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4/26/85

CONTRACT NO:

NAS9-17151

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SUBJECT

The Behavior of Renal-Regulating Hormones
During Hypogravic Stress

(NASA-CR-171877) THE BEHAVIOR OF
RENAL-REGULATING HORMONES DURING HYPOGRAVIC
STRESS (Management and Technical Services
Co.) 62 p HC AC4/EF A01

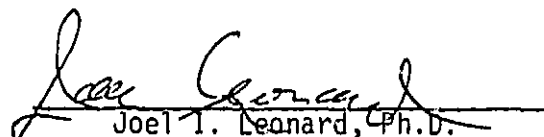
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The regulation of fluid and electrolyte behavior during space flight is believed to be under control, in large part, of a group of hormones which have their major effects on renal excretion. The hormones which have come under the most intense study include renin-angiotensin, aldosterone, and anti-diuretic hormone (ADH). This study report contains an analysis of the regulatory systems of these renal-regulating hormones as they act individually and in concert with each other. The analysis was based largely on simulations of the mathematical model of Guyton. A generalized theory is described which accounts for both short-term and long-term behavior of this set of hormones.


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THE BEHAVIOR OF RENAL-REGULATING HORMONES
DURING HYPOGRAVIC STRESS

Prepared for
National Aeronautics & Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

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1985

This work was supported by the following NASA contracts:

NAS9-15487, NAS9-16328, NAS9-15850, NAS9-17151

ABSTRACT

The Behavior of Renal-Regulation Hormones During Hypogravic Stress

Homeostatic correction of fluid volume disturbances in zero-g results in reductions of total body water and plasma volume as well as major electrolytes such as sodium. Regulation of these compartments require the participation of renal-thirst mechanisms in general, and hemodynamic, neural, and hormonal controllers in particular. A group of renal-regulating hormones, consisting of anti-diuretic hormone (ADH), aldosterone, and renin-angiotensin, have been the focus of many space-flight related studies. An understanding of their role promises to reveal much about the mechanisms which control renal excretion of fluids and electrolytes during exposure to weightlessness. However, the behavior of these hormones has been difficult to interpret or to reconcile with endocrine data obtained from one-g analogs of weightlessness such as water immersion, head-down tilt, and bed rest. The purpose of the present study was to examine these data, describe the major characteristics of the hormone responses, and to assess the controlling mechanisms.

The first section of the report concerns the detailed analysis of only one of these hormones, ADH. The second section extends the analysis to include aldosterone and angiotensin, as well as propose a more generalized theory of renal-endocrine behavior during hypogravic stress.

The primary techniques used in this analysis was the computer simulation of a mathematical model developed by Guyton and modified for application to space-flight stress. This model contains many elements which represent the dynamic interactions between acute and long-term adaptive control of the body fluids and the cardiovascular system.

The overall conclusion of this study is that the renal-regulating hormones each appear to respond acutely to volume disturbances and chronically to electrolyte disturbances. During hypogravic maneuvers this leads to an initial suppression of hormone levels and a long-term effect which varies depending on metabolic factors (such as diet, sweat loss, physical activity, and muscle atrophy) that can alter the plasma electrolytes. In addition, the simulations reveal that if pressure effects rapidly normalize, a transition phase may exist which leads to a dynamic multi-phasic endocrine response. Because of these complex and often competing stimulating factors, and the different modes of response, it is difficult to predict the behavior of hormone levels in the plasma or urine, except perhaps by using computer models. Indeed, this may explain why such variable findings are often reported for apparently similar bed-rest or head-down tilt studies. Verification of this hypothesis requires the collection of data which is currently lacking, including measurements of endocrine behavior during the acute phase of space flight and measurement of various circulatory pressures during the longer-term periods of hypogravity. In addition to a knowledge of electrolyte behavior in the body fluids, it is crucial to control such metabolic factors as diet, physical activity, and circadian rhythms.

THE BEHAVIOR OF RENAL-REGULATING HORMONES DURING HYPOGRAVIC STRESS

1.0 INTRODUCTION

It is now well established that exposure to weightlessness results in a significant redistribution of body fluids. Acute changes include the movement of blood from the lower extremities toward the central circulation (because gravitational pooling forces are negligible in zero-g), and transcapillary shifts in the lower body (absorption) and upper body (filtration). Homeostatic correction of these volume disturbances results in reductions of total body water and plasma volume and requires the participation of renal-thirst mechanisms. Losses of intracellular and extracellular fluids are accompanied by appropriate electrolyte losses which involve selective renal handling. These processes are in large part under hemodynamic, neural, and hormonal control. In particular, a group of renal-regulating hormones, consisting of anti-diuretic hormone (ADH), aldosterone, and renin-angiotensin, have been the focus of many space-flight related studies. A knowledge of endocrine behavior can be valuable in elucidating fluid volume and electrolyte disturbances, as well as in revealing the mechanisms which control renal excretion of fluid and electrolytes during weightlessness.

Hormonal studies from a number of hypogravic experiments (including space flight and zero-g analogs such as water immersion, bed rest, and head-down tilt) have been difficult to interpret. The results are often inconsistent, conflicting, and paradoxical in relationship to known concepts of endocrine control. For example, the extensive Skylab studies have revealed the following: wide differences between individual crewmen's ADH responses, reductions in ADH accompanied by normal or decreased urine flow, increases in sodium-retaining aldosterone in the face of a developing natriuresis, and elevated levels of angiotensin (known to be stimulated by hypovolemia) at a time when there is an accumulation of fluid in the upper body. It has been difficult to obtain supporting evidence that would help explain anomalous hormonal behavior and in some cases, as in acute exposure to

weightless space flight, records of important dynamic events are entirely lacking. The purpose of the present study is to subject the diversity of hormonal data that has accumulated to date to the rigorous analysis provided by mathematical modeling and computer simulation. The desired result was to unravel the ambiguities and arrive at a common testable hypothesis.

An understanding of the endocrine responses to weightlessness involves a number of complex and interrelated systems including those involving fluid and electrolyte regulation, circulatory and renal dynamics, body biochemistry, and metabolic function. A mathematical model which can integrate these physiological functions should be well suited to provide a qualitative understanding of the overall system's general regulatory behavior and a quantitative interpretation of the specific findings from space-flight related research. Such a model was developed a number of years ago by Guyton and co-workers (Guyton et al., 1972; White, 1973) and subsequently modified for application to the stresses of gravity and weightlessness (White, 1974; Leonard and Grounds, 1977; Leonard et al., 1978). The Guyton model represents an attempt to understand the interactions between acute and long-term adaptive control of the body fluids and the circulation (Leonard, 1985). As such, the model has proved valuable in understanding system behavior, testing hypotheses, and interpreting data for the related stresses of water immersion (Leonard, 1982b), supine bed rest (Fitzjerrell et al., 1975; Leonard and Grounds, 1977), head-down tilt (Leonard et al., 1978; Srinivasan and Leonard, 1982; Leonard, 1984a), and space flight itself (Leonard et al., 1977, 1979; Leonard, 1982a).

The use of models often suggests new ways to look at data which has already been analyzed by more traditional methods. The analysis of hormonal behavior, for example, must consider a variety of controlling factors (such as blood pressures, plasma electrolyte concentrations, and other biochemical agents). These controlling factors may act competitively by stimulating hormone secretion in opposite directions, and affect more than one hormone to different degrees. The ability to adjust model parameters, clamp certain variables at pre-determined values, modify feedback circuits, and rapidly perform simulations which quantitatively compare model responses with data, permits the user of modeling techniques to assist in unraveling these multiple, overlapping, and competing factors. In addition, the dynamic

capabilities of the model indicate time-dependent adaptations and provide a basis for relating short-term and longer-term stress responses. By this means, we demonstrated that experimental flight data is more easily interpretable if analyzed as a time-continuous process involving an acute and chronic phase (Leonard et al., 1977). Observations from one set of experiments during the acute phase may not be comparable to findings from other identical or similar experiments made during the chronic phase. While this may appear obvious, the underlying reasons that make it so are often unclear. Modeling often suggests a basis for understanding counter-intuitive behavior by a rigorous consideration of the adaptive characteristics of complex systems.

