLIGHT MONTH</u>
	(N=9)	(N=9)	(N=6)	(N=3)
Nitrogen (g)	3.2	- 1.7	0.2	0.2
Potassium (meg)	17.0	4.0	9.3	8.7
Calcium (mg)	8	-18	-170	-168
Phosphorus (mg)	180	-24	64	20
Magnesium (mg)	26	16	25	15

TABLE 4

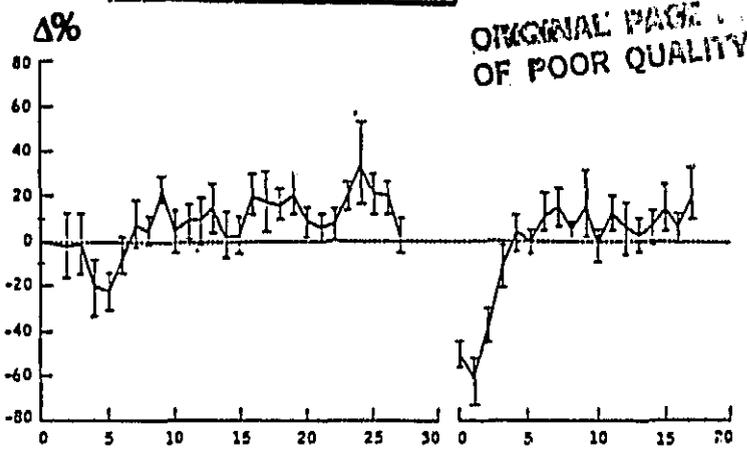
CHANGES IN PLASMA ELECTROLYTE CONCENTRATIONS
IN SKYLAB CREW (N=9)

<u>ELECTROLYTE</u>	<u>PREFLIGHT</u> *	<u>INFLIGHT</u>
Na ⁺ (meq/l)	142.2 ± 2.6	137.7 ± 1.5**
K ⁺ (meq/l)	4.07 ± 0.13	4.23 ± 0.12**
Ca ⁺⁺ (meq/l)	9.52 ± 0.31	10.23 ± 0.23**
PO ₃ ⁼ (meq/l)	3.35 ± 0.54	3.96 ± 0.54
Cl ⁻ (meq/l)	100.3 ± 5.3	95.7 ± 1.7**
Osmolarity (mosm/l)	291.0 ± 2.8	286.4 ± 3.1**