A guiding hypothesis in this study was that alterations observed in endocrine function can be accounted for by normal physiological feedback regulatory processes. It follows, therefore, that all stresses which induce headward fluid shifts may be presumed, in the absence of other influences, to lead to similar responses. Accordingly, it appears reasonable to compare results from such diverse stresses as water immersion, head-down tilt, supine bed rest and space flight. This argument, in fact, is one basis for utilizing certain experimental one-g studies as analogs of space flight and making inferences regarding true weightlessness. In the process of integrating this data one must be aware of the fact that each of the hypogravic maneuvers presented here has been studied over a different time-frame (see Figure 1). Thus, water immersion studies are typically studied during a single laboratory session of approximately 4 to 6 hours; head-down tilt studies have been reported for periods of 24 hours to a week; supine bed rest has been carried out over a larger range of time spans, but in those cases where endocrine measurements were performed, the length of study was less than one month; exposure to weightless space flight was extended to three months during the last of the three Skylab missions. It can also be observed in Figure 1 that data are not often available in the cases of bed rest and space flight during the early portions of the study. Thus, the acute responses to the initial zero-g headward fluid shifts can presently be inferred only from data collected during water immersion and the less frequently studied head-down tilt maneuvers. When one compares the longer-term endocrine responses from space flight to those of other ground-based studies considerable divergences

HYPOGRAVIC-STRESS STUDIES

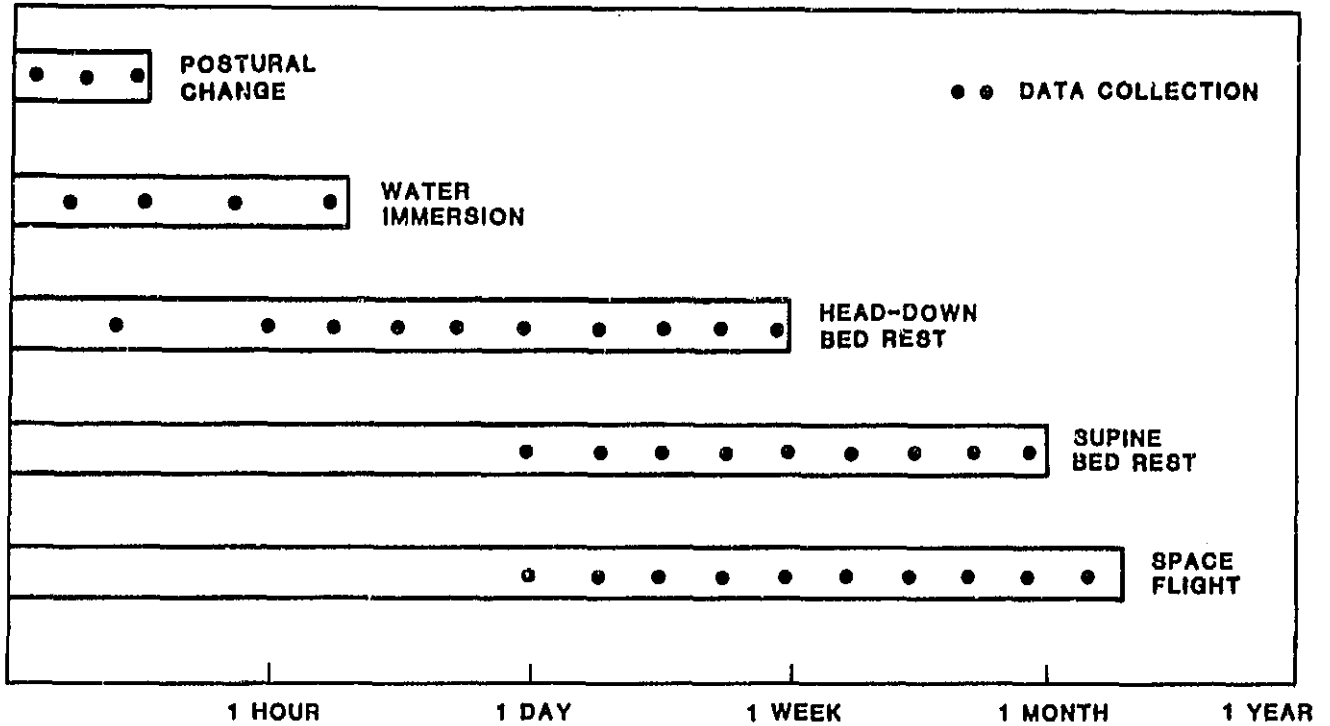


Figure 1

are found. It is also not uncommon to find quite opposite results for so-called identical studies; that is, between one bed-rest study and another. These differences may be caused by fundamental differences in stresses such as the immobilization of bed rest versus the ambulatory nature of working in a space laboratory. More subtle differences may exist that can be just as significant, such as the degree of metabolic activity, the physical condition of the subjects, and the amount and composition of their diet. An important aspect of the present study is the identification and reconciliation of some of these factors.

This report is part of a larger study devoted to understanding the entire range of circulatory, fluid, electrolyte, and metabolic disturbances in space flight (Leonard, 1984b). In this case the particular emphasis is on understanding the behavior of three major renal-regulating hormones. The first section of the report concerns the analysis of only one of these hormones, ADH. A second section will extend the analysis to include aldosterone and angiotensin, as well as propose a more generalized theory of renal-endocrine behavior during hypogravic stress. It is recognized that other hormones such as natriuretic factor and prostaglandins are also important controllers of renal excretion of fluids and electrolytes. However, the discovery of these agents and their specific mechanisms of action is of more recent vintage. Little or no information is available regarding their behavior or function during space flight or simulated space flight. Therefore, this report will only discuss the three renal-regulating hormones which have been most extensively studied.

2.0 ANALYSIS OF ADH BEHAVIOR DURING HYPOGRAVITY

An analysis of ADH regulation and its behavior during hypogravity will serve to illustrate the problems associated with a larger class of hormones. The characteristics of these hormones include the following: they are under the control of multiple factors, they exert a significant influence on renal excretion of water or salts, they have been studied extensively during space flight itself or space-flight related experiments, and their behavior during these experiments has been difficult to interpret in relation to known

concepts of endocrine control. A description of the gross characteristics of ADH control will provide a context in which to understand the experimental flight data that will be presented later.

Dual Control Concept of ADH Release

It is well known that ADH secretion inhibits urine formation. However, the role of ADH in overall fluid-electrolyte regulation is not settled. To a large extent, the difficulty stems from the occasionally opposing functions that ADH plays in two separate feedback pathways, one controlling blood volume and the other controlling plasma osmolarity. Gauer and associates (1970) are proponents of the hypothesis that ADH is primarily involved in regulating extracellular fluid balance. They believe that ADH reliably responds to minor disturbances in central blood volume as reflected by pressure changes in the cardiac atria. Alternatively, Goetz and colleagues (1975) are representative of a group of investigators who claim that ADH secretion is not sensitive to small changes in blood volume and that the osmoreceptor-ADH pathway is sufficient to explain normal regulation of both extracellular volume and tonicity.

Guyton and co-workers (1975) have attempted to integrate both these points of view by proposing an integrative mechanism for fluid-electrolyte balance (see Figure 2). The elements in this scheme include a volume receptor-ADH pathway that responds to acute, rather than prolonged, volume (and therefore atrial pressure) disturbances. The lack of long-term effectiveness of this pathway is credited to receptor adaptation. This is consistent with the concept that volume receptor tissues are elastic and adapt to changing pressures within reasonable periods of time (i.e., 24 to 48 hours). Thus, pressure changes, if maintained, exert a smaller and smaller influence on ADH. Guyton's concept also includes a sensitive osmotic receptor-ADH pathway that can override inputs from the volume receptors, and an ADH-thirst drive which receives inputs from both volume and osmoreceptors. In this view, ADH has a short-term role in contributing to the correction of large changes in blood volume, but it has an even more important responsibility (together with thirst-drive) for long-term control of plasma osmolarity. (Inasmuch as sodium contributes about 95 percent to total extracellular osmolarity, this mechanism

DUAL CONTROL CONCEPT FOR ADH RELEASE

Osmo. vs Volume Control

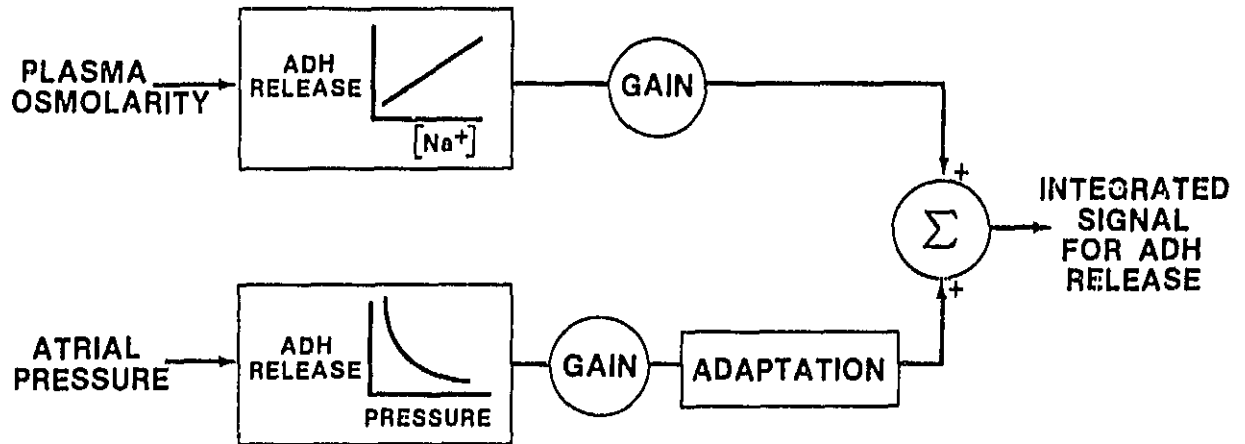


Figure 2

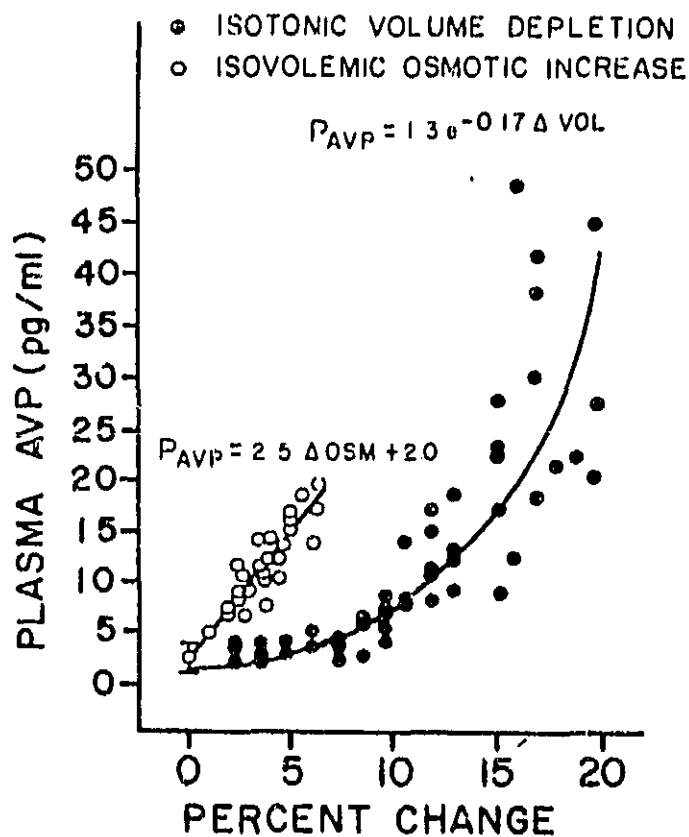
becomes essentially a means for controlling plasma sodium concentration.) The ability of volume receptors to adapt to sustained volume disturbances, the decreased effectiveness of ADH on urine output over long periods of time, and the fact that there are other more powerful mechanisms available for long-term control of blood volume (i.e. especially the renal-body fluid pressure control mechanism; see Guyton et al., (1975)) support the argument for a minor role of ADH in the long-term control of body fluid volume.

Guyton's concepts of ADH control are supported by the studies of Robertson (1981) and Dunn et al., (1973). Specifically, it has been shown that ADH has a sensitive, linear dependency on plasma osmolarity while the corresponding sensitivity on blood volume is highly non-linear, showing little influence at small volume changes and a larger influence (larger than the sensitivity to osmolarity) at volume changes greater than 15 to 20 percent of total blood volume (see Figure 3). Therefore, it appears that under certain stressful conditions, large, acute changes in blood volume can become the dominant factor controlling ADH secretion, while under most normal physiological conditions ADH responds to, and regulates, changes in plasma osmolarity. (It is important to note, however, that the most compelling evidence leading to these conclusions (i.e., data of Figure 3), concerned the influences of low pressure and increased osmolarity on increases of ADH, and not the reverse situations leading to ADH suppression which is of prime interest in the weightlessness response.) Interpretation of disturbances in ADH levels must, therefore, take into consideration the dual volume osmo-receptor pathways affecting ADH, the relative sensitivities of these volume receptors, and their ability to adapt.

Review of Experimental Data

It would be useful to review the ADH responses of space flight, and, especially, to compare those findings to observations from other hypogravic stress studies performed in a one-g environment. Also, in accord with the concepts presented above, interpretation of this data would require some knowledge of the two major ADH stimulants that accompany the hormonal responses; i.e., changes in atrial or central venous pressures and plasma sodium concentrations.

EFFECT ON ADH CAUSED BY CHANGES IN PLASMA OSMOLARITY OR BLOOD VOLUME



From Dunn, et al (1973)

Figure 3

A review of the pertinent literature reveals that, surprisingly, no studies have been reported that simultaneously measure the ADH, pressure, and plasma sodium concentration responses to either water immersion, head-down tilt, bed rest or space flight. Only in the case of water immersion is it possible to piece together this information from several different studies. In all other cases, data concerning either sodium concentration or more regularly, central venous pressure, is lacking. The reasons for this scarcity of data may be presumed to be related to the difficulty of directly measuring central venous pressure by indwelling catheters and the relative unavailability of a sensitive radio-immunoassay for ADH.

A representation of the data which is available is presented in the Appendix and summarized in qualitative form in Figure 4. For convenience, the response of each parameter shown here will be described first, and this will be followed by an attempt to integrate these experimental findings in terms of the regulatory concepts of ADH.

1) ADH Response:

Several investigators (Epstein et al., 1975; Greenleaf et al., 1980) have now documented the reduction in plasma ADH during water immersion that was predicted some years ago by Gauer and Henry (1963). In these studies ADH was found to be reduced by at least 50 percent of control within one to two hours and remained at these levels until the end of the immersion period (about 4 to 8 hours after the start of the study). The head-down tilt studies (-5°) by Blomqvist and co-workers (Nixon et al., 1979; Blomqvist et al., 1980) found a more gradual suppression of plasma ADH, whereby it reached a minimum at five hours but then returned to and rose above (+60 percent) control levels at the end of 24 hours, the terminating point of the tilt study. Thus, an interesting biphasic response was noted in these one-day studies.