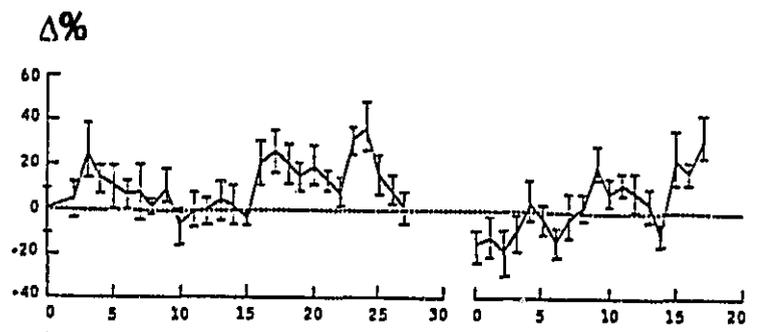
* MEANS ± SD

** Inflight significantly different than preflight (p < .05)

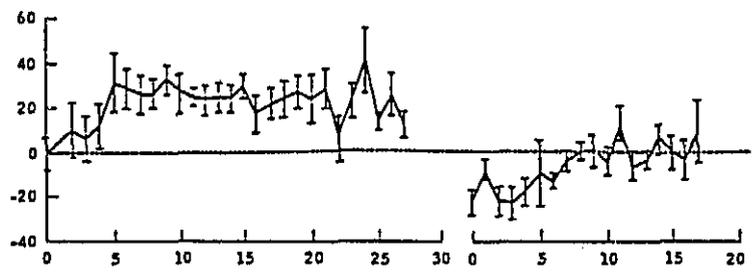
A) URINARY SODIUM



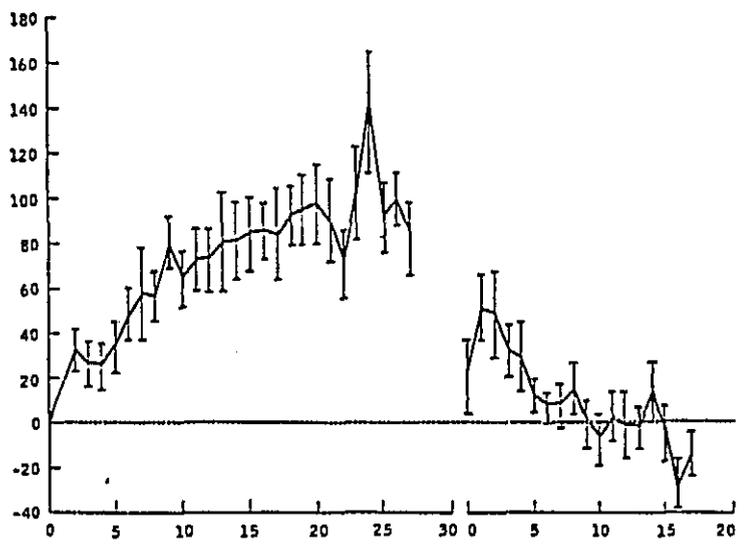
B) URINARY POTASSIUM



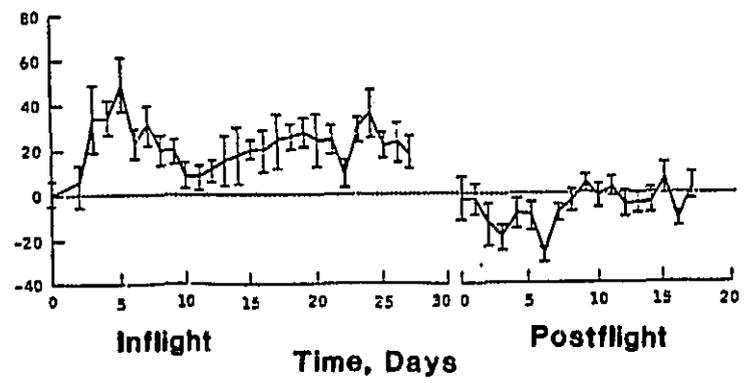
C) URINARY MAGNESIUM



D) URINARY CALCIUM



E) URINARY PHOSPHATE



F) URINARY OSMOLARITY

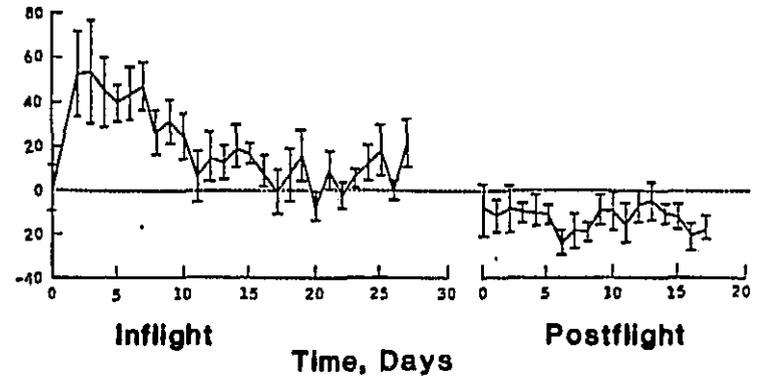


FIGURE 4

Daily urinary excretion of electrolytes of Skylab crew during first month inflight and postflight period. Each point represents mean (\pm SE) of nine subjects. Values are expressed as percent change from preflight mean. Data from mission day one is not available.

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g) Endocrine Function:

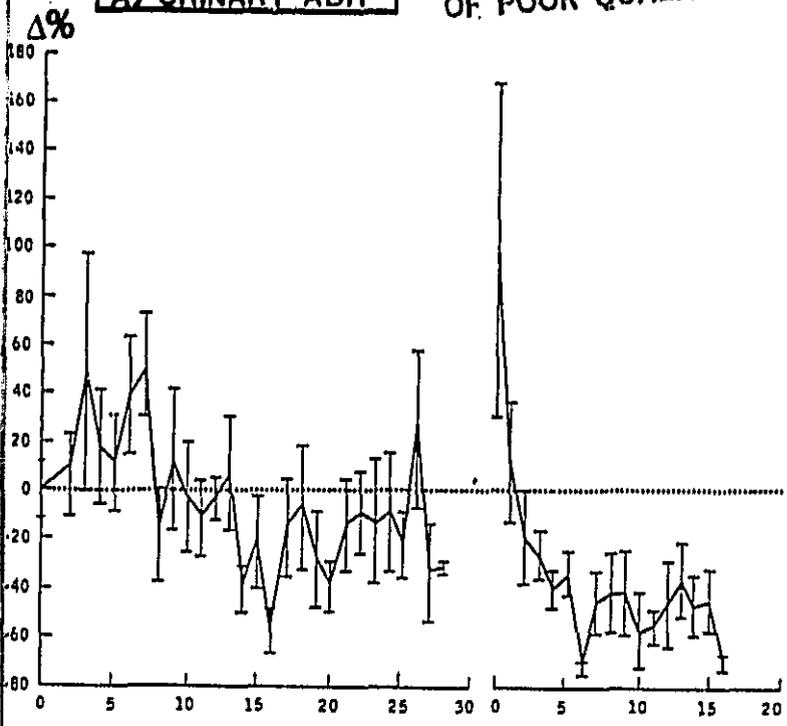
Endocrine changes which reflect alterations in fluid-electrolyte status, physical stress, and tissue metabolism were observed in analyses of blood and urine. Examination of the data from the first month in flight (Figure 5) revealed elevations in plasma angiotensin, urinary aldosterone, and urinary cortisol throughout this period; the highest levels were reached early in flight. Urinary ADH was elevated during the first week in flight, but was depressed during the latter half of the first month. All the hormones shown in Figure 5 reached maximum values on the first or second day of recovery. These substances are released during periods of general stress, but they are also sensitive to specific stressors, including plasma levels of electrolytes and blood pressures.

In many cases, the measured levels of these hormones can be plausibly correlated with other known changes. For example, increased angiotensin and aldosterone can account for the elevated renal potassium rates of excretion. Elevated cortisol levels undoubtedly contribute to muscle catabolism and increased nitrogen and potassium loss. The behavior of ADH qualitatively exhibits the expected inverse correlation with urine output during the in flight and postflight period. The elevation of the catecholamines (epinephrine and norepinephrine) early in flight and on the day of recovery, together with cortisol changes, indicate acute stress responses.