An extended head-down tilt study of seven days was conducted as part of a joint US/USSR hypokinesia investigation (Joint US/USSR Hypokinesia Study, 1979). During the seven days of head-down tilt, plasma ADH was reduced on Day 2 (-18 percent) and Day 7 (-65 percent) but was elevated at an intermediate

OSMOLARITY AND VOLUME CONTROL INFLUENCES ON ADH

	WATER IMMERSION	HEAD-DOWN TILT			BED REST	SPACE FLIGHT		
	6 HR	6 HR	24 HR	7 DAY	2 - 5 WK	1	2	3 MO
PLASMA SODIUM CONCENTRATION	↓	↔ [?]	↔ [?]	↓	↓	↓	↓	↓
CENTRAL VENOUS PRESSURE	↑	↑	↓	↓?	?	?	?	?
ADH	↓	↓	↑	↓	↑OR↓	↑	↓	↓

Figure 4

point on Day 4 (+34 percent). The average decrease of these samples was -16 percent. In these same subjects, urinary ADH was found to be reduced on Day 1 (-12 percent), but was elevated on the average thereafter (+28 percent). It is not apparent why urinary and plasma ADH measurements gave different results in this study, but plasma ADH will be considered the primary measurement in this report. ADH has been measured in supine bed rest in several studies of two to four-week durations. As noted from the summary in Appendix Table A-2, these responses were quite variable, ranging from -33 percent to +56 percent. An assessment of these one-g results is made difficult because of the different stresses involved and the different times at which measurements were obtained. Taken as a whole, however, it seems plausible to suggest that ADH is diminished at a time when the most dramatic fluid volume disturbances are occurring during the acute phases of both water immersion and head-down tilt. In each case, the acute phases may last at least five to six hours. Thereafter, however, the data are more equivocal, for example: no extended results are available from water immersion, 24 hours head-down tilt indicates a return to and above control values, 7-day head-down tilt suggests a continued reduction of plasma ADH, and supine bed-rest results are variable.

The most complete set of hormonal observations during space flight was collected during the three Skylab missions lasting from one to three months. All nine Skylab astronauts were exposed to weightlessness for at least 28 days. Daily urinary ADH measurements of each three-member crew for this time period (with the exception of the first day of flight for which no measurements were made) are shown in the Appendix, Figure A-1. There is considerable variation between the crew of the 28-day flight and the other two flight crews, but a general trend appears to exist whereby ADH gradually becomes suppressed during the first month of flight. This trend is more readily visualized in Figure 5 by averaging the results of the nine subjects for both the first 28 inflight days and the first 17 postflight days. On the average, ADH is elevated during the first week inflight and thereafter is suppressed. The crews which remained in space longer than one month (not shown) also exhibited a diminished ADH throughout the second and third months. Significantly, urinary ADH increased dramatically on the first postflight day,

URINARY ADH DURING AND FOLLOWING SKYLAB MISSION (N-9)

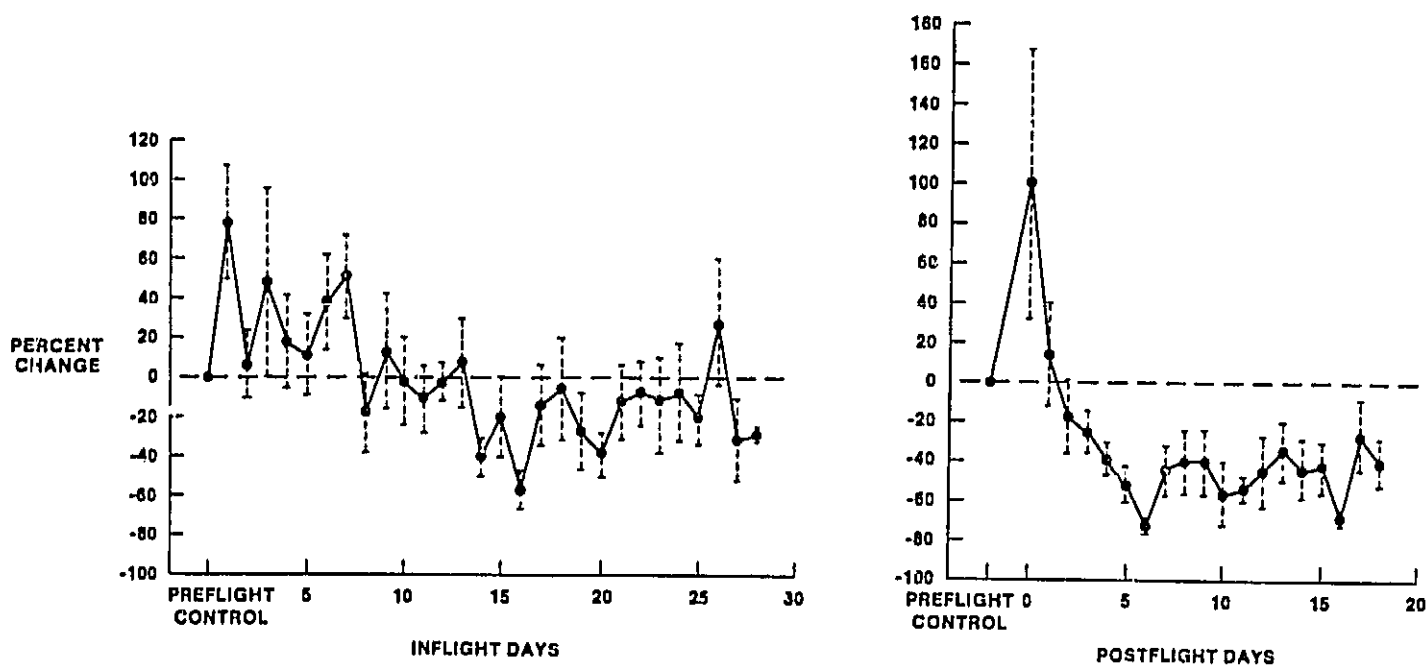


Figure 5

which is consistent with the assumption that ADH was suppressed on the first inflight day, a day during which ADH data were not collected. On the average, therefore, a picture emerges whereby ADH may be presumed to be suppressed on the first inflight day and also after a week of flight, rising transiently during the time between these periods.

ii) Plasma Sodium Concentration

As data accumulates, it is becoming apparent that there is a small but significant decline in plasma sodium concentration (and plasma osmolarity) in humans subjected to space flight and other forms of hypogravic stress (see Appendix, Figure A-2). During water immersion, reductions of up to 5 meq/liter have been observed as early as the first hour (Khosla and DuBois, 1979), with slightly smaller changes of 2 to 3 meq/liter occurring over the first 4 to 8 hours (Epstein et al., 1975; Greenleaf et al., 1980). Changes of similar magnitude (i.e., 2 to 5 meq/liter) have been reported for the 7-day head-down tilt study mentioned previously, the supine bed rest studies of Chobanian et al. (1974) and Johnson and Mitchell (1977), and the Skylab missions (Leach and Rambaut, 1977). There are also a number of ground based studies in which plasma sodium concentration did not decline, but with only one or two exceptions, ADH measurements were not performed at the same time. Therefore, those studies were not included in the analysis of Figure 4. Of the studies considered here, only the head-down tilt study of Nixon et al., (1980) reported that plasma sodium concentrations did not change. However, their data were not presented; thus, question marks are shown in Figure 4.

Whether or not a decrement in plasma sodium concentration is part of the normal response to weightlessness or is due to other factors is not yet known. Several investigators have hypothesized that during the acute stress of water immersion there may be an influx of hypo-osmotic interstitial (and perhaps intracellular) fluid from the legs into the circulation (Greenleaf et al., 1981; Khosla and DuBois, 1979). Longer-term changes in plasma sodium may be maintained by dietary alterations. Changes in the absolute and relative amounts of water and salt in the diet are known to occur in water immersion and bed-rest studies, and these undoubtedly do play a part in influencing plasma electrolyte concentrations. (A model analysis of dietary effects will

be illustrated in section 3.0 of this report.) However, the data reported in most studies are inadequate to assess the influence of diet. Nevertheless, in space flight itself, it was found (in the Skylab crew) that dietary intake of water and sodium did not change by more than a few percent from control levels (Leonard et al., 1977). In fact, the sodium and water ratio of the diet increased mildly, so that this effect cannot explain the decrease in plasma sodium concentration nor its failure to return to normal over a three month period of weightless space flight.

The fact that hyponatremia persists over long periods of time during space flight is somewhat puzzling for the following reasons: a) there was no dietary cause; b) human thirst and renal mechanisms are highly suited to maintain normal sodium levels within narrow limits; c) the hormones known to regulate water and salt were at levels appropriate to correct a hyponatremic condition (that is, sodium-retaining aldosterone was high and water-retaining ADH was low); and d) in spite of these hormonal changes favoring a sodium-poor urine, the Skylab crew actually exhibited sodium-enriched urine, thus acting to maintain the hyponatremic condition. One can only speculate about the adaptive value of maintaining a hyponatremic body fluid. Decreased serum sodium found during chronic sodium depletion studies has been interpreted as maintaining the extracellular volume at the expense of extracellular osmolarity (Andreoli et al., 1977). Applying this interpretation to the space-flight situation, it may be hypothesized that correction of hyponatremia would be maladaptive, because it could involve excretion of extracellular fluid volumes which are already significantly reduced.

iii) Venous Pressure

Because intravascular fluid disturbances cause a greater volume change in the highly compliant venous portion of the circulation than they do in the arterial circulation, a knowledge of central venous pressure would significantly contribute to the interpretation of fluid redistribution during hypogravic maneuvers. For example, the rise in central venous pressure accompanying headward fluid shifts reflects the magnitude of central hypervolemia, the degree of cardiopulmonary receptor stimulation which affects sympathetic and endocrine activity, and ultimately, the extent of homeostatic correction of the pressure disturbance by either volume reduction or increased

vascular capacitance. In spite of the importance of this measurement, it is surprising that there is such a scarcity of data reflecting changes in the pressure of the venous circulation.

Two groups of workers (Arborelius et al., 1972; Echt et al., 1974) found a dramatic rise of 12 to 15 mmHg in transmural central venous pressure at the onset of water immersion. Following this initial increase there appeared to be a slight, steady decline during the next three hours, the longest time for which central venous pressure measurements are known in immersion. However, even after three hours, central venous pressure (and cardiac output) was considerably elevated. In partial support of the immersion results are the findings from measurements of lower body positive pressure (LBPP) in monkeys (Kass et al., 1980) and in humans (Echt et al., 1972). These results indicate an increase in central venous pressure that is maintained for several hours and possibly even several days (Moore-Ede, private communication). However, in head-down tilt studies lasting up to 24 hours in man (Gauer and Hull, 1954; Nixon et al., 1979), or up to seven days in rats (Popovic, 1981), central venous pressure rises as expected; but, in contrast to water immersion and LBPP findings, central venous pressure (and cardiac output) then falls to control, and in some cases, below control. The possibility of central venous pressure diminishing below control levels is of particular interest, because such a prediction was suggested from computer model simulations of bed rest some time ago (Fitzjerrell et al., 1975) and received confirmation by indirect central pressure measurements during U.S. (Kirsch et al., 1984) and Soviet space missions (Yuganov, et al., 1977).

It appears that the central venous pressure response to water immersion is somewhat different than that observed for head-down tilt. The circulatory responses (venous pressures and cardiac output) are of greater magnitude during immersion compared to head-down tilt (12 to 15 mmHg versus 2 to 5 mmHg) and persist at least for several hours rather than returning to baseline. These differences may reflect the specific hydrostatic conditions that are associated with upright immersion, including a transthoracic pressure gradient and compression of submerged tissues (Nixon et al., 1979). It is also possible that the central shift of fluids is larger during immersion than during head-down tilt. The transient behavior of central venous pressure

during head-down tilt is supported by intravenous blood infusion studies in which one liter of blood (similar to the 700 ml increase in central blood expansion measured in immersion) causes an instantaneous rise in central venous pressure similar to that measured in immersion (Guyton et al., 1973). However, compensating mechanisms (i.e., blood volume normalization, stress relaxation of the capacitance vessels, and increased flow resistance) permit the central venous pressure to return to normal within an hour or so. Extended measurements during water immersion are warranted, however, before a definitive comparison between immersion and head-down tilt can be made.

As summarized in Figure 4, central venous pressure has only been measured directly during the first three hours of water immersion and the first 24 hours of head-down tilt. After an initial increase, central venous pressure may fall toward normal or below. No direct measurements have been performed during long-term bed rest or space flight. In one bed-rest study (Joint US/USSR Hypokinesia Study, 1979), the end-diastolic volume (which may be taken to be a gross estimate of venous pressure changes) was reduced during the first four days of head-down tilt before rising on the seventh and last day. Speculation that central venous pressure remains elevated during long-term space flight (Gauer, Space Science Board, 1979) is yet to be confirmed. An experiment aboard the recent Spacelab-1 seven-day flight showed peripheral venous pressure to be below control after one-day exposure to zero-g (Kirsch et al. 1984).

iv) Interpretation of Data

Of all the data presented, representing a variety of stress conditions and a large range of stress exposure times, the easiest to explain are the acute responses (first several hours) and the longer-term responses (two to three months). Intermediate-term studies exhibit conflicting results which are substantiated by incomplete data.

In water immersion studies, the acute suppression of ADH, measured in both plasma and urine during the first six hours of stress, is entirely consistent with the observed changes of plasma sodium concentration and central venous pressure. It is not easy, however, to conclude which of these

stimuli has the predominant effect. According to the ADH dose-response curves of Figure 2, the changes reported for plasma osmolarity and for central volume disturbances during immersion lie in the ranges where ADH could be significantly altered. One group of water immersion investigators support the notion that ADH responds primarily to blood volume receptor influence (Gauer, 1975; Epstein 1976, 1978; Greenleaf et al., 1980). More recently, other investigators have suggested that ADH suppression during water immersion is due to sodium concentration changes alone (Greenleaf, et al., 1981; Kosola and DuBois, 1979). It appears that simultaneous measurements of plasma sodium, central venous pressure, and ADH have not been made in a single immersion study; likewise, no attempts have been made to control the ADH stimulating factors at fixed levels. These types of studies are important to discern the relative significance of each component of a multi-pathway feedback loop.

In spite of these uncertainties, it is useful to note that diminished values of ADH have been reported or can be inferred from data obtained during the first day of water immersion, head-down tilt, and space flight. Significant concurrent fluid shifts and central hypervolemia were probably strong enough to elicit that ADH response. Also, in several cases, it has been stated that plasma sodium is not altered during this time-frame (Nixon, et al., 1979; Epstein et al., 1975). Therefore, it is reasonable to conclude that volume control of ADH is undoubtedly present, and that osmolar control is of a secondary nature, probably depending upon the degree to which plasma sodium may be changing. The benefits of a strong ADH-renal response to acute volume loads are obvious.

The predominance of acute volume control of ADH may also be concluded from the head-down studies of Nixon et al. (1979), who demonstrated that ADH and central venous pressure are inversely related, even when central venous pressure returns to and falls below control levels by 24 hours after tilt. That is, as central venous pressure declines from its maximum value, ADH begins to rise from its minimum value. Nixon's study also suggests that the acute rise in central venous pressure and the suppression of ADH may be only a transient phenomena, because these quantities reverse direction between 2 and 24-hours.

The interpretation of data is much less certain for head-down tilt, bed rest, or space flight studies carried out beyond one day. Not only are ADH responses equivocal, but central venous pressure measurements are not available during this time period (see Figure 4, and Appendix A-1). Plasma sodium concentration, however, has been consistently reduced in a number of instances throughout the entire period of study. The most long-term studies of ADH on record were those of the Skylab missions; these studies showed that urinary ADH is significantly reduced, on the average, after the first week of flight and until the end of the mission nearly three months later (see Figure 5). The degree of ADH suppression during these chronic states is entirely consistent with the observed hyponatremia and with the concept that ADH subserves the long-term control of plasma osmolarity. Although a decline in ADH is also consistent with an unmeasured elevated central venous pressure (expected by some investigators), the direction of central venous pressure may be of little consequence if volume receptor adaptation occurs.

The picture that emerges from this mixture of data is certainly not complete and interpretation cannot be conclusive. However, it appears that suppression of ADH is observed immediately following headward fluid shifts and during chronic hypogravic conditions such as prolonged space flight. In between these two states, the ADH response appears to be quite variable. Similar responses were unexpectedly observed during computer simulations of hypogravic maneuvers. Further investigation of model behavior resulted in an hypothesis that is largely consistent with, but is not proved by, the data reviewed above. Accordingly, ADH responds acutely to the volume disturbances of headward fluid shifts. Later, after blood volume correction has occurred, ADH appears to be under osmo-control. A transition period between these two states may find ADH varying considerably as it responds to the influences of changing central venous pressure and plasma sodium concentration, as well as to volume receptor adaptation. The remainder of this section will be devoted to discussing the simulation studies which form the foundation for this hypothesis.