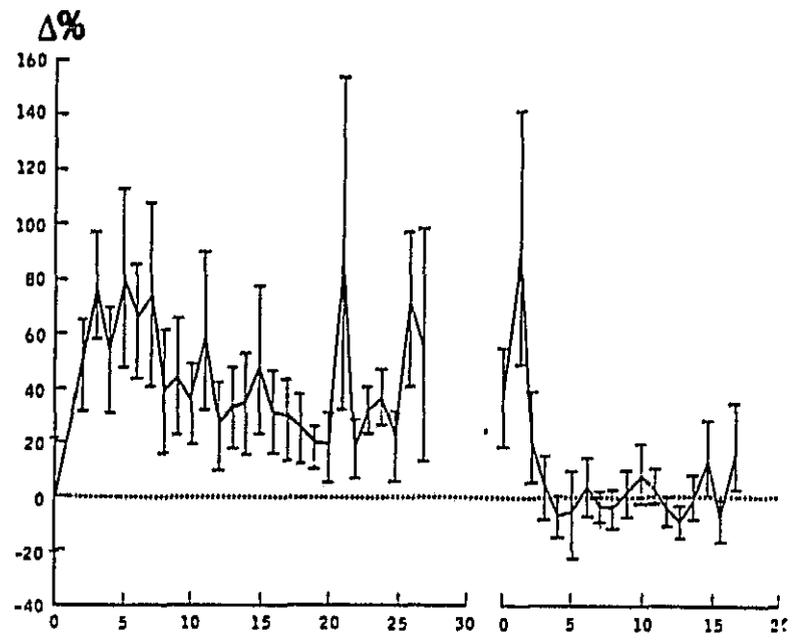
Interpretation of these changes is difficult because of the multiple competing factors which influence hormonal secretion rates and the various target sites they affect. In some cases, the hormone changes appear paradoxical. For example, angiotensin is a powerful vasoconstrictor in addition to its action as an aldosterone stimulator. It is usually released in response to hypovolemia, so it is not clear why angiotensin is elevated in zero-g (and also bed rest), at a time when there is a tendency for central blood volume expansion. ADH is also a potent pressor agent, in addition to its known effects on water excretion. However, this hormone is depressed during periods when angiotensin is elevated. In addition, the behavior of ADH was quite different on the three missions, as indicated in Figure 6. ADH levels were elevated on the shortest mission, but were reduced throughout the

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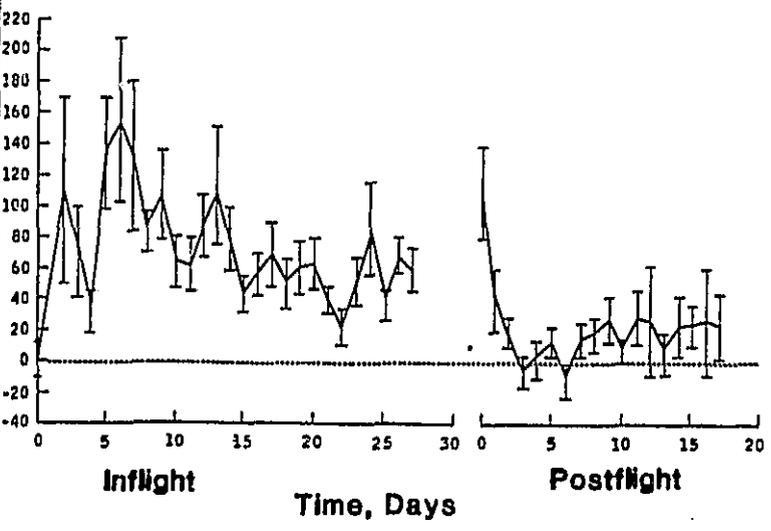
A) URINARY ADH



B) URINARY ALDOSTERONE



C) URINARY CORTISOL



D) PLASMA ANGIOTENSIN

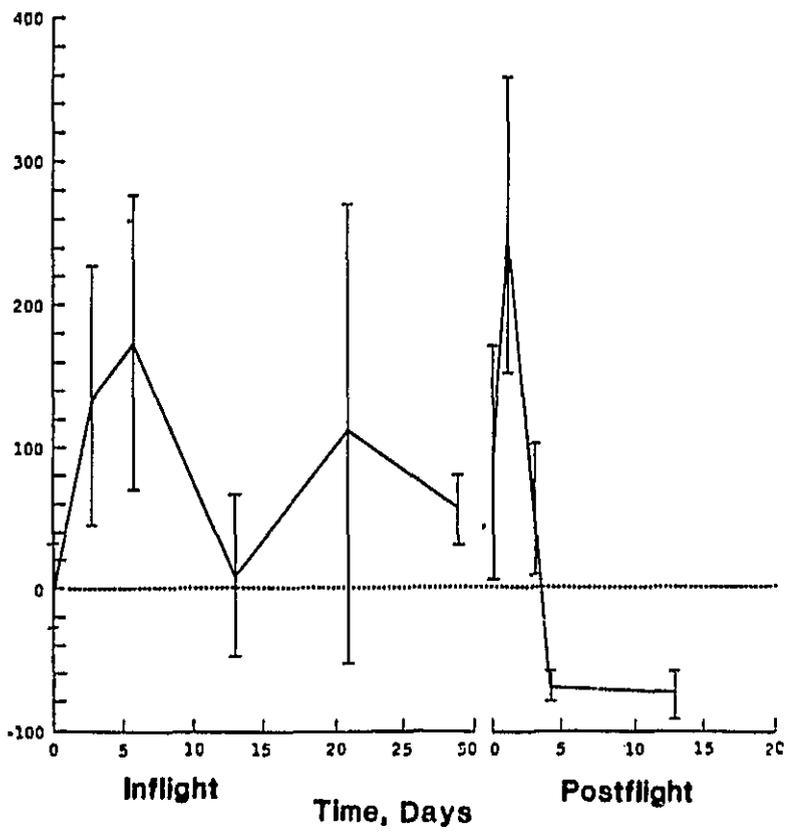


FIGURE 5

Hormonal Response of Skylab Crew during the first month inflight and the first two weeks postflight. Data from first mission day not available.

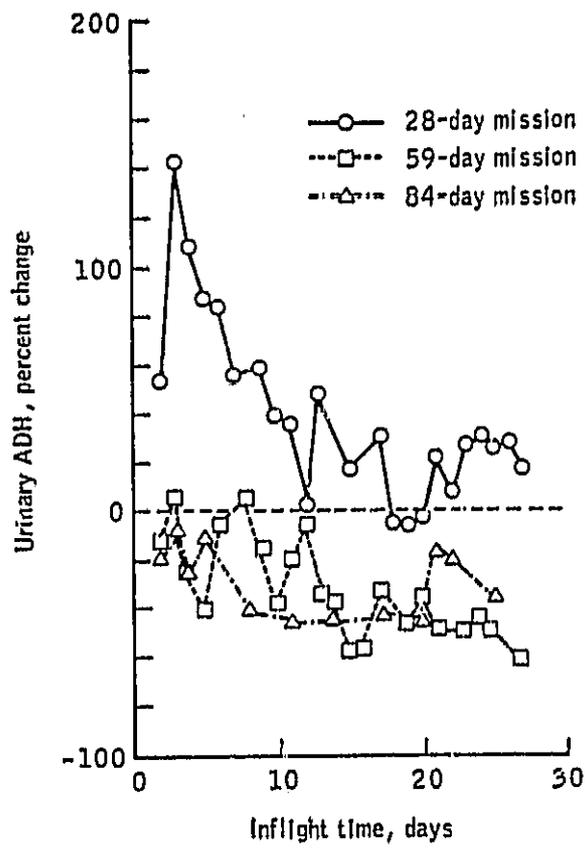


FIGURE 6

Comparison of variation of urinary ADH in a Skylab crew (N=3) during first inflight month of each mission. Values are expressed as percent change from preflight mean.

other two missions. In another case, aldosterone is a well-known promoter of renal sodium retention. Therefore, the elevated levels of aldosterone are inconsistent with the enhanced excretion of sodium. This is possibly evidence of a previously suggested natriuretic factor which may be operative in space flight.

h) Renal Function:

Alterations in renal function during Skylab were indicated by minor changes in creatinine clearance, low levels of uric acid in urine and plasma, and increased secretion of angiotensin. As discussed above, the fluid-regulating hormones and the degree of water and salt excretion all were altered during the entire three-month period of study. However, there is no firm evidence at present to warrant the belief that renal function was impaired. Rather, the renal system was probably responding to the demands of removing ordinary waste products from the body in addition to the extra demands of removing products created by the adaptive space-flight processes. An understanding of renal function in the weightless environment is made more difficult by the necessity to study the large number of biochemical agents which control and are controlled by the kidneys, as well as the complexity of the regulatory processes associated with that organ. A major emphasis of the present study was directed toward the systematic study of these processes.

Identification of Problem Areas

Overall, this analysis has identified a number of physiological events important to an accurate assessment of fluid-electrolyte disturbances during space flight. These events fall into a small number of categories which include: a) the redistribution of fluids between various compartments such as intracellular/extracellular, plasma/interstitium, lower body/upper body; b) the changes in quantity and concentrations of the body electrolytes as they affect the loss of fluids from the body and osmotic shifts with the body; c) the separate effects of short and long-term neural, hormonal and hemodynamic regulators of the circulatory-renal system as they influence the above processes; and d) the changes in intake, sweat losses, and body tissue

catabolism of not only water, but of the major electrolytes as they effect the transient and steady-state renal and plasma concentration responses. Within each of these areas there were found experimental observations which, on the surface, appeared paradoxical and whose etiology was not obvious. A representative portion of this list is summarized in Table 5.

The analysis which was necessary to resolve the issues listed in Table 5 required addressing various elements of the circulatory, fluid, electrolyte, hormonal, and renal systems. It is no longer adequate to answer any one of these questions without considering the effects on other related systems. That is, an interpretation of these Skylab findings should take place within the context of considering a total integrated control network. The use of systems analysis and mathematical modeling of the relevant physiological control systems is well suited to this task. The results of that extensive analysis are not within the scope of this report and may be found elsewhere (Ref. 1-22). However, it would be desirable to provide a summary interpretation of the space-flight data based on those analyses. An interpretation of many of the individual biochemical and fluid changes observed during space flight are provided in Table 6. An integration of these findings and interpretations into a picture of acute and chronic adaptation to weightlessness is discussed below.