Separate Effects of Pressure and Osmolarity on ADH

The effects of each major stimulus for ADH-secretion are illustrated schematically in Figure 6. These graphs are based on simulations of the Guyton model. Numerical values have been omitted from both scale axes to emphasize the qualitative aspects of the changes. The upper part of Figure 6 demonstrates two types of central venous pressure scenarios during hypogravic stress when the osmolarity influence is removed (i.e., sodium concentration is held constant at its control value). Curve A represents the concept favored by Gauer and co-workers, namely, that the central venous pressure remains elevated, while Curve B illustrates the general behavior of central venous pressure measured during the head-down tilt studies of Blomqvist and co-workers. In the latter case, central venous pressure rises only transiently before diminishing below control. The ADH responses to each of these cases are shown by the curves labelled A and B, respectively. As expected, ADH is inversely related to central venous pressure changes. The volume-receptor adaptation effects of the model were turned off during these simulations. It should be noted that both of these pairs of pressure-ADH responses have been observed in humans. The curves labelled A have been reported during water immersion (Echt et al., 1974; Greenleaf et al., 1980), while the curves labelled B are similar to those found by Nixon, et al., (1979). In those studies, however, there was no attempt to maintain the constancy of plasma sodium concentration.

The lower part of Figure 6 shows the simple direct relationships between plasma sodium concentration and ADH when central venous pressure is maintained at constant normal levels. Small incremental increases in plasma sodium concentration are induced by the model during hypogravic stress simulations unless a natriuretic factor is introduced, in which case plasma sodium concentration is depressed.

Note that a combination of decreased plasma sodium concentration and depressed central venous pressure responses should result in opposite influences on ADH (see the four curves labelled B). Inasmuch as these conditions have been observed during various hypogravic maneuvers, it is easy to understand why a quantitative analysis using a computer model would be useful for predicting the dynamic behavior of the integrated ADH response.

SEPARATE EFFECTS OF PRESSURE AND OSMOLARITY ON ADH DURING HYPOGRAVIC STRESS

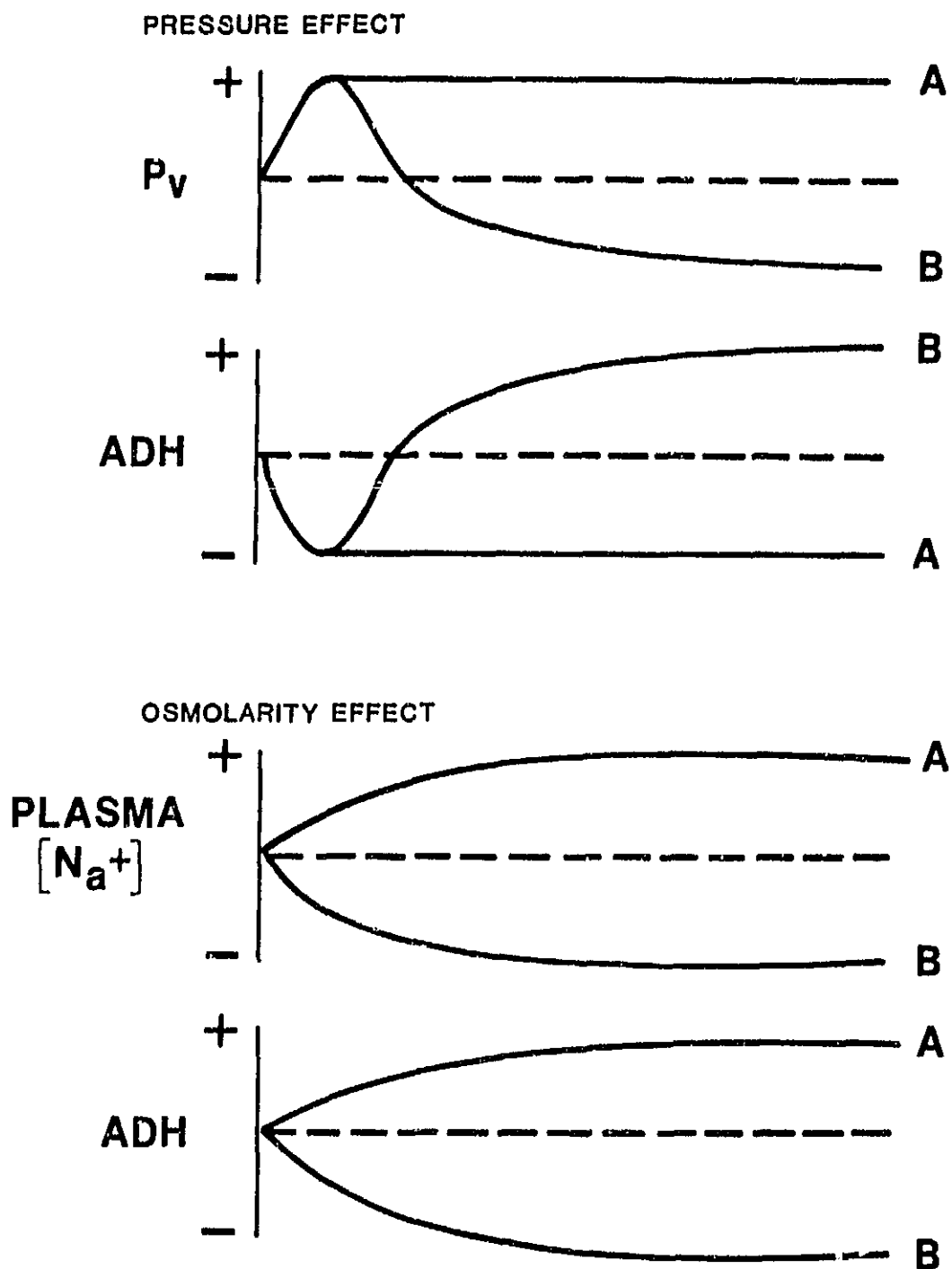


Figure 6

Combined Effects of Pressure and Osmolarity Disturbances

In order to illustrate the complex nature of the ADH response during simultaneous pressure and osmolarity disturbances, four simulations of head-down tilt were performed (Figure 7). These consisted of two types of sodium control, one leading to hypernatremia (Case A) and one leading to hyponatremia (Case B), and two types of ADH control, one osmolarity-sensitive (Case 1) and one pressure-sensitive (Case 2). Head-down tilt was simulated in the model by adjusting the angle with respect to the horizontal to -4° . (See Leonard, 1982 for a complete description of the methods used to simulate head-down tilt.) In the model, ADH secretion was made more sensitive to plasma sodium concentration or central venous pressure by altering the gain parameters shown in Figure 2. All four simulations predicted an almost identical central venous pressure response to head-down tilt which was in basic agreement with the data of Nixon et al., (1979). However, the ADH response of the model was quite different depending upon the plasma sodium concentration and type of control imposed upon the ADH subsystem.

Consider first the response of the model for the case of hypernatremia combined with an osmo-sensitive ADH controller. This response (see Fig. 7, Curve A-1) indicates the behavior exhibited by the Guyton model as it was originally conceived (Guyton et al., 1972). It can be noted that ADH remains depressed for about only 15 minutes before hypersecretion of ADH begins. This behavior now appears unrealistic when compared to either water immersion or head-down tilt data.

Therefore, the model was modified in two ways. First, a natriuretic factor was added to the model which allowed excess sodium renal excretion and the development of hyponatremia to occur in the face of acute headward fluid shifts. Hyponatremia is often observed in water immersion, bed rest and space flight as discussed earlier. The second modification involved increasing ADH sensitivity (gain) of ADH to atrial pressure changes at the expense of ADH sensitivity to plasma sodium concentration changes. This latter modification was suggested by the data of Dunn et al., (1973) which demonstrated (in mice) that ADH is more sensitive to osmolarity than to small changes in pressure at the normal operating point, while the relative sensitivity to pressure (or blood volume) increases dramatically for larger changes in volume.