Interpretation of Skylab Findings

There is unequivocal evidence that hypogravic stresses such as bed rest, water immersion, and space flight result in significant fluid redistribution within the body. The removal or reduction of the hydrostatic pressure in the blood column, coupled with the normal tissue elastic forces and muscle tone of the lower body, results in shifts of blood and tissue fluid from the lower body to the intrathoracic circulation. The consequences of this event are widespread and long lasting, as suggested by Figure 7. As a result of central volume expansion, a complex set of reactions is presumed to occur: a) stimulation of all cardiopulmonary pressoreceptors and decreased sympathetic activity; b) increased blood pressures and secondary decreases in peripheral resistance, promoting enhanced renal blood flow; c) altered secretion of the

TABLE 5

CRITICAL AREAS IDENTIFIED IN ANALYSIS OF FLUID-ELECTROLYTE SYSTEMS

OBSERVATIONS	QUESTIONS
<p>Significant losses of water, sodium, and potassium were measured directly or indirectly in the Skylab crew.</p>	<ul style="list-style-type: none"> i) What was the overall magnitude and time course of the losses? ii) From what body compartments did these quantities originate? iii) What components of the metabolic balance were most significantly altered: intake, excretion, or sweat losses? iv) What regulatory mechanisms were predominantly involved in controlling the initial loss of fluids and electrolytes as well as in the final approach toward a new homeostatic level?
<p>After the first several days of flight, inflight phase was characterized by somewhat higher excretion rates of fluids and major electrolytes.</p>	<ul style="list-style-type: none"> i) Does this imply continuous loss of the fluids and electrolytes from the body, or does it reflect an alteration of intake or sweat components as suggested by metabolic balance studies? ii) What are the mechanisms required to accomplish this and are they consistent with observed biochemical changes?
<p>Fluid losses from the legs occurred rapidly at the onset of zero-g and were unexpectedly large.</p>	<ul style="list-style-type: none"> i) From what compartments does this fluid originate? ii) What are the forces which drive it from the legs? iii) Is this fluid eventually excreted from the body or is there a residual volume remaining? iv) If residual volume is stored in upper body as has been postulated, does this represent long-term stress with regard to volume receptors or do these receptors adapt?
<p>Urine volumes were reduced during the first week inflight, coinciding with mean increases in ADH.</p>	<ul style="list-style-type: none"> i) Is the Henry-Gauer reflex, which predicts a diminished trend of ADH and a diuresis during acute zero-g stress, not operative in this instance? ii) What factors are capable of modifying or reversing this reflex and can they quantitatively account for the observed renal excretion?

TABLE 5 (CONTINUED)

OBSERVATIONS	QUESTIONS
<p>Urinary ADH was significantly depressed during the latter part of the inflight phase, while urine volume was only slightly elevated.</p>	<ul style="list-style-type: none"> i) What are the factors causing the ADH response? ii) What other competing factors are present, including longer term adaptive mechanisms that maintain reduced ADH levels and that prevent urine volumes to be even higher than would be expected on Earth?
<p>The measured loss ratio of potassium: intracellular water is not consistent with values expected from normal cell composition.</p>	<ul style="list-style-type: none"> i) Does this reflect measurement error or are other factors such as altered extracellular osmolarity involved? ii) What are the factors which permit potassium extrusion from the intracellular compartment to occur?
<p>Aldosterone was increased in space flight accompanied by an increased sodium excretion.</p>	<ul style="list-style-type: none"> i) Is this paradoxical relationship (in terms of one-g physiology) explained by other factors which influence aldosterone release or sodium excretion? ii) Is this an instance of sodium escape from aldosterone? iii) What factors caused excess sodium excretion to occur in the face of hyponatremia and elevated aldosterone?
<p>Angiotensin was apparently increased during space flight.</p>	<ul style="list-style-type: none"> i) What mechanisms are responsible for the elevations in angiotensin in a situation where there is a tendency toward upper body fluid congestion and increases in central blood pressures which are usually associated with depressed angiotensin? ii) How is it possible to reconcile the increased angiotensin and aldosterone levels in space flight with the findings from water immersion studies, which show an opposite effect?
<p>Plasma osmolarity and plasma sodium concentration were slightly reduced, urine osmolarity was increased.</p>	<ul style="list-style-type: none"> i) How can these findings be reconciled when it would be expected that while dilute urine would be associated with hypotonic plasma, decreased ADH and increased aldosterone? ii) What are the factors causing the hypotonic plasma and why does this phenomena persist when the renal-thirst reflexes are capable of exerting exquisite control of body fluid osmolarity?

TABLE 6

INDICES OF FLUID-ELECTROLYTE STATUS OBSERVED ON SKYLAB
WITH INTERPRETATIONS FROM COMPUTER MODEL ANALYSIS

QUANTITY	OBSERVATION	SUGGESTED ETIOLOGY
LEG VOLUME	DECREASED 1.5 LITERS IN TWO DAYS AND SMALLER LOSSES THEREAFTER	FLUID LOSS FROM VASCULAR, INTERSTITIAL AND POSSIBLY INTRACELLULAR COMPARTMENTS,
TOTAL BODY WATER	DECREASED 1.1 - 1.4 LITERS IN 2 DAYS, TENDENCY TO PARTIALLY RECOVER IN CREWS THAT WERE MOST DEHYDRATED	FLUID LOST APPEARS TO BE DERIVED FROM LEGS, BODY WATER FALLS BY COMBINATION OF SHORT-TERM DIURESIS (NOT OBSERVED) AND DECREASED INTAKE,
EXTRACELLULAR SODIUM	DECREASED ABOUT 100 MEQ IN TWO DAYS AND STABLE THEREAFTER	SODIUM LOSS ACCOMPANIES EXTRACELLULAR WATER LOSS. NATRIURESIS MAY OCCUR, BUT PRIMARY LOSS RESULTS FROM DECREASE IN INTAKE.
EXCHANGEABLE BODY POTASSIUM	DECREASES MORE GRADUALLY THAN SODIUM; 240 MEQ LOST THROUGHOUT MISSION.	LOSS OCCURS PRIMARILY OVER FIRST MONTH; DERIVED FROM INTRACELLULAR FLUIDS; EARLY DECREASED INTAKE AND PROLONGED ELEVATION OF RENAL POTASSIUM IDENTIFIED AS AVENUES OF LOSS.
INTRACELLULAR WATER	DECREASED ABOUT 0.5 LITERS	CELL FLUIDS AND POTASSIUM LOSS ASSOCIATED WITH GRAVITY UNLOADING AND MUSCLE DISUSE ATROPHY; FLUID LOSS PROPORTIONALLY LESS THAN POTASSIUM, BUT CAN BE EXPLAINED ON BASIS OF HYPOTONIC EXTRACELLULAR FLUID.
INTERSTITIAL FLUID	NO CHANGE	LYMPH FLOW AND TISSUE GEL TEND TO RETURN INTERSTITIUM TO ORIGINAL STATE AFTER INITIAL UNLOADING.

(CONTINUED)

TABLE 6 (CONTINUED)

QUANTITY	OBSERVATION	SUGGESTED ETIOLOGY
PLASMA VOLUME	DECREASES 10-15%	INITIAL LOSS ASSOCIATED WITH DECREMENTS IN TOTAL BODY WATER; LOSS IS MAINTAINED BY MECHANISMS WHICH REGULATE HYPERVOLUME; PLASMA VOLUME LOSSES MAY REPRESENT NEARLY HALF OF BODY WATER LOSSES.
HEMATOCRIT	INCREASED 10% ACUTELY AND DIMINISHES SLOWLY	RESULTS FROM EARLY LOSS OF PLASMA VOLUME FOLLOWED BY MORE GRADUAL DECREMENTS OF RED CELL MASS.
INTAKE OF FLUIDS AND ELECTROLYTES	DECREASED EARLY IN FLIGHT; OTHERWISE SIMILAR TO PREFLIGHT	SPACE SICKNESS ANOREXIA MAY BE RESPONSIBLE FOR INTAKE REDUCTIONS UP TO 40% PERSISTING UP TO A WEEK IN A FEW CREWMEMBERS. RESPONSIBLE IN LARGE PART FOR FLUIDS AND ELECTROLYTES LOST EARLY IN FLIGHT.
URINE VOLUME	DECREASED ABOUT 20% FIRST WEEK; SLIGHTLY ABOVE CONTROL THEREAFTER	NO DIURESIS OBSERVED FIRST DAY, POSSIBLY DUE TO LACK OF VOID-BY-VOID SAMPLING. DECREASE ASSOCIATED WITH REDUCED INTAKE OF FLUIDS. LONG-TERM RESPONSE RESULTS FROM DECREASED EVAPORATIVE WATER LOSS.
SODIUM EXCRETION	DECREASED ABOUT 10% EARLY INFLIGHT AND INCREASED ABOUT 12% ABOVE CONTROL THEREAFTER	EARLY DECREASE ASSOCIATED WITH REDUCED INTAKE AND HIGH ALDOSTERONE LEVELS; LATER INCREASE REFLECTS REDUCED SWEAT LOSSES RATHER THAN CONTINUOUS BODY LOSS. NOT CLEAR HOW EXCRETION INCREASES WHEN ALDOSTERONE IS ELEVATED; THIS "ESCAPE" FROM ALDOSTERONE MAY BE MEDIATED BY A NATRIURETIC FACTOR.