COMBINED EFFECTS OF PRESSURE AND OSMOLARITY ON ADH DURING HEAD DOWN TILT

CASE A: HYPERNATREMIA

CASE B: HYPONATREMIA

CASE 1: OSMOSENSITIVE CONTROLLER

CASE 2: PRESSO-SENSITIVE CONTROLLER

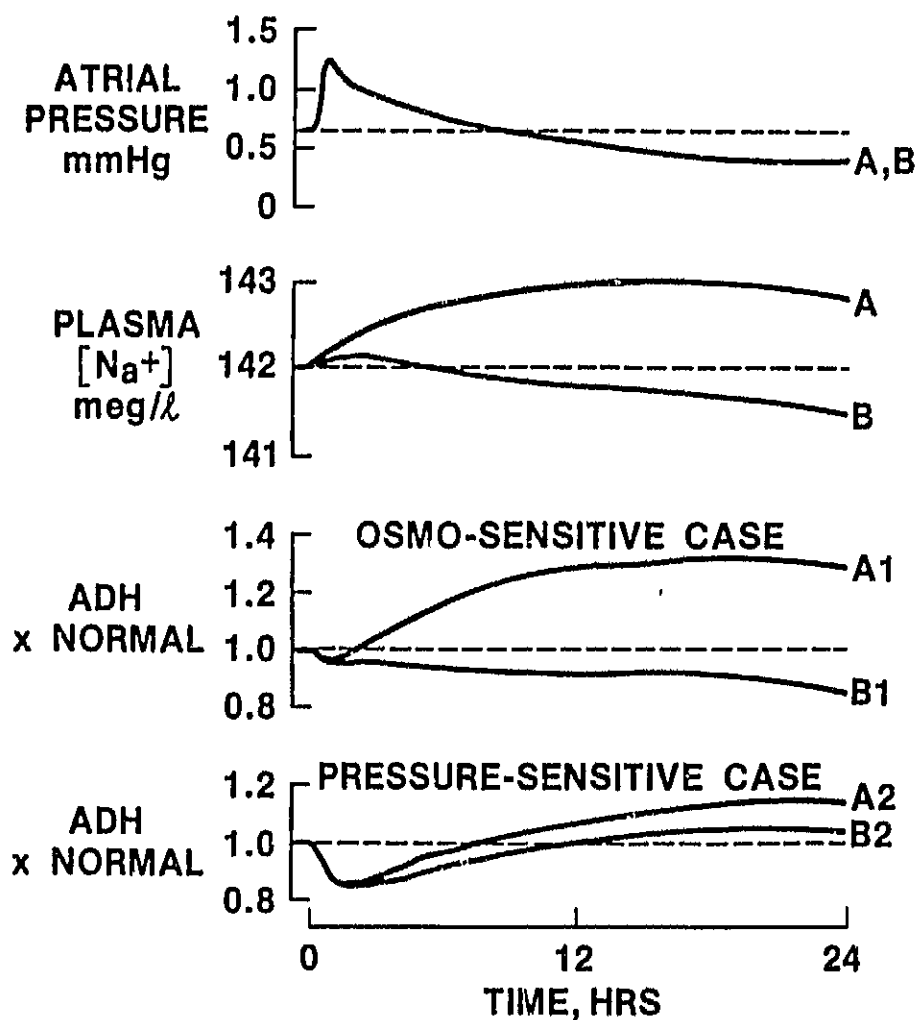


Figure 7

When the natriuretic factor was included (to produce hyponatremia), together with an osmo-sensitive ADH controller, a decrease in ADH was predicted (Fig. 7, Curve B-1) consistent with known water-immersion data and early periods of head-down tilt. But both ADH recovery and overshoot associated with more prolonged exposures to head-down tilt were absent from the simulation. This latter phenomena was, however, predicted by the model for the case where ADH was made pressure sensitive. In fact, for the pressure-sensitive case, the same general biphasic response was predicted whether plasma sodium concentration was above or below control levels (Fig. 7, Curves A-2 and B-2).

These responses can be easily understood in terms of the system diagram of Figure 2. For example, in Case A-2, ADH is under the influence of primarily atrial pressure, so that the initial increase in pressure causes ADH to fall; later, when pressure falls, ADH rises. The smaller effect of plasma sodium is such that an increased sodium concentration will cause ADH to rise somewhat higher than if it were responding only to pressure changes.

Therefore, the conclusion drawn from this analysis is that the original formulation of the Guyton model (which attributes a higher sensitivity to osmolarity-control) may not be correct. Specifically, ADH control appears to be under the influence of pressure-sensitive receptors during both water immersion (up to 5 hours) and head-down tilt (up to 24 hours). This conclusion is in basic agreement with those reached by the experimental studies of Gauer (1975), Greenleaf et al. (1981), and Nixon et al. (1979).

Longer-Term ADH Response: Effects of Pressure Receptor Adaptation

In contrast to the biphasic response of central venous pressure, whereby venous pressure first increases and then decreases below control and remains depressed, it is also useful to consider the other alternative; namely, that central venous pressure remains elevated throughout long-duration exposures of hypogravity. As explained previously, both scenarios have been suggested by ground-based studies and they are awaiting the insight resulting from direct space-flight measurements. Figure 8 illustrates the generalized results obtained from a simulation study in which the ADH response to these two

VARIOUS SCENARIOS OF ADH RESPONSE DURING SPACE FLIGHT

(Assumes Hyponatremia)

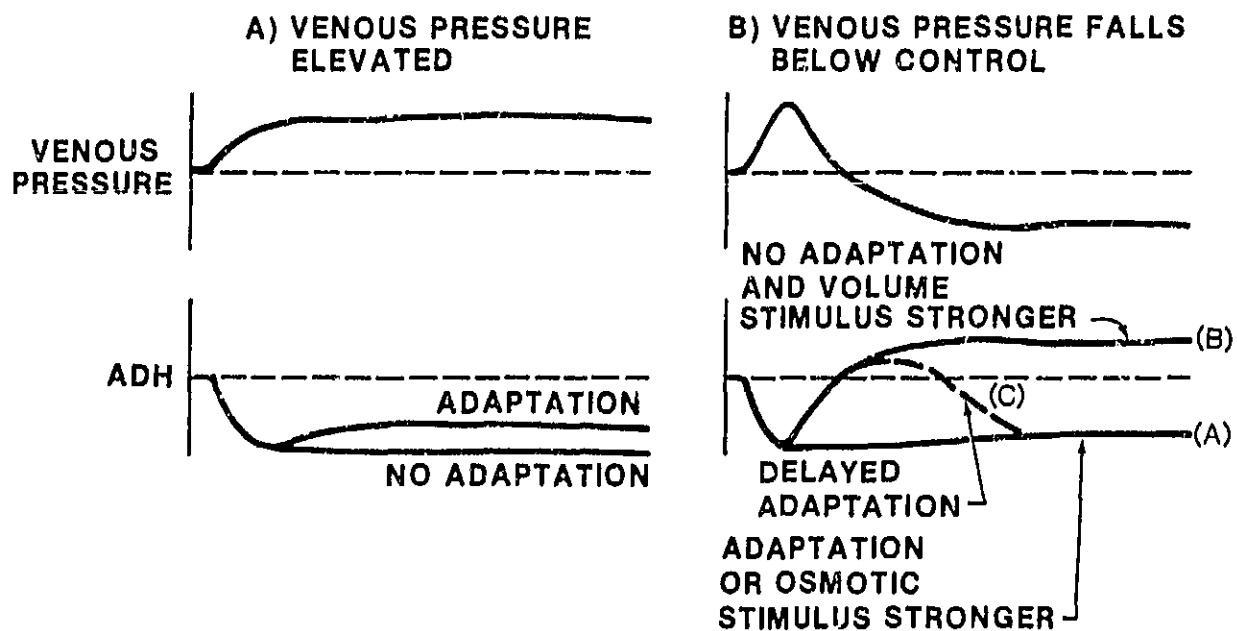


Figure 8

scenarios were considered. The existence of hyponatremia was assumed for both scenarios in agreement with existing data.