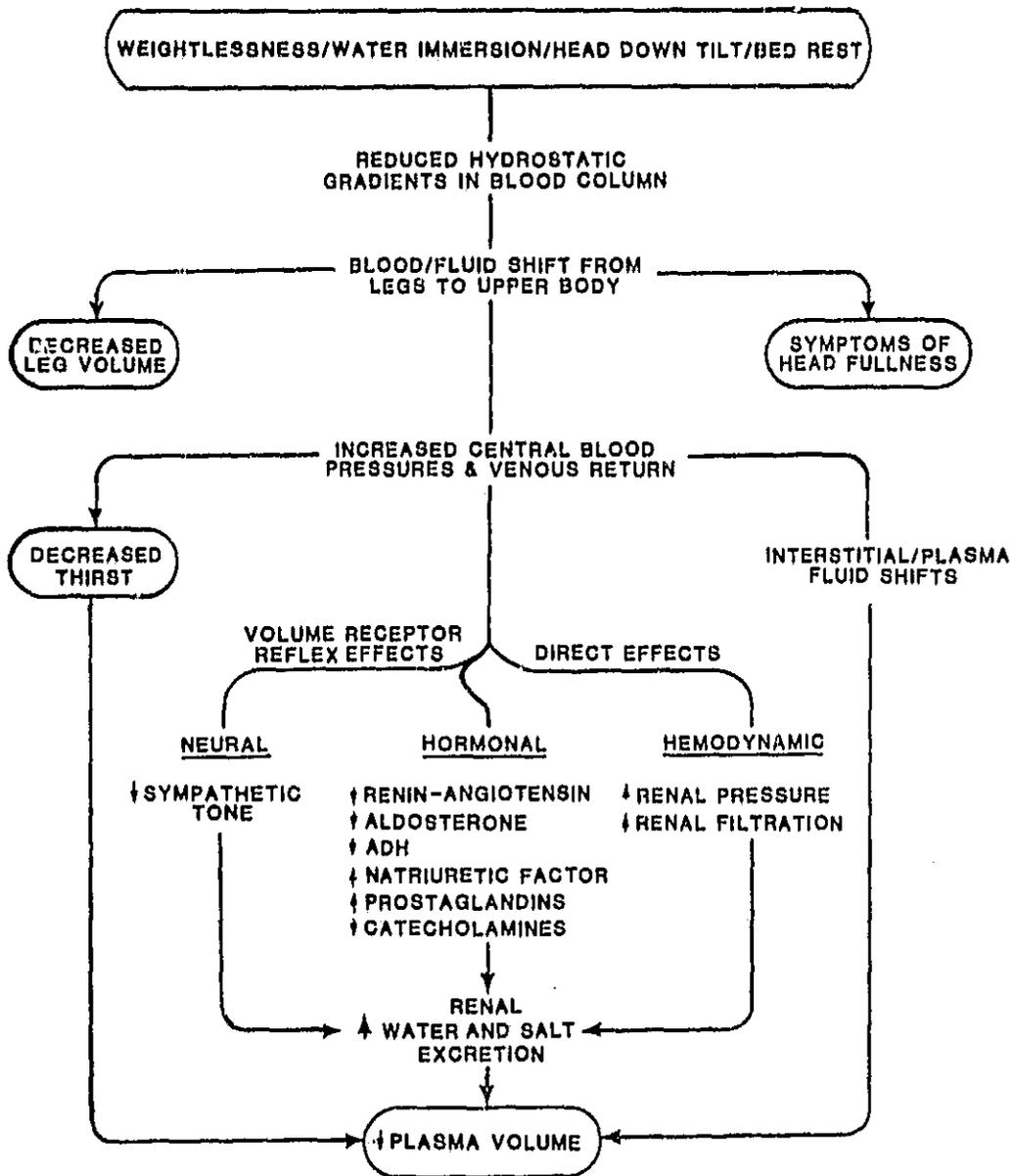
(CONTINUED)

TABLE 6 (CONTINUED)

QUANTITY	OBSERVATION	SUGGESTED ETIOLOGY
POTASSIUM EXCRETION	INCREASED ABOUT 10% THROUGHOUT FLIGHT	REFLECTS BOTH CELLULAR LOSS AND PERHAPS DECREASED SWEAT LOSSES. GOVERNED PRIMARILY BY INCREASED ALDOSTERONE AND INCREASED PLASMA POTASSIUM.
EVAPORATIVE WATER LOSS	DECREASED ABOUT 10%	UNEXPECTED DECREASE MEASURED INDIRECTLY; POSSIBLY RESULTING FROM SUPPRESSED SWEATING.
SODIUM AND POTASSIUM SWEAT LOSSES	DECREASED	MEASURED INDIRECTLY; PERHAPS DUE TO SUPPRESSED SWEAT WATER LOSSES AND BELIEVED TO BE OF SAME MAGNITUDE (ABOUT -30%).
URINE [Na ⁺]	INCREASED ABOUT 10%	PARADOXICAL FOR REDUCED ADH AND ELEVATED ALDOSTERONE COMBINATION; HOWEVER, EXPECTED ON BASIS OF STEADY-STATE ANALYSIS SHOWING NET SODIUM INTAKE (DIET - SWEAT) GREATER THAN NET FLUID INTAKE.
PLASMA [Na ⁺]	DECREASED ABOUT 3% THROUGHOUT FLIGHT	TOTAL OSMOLARITY ALSO DECREASED; CAUSE NOT KNOWN. NATRIURETIC FACTOR MAY BE INVOLVED IN EXCRETION OF SODIUM.
PLASMA [K ⁺]	INCREASED 2 - 4%	INTRACELLULAR POTASSIUM LOSS AND POSSIBLY DECREASED SWEAT LOSSES CONTRIBUTE TO THESE RESULTS.
ANGIOTENSIN	INCREASES ABOUT 100% IN PLASMA	ETIOLOGY NOT CLEAR IN LIGHT OF SUSPECTED HYPERVOLEMIA OF UPPER BODY; DECREASED PLASMA SODIUM CONCENTRATION CAN EXPLAIN PART OF INCREASE.
ALDOSTERONE	INCREASED ABOUT 100% IN URINE	SEVERAL FACTORS CAN EXPLAIN CHANGE: INCREASED PLASMA POTASSIUM, INCREASED ANGIOTENSIN, DECREASED PLASMA SODIUM.

TABLE 6 (CONTINUED)

QUANTITY	OBSERVATION	SUGGESTED ETIOLOGY
ANTI-DIURETIC HORMONE (ADH)	INCREASED ON FIRST MISSION, DECREASED LAST TWO MISSIONS.	DECREASED ADH EXPLAINED ON BASIS OF DECREASED PLASMA OSMOLARITY, ROLE OF VOLUME RECEPTORS NOT CLEAR, BUT HYPERVOLEMIA COULD HAVE ALSO CONTRIBUTED. RESULTS OF FIRST MISSION ARE PARADOXICAL.



FLUID - SHIFT HYPOTHESIS

FIGURE 7

fluid-electrolyte regulating hormones including ADH, the renin-angiotensin-aldosterone triad, catecholamines, and possibly a natriuretic agent, as well as renal prostaglandins; d) enhanced renal excretion of fluid and electrolytes as a result of the alterations in sympathetic activity, hormone secretion, and blood pressures and flows; e) increased transcapillary filtration of plasma into the interstitium, and, f) a decrease in thirst following reduction in angiotensin levels and augmented by space motion sickness anorexia. The net result of these processes is the loss of extracellular fluid and electrolytes, which has been observed frequently during and following weightless space flight.

Most, if not all of the rapidly acting mechanisms described above (which serve to correct the original blood volume disturbance) would most likely be observed only during the first hours of a hypogravic stress. However, on the basis of 24-hour metabolic balances, urine flow in the Skylab crew was not increased, and the entire loss of body fluids could be accounted for by deficit fluid intake (possibly as a result of space motion sickness). Computer simulation analysis of the acute stress period indicated that a reduction in fluid intake always diminished, but did not abolish, the diuresis response and immediately following this diuresis, renal excretion decreased below control. Thus, it is postulated that a diuresis was not observed because void-by-void urine samples could not be obtained and because an early diuresis would be masked in a 24-hour pooled sample in the presence of diminished intake. The short-term renal response to space flight in well hydrated subjects is not yet known.

Whatever the mechanism, most of these early losses were probably derived from observed decrements in leg volume involving a contraction of the plasma and the interstitial (and possibly intracellular) fluid spaces of the lower limbs. By the end of the first two days in space, the reduction in body water and body sodium was largely complete (see Figure 2). Also, during the early stages of flight, significant quantities of potassium escape from intracellular compartments. This may be deduced from increased renal excretion of potassium, elevated plasma potassium, increased levels of cortisol and aldosterone which are involved in releasing and controlling potassium, and potassium balance studies on which the data of Figure 2 is based.

The more prolonged adaptive phase was characterized by a new water and sodium steady-state and a slightly negative balance of potassium. The modest increase of water and sodium excretion throughout this adaptive phase did not necessarily reflect continued whole-body loss, inasmuch as excretion could have been offset by a decreased sweat component. Both a steady-state metabolic balance analysis and model simulation analysis supported this concept. The continued loss of body potassium is expected from the atrophy of lean body tissue, a consequence of gravity unloading and muscle disuse.

Model simulation ascertained the importance of autonomic, hemodynamic, and hormonal regulators of circulatory and renal function during the chronic phase. These pathways were influenced by fluid shifts between body compartments, altered metabolic balance, potassium loss from the cells, and plasma electrolyte concentrations. On the basis of model analysis, it appears that plasma volume is depressed about one-half liter throughout the flight. This prediction is supported by postflight measurements. The failure of the plasma volume to return to normal in zero-g is presumptive evidence of the presence of blood volume controllers responding to the tendency of fluids to pool headward. During the adaptive phase of flight, angiotensin and aldosterone presumably reversed direction from the suppression hypothesized in the acute stress state. Increased release of these substances can account for the elevated rates of excretion of renal potassium. It was necessary to introduce a natriuretic factor in the model (responding to central blood volume expansion) to obtain realistic simulations of enhanced sodium excretion in the face of elevated aldosterone, and also to generate the hyponatremic plasma that was observed. For all Skylab subjects, ADH exhibited the expected inverse correlation with the urine output; on average, ADH increased during the first ten days and was suppressed thereafter. The elevation of plasma angiotensin I is less easy to understand. Since renin-angiotensin is usually released in response to hypovolemia, it is not clear why angiotensin is elevated in zero-g (and also in some bed-rest studies) at a time when there is a tendency for central blood volume expansion. A mild reduction in plasma osmolarity and sodium concentration occurred early in flight and continued through the longest mission. The mechanisms which maintain this condition are not clear. However, the combination of mild hypo-osmolarity and hyperkalemia helps account, at least in part, for the increases in angiotensin and aldosterone and decreased ADH.

One of the more consistent findings in astronauts returning from space flight of any duration has been a loss in body weight. The dynamic behavior of this weight loss during flight was observed for the first time in the Skylab program. An analysis method was developed during the current systems analysis program to numerically determine the major components of body weight loss in terms of continuous time profiles for body water, body protein, body fat, body potassium, and body sodium (Ref. 12). The basis of the approach was a group of metabolic models for water, mass, and energy balance, which, when combined with whole-body measurements, allowed sequential accumulation of daily balance without incurring unreasonable error. The general conclusion of this study was that little more than half of the weight loss observed during the Skylab mission can be attributed to loss in lean body mass, the remainder being derived from fat stores. As a working hypothesis, we have assumed the following: a) acute water and sodium losses are obligatory as a result of normal physiological responses to headward shifts of fluid in zero-g; b) protein and intracellular mineral losses are primarily a result of disuse atrophy of postural muscles and may be obligatory in weightlessness (without appropriate exercise), although the losses appear to stabilize after about a month in space; c) fat losses are more variable and are probably dependent on the usual one-g influences of diet and exercise; and d) if present, the anorexia associated with space motion sickness will augment fat and protein losses by virtue of a caloric deficiency and will enhance water loss as a result of reduced fluid intake. These conclusions must be considered tentative because of the indirect method of estimation and because adequate experimental controls for assessing the role of diet and exercise in weightlessness were not available.

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