Longer-term behavior of pressure disturbances should also consider the effects of pressure receptor adaptation (Guyton et al., 1975). According to this concept of adaptation, any sustained pressure change will eventually cause creep of the elastic receptor tissues until afferent signal strength normalizes. In the model, this effect (see Figure 2) is simulated by permitting the influence of the pressure differential on ADH secretion to wane exponentially over a reasonable period of time (i.e., one to three days).

Considering the case whereby venous pressure remains elevated (in the presence of hyponatremia), the model predicts a simple suppression of ADH due to both pressure and osmotic influences. ADH may rise somewhat if adaptation occurs, but it will still remain depressed due to the influence of diminished plasma sodium concentration. In this situation, adjustment of the model's relative gain values (used for pressure and osmolarity influences) will not alter the general conclusion; ADH will still decrease.

In the second case, it is assumed that central venous pressure rises only transiently before declining below control levels. The initial decline in ADH, while central venous pressure increases, is identical to the simulation results shown on the left side of Figure 8. However, as central venous pressure begins to diminish, ADH becomes responsive to the opposing influences of low pressure and osmolarity. The ultimate behavior of this next portion of the ADH response is a function of: a) the magnitude of the pressure and osmolar disturbances, b) the relative sensitivities of these stimuli on ADH secretion, and c) the presence or absence, and the time constant, of pressure receptor adaptation. If the osmotic stimulus is stronger than the influence of falling central venous pressure, ADH will remain depressed, whether or not adaptation occurs (Curve A). If the volume stimulus is stronger than the osmotic stimulus, ADH will subsequently increase above control, where it will remain should adaptation not occur (Curve B). However, if adaptation to the decrease in central venous pressure occurs and is somewhat delayed, it is possible that ADH will show, subsequent to its initial decline, the biphasic response indicated by the dashed line (Curve C).

In this case, the long-term ADH response is essentially entirely due to osmotic influences.

Current Hypothesis of ADH Control During Hypogravity

We have singled out the last case (Figure 8, Curve C) as a plausible, but unproven, hypothesis that accounts for many of the results observed under a variety of hypogravic conditions, including water immersion, bed rest, head-down tilt, and particularly, space flight. This hypothesis, the essential elements of which are shown in the stimulus-response curves of Figure 9, is based on the following assumptions: a) the central venous pressure response is similar to that obtained during head-down tilt (i.e., an initial increase in central venous pressure occurs as fluids shift headward; this is followed by a decline in pressure, which possibly falls below control for a time); b) hyponatremia develops in hypogravity as has been shown in both short-term and long-term studies; and c) ADH is primarily pressure/volume sensitive during the acute phase which may last until pressures begin to decline toward control levels, after which time the sensitivity gradually shifts to favor osmo-control due to some form of volume-receptor adaptation or pressure normalization.

Although based on several assumptions that have not yet been tested, this hypothesis appears to explain the varied responses summarized in Figure 4. These responses include the early decreases in ADH observed in and expected from water immersion and space flight studies, respectively, a diminished ADH during the last two months of space flight, and the equivocal responses between these two points in time due to competition between pressure and osmo-control.

The triphasic ADH behavior of Figure 9 is perhaps the most complex result of this hypothesis. Other possible responses have been shown in Figure 8. The peak formed by the second and third phases of the ADH response in Figure 9 may not occur if adaptation occurs quickly and/or if osmotic stimuli exert a consistent, predominant influence.

CURRENT HYPOTHESIS FOR ADH CONTROL DURING SPACEFLIGHT

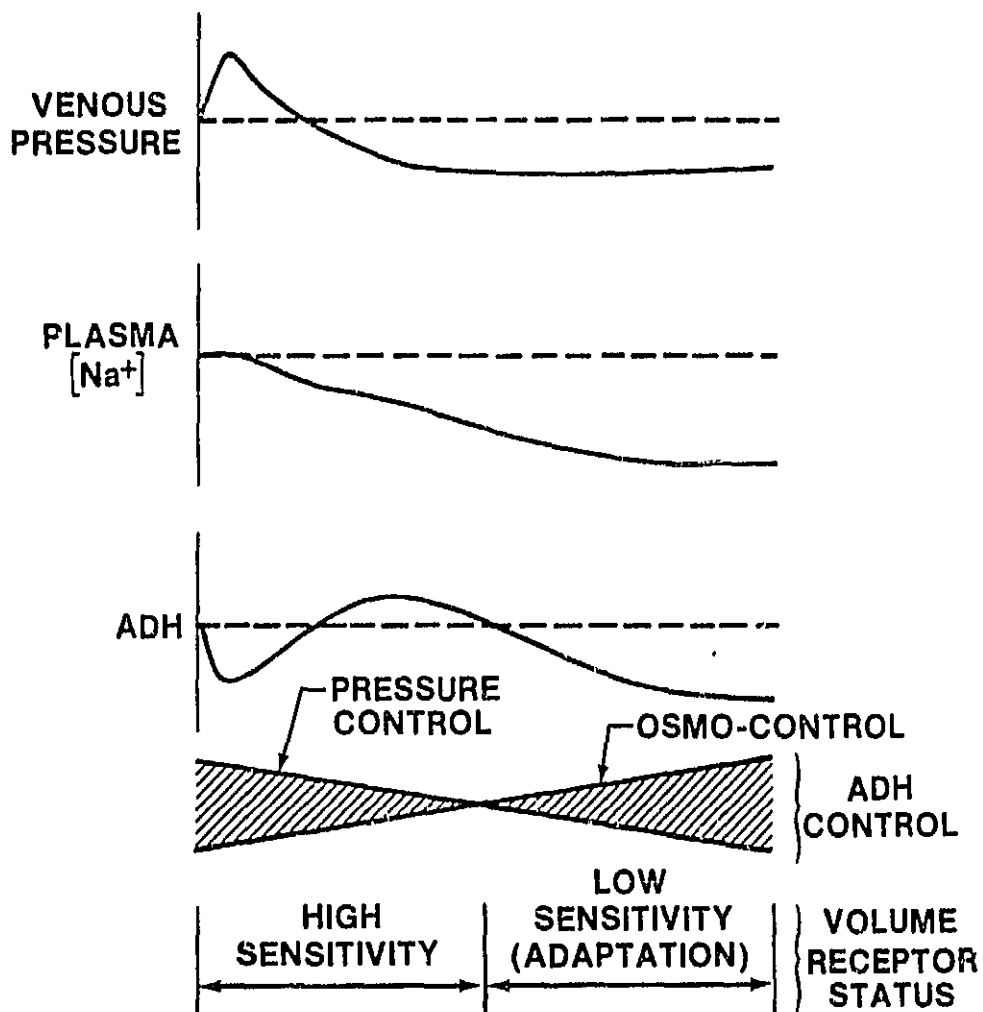


Figure 9

A major assumption of this hypothesis is that ADH is under the long-term influence of only plasma osmolarity. Pressure influences may not be important during chronic hypogravic exposure; blood pressures may normalize as central hypervolemia is relieved or as volume-receptor adaptation occurs. If so, under certain dietary regimes (or other metabolic influences) plasma sodium may increase rather than decrease as considered thus far in this analysis. Thus, a long-term elevation of ADH is consistent with the above hypothesis. That ADH is primarily responsive to chronic osmotic changes in space flight is also consistent with the view that this hormone is a powerful long-term controller of plasma osmolarity (Guyton et al., 1975).

3.0 INTEGRATED ANALYSIS OF ADH, ALDOSTERONE, AND ANGIOTENSIN

The analysis of the ADH response that was presented in the previous section will be extended to aldosterone and angiotensin in this section. This analysis includes a review and comparison of hormone behavior during various hypogravic stresses and over a spectrum of exposure times. Also, a theoretical analysis of the stimulating factors that control the release of each hormone is included. A validation of the theory is presented by a comparison of hormone behavior predicted by the model vs. that measured during experimental studies. Finally, an attempt will be made to identify common threads or mechanisms that could link the action of these hormones together.

Comparison of Hormone Behavior

Figure 10 organizes the endocrine data from a number of hypogravic studies, whether performed in one-g or zero-g, into a qualitative, composite description. This is similar to the analysis of ADH responses that was presented in Figure 4, but has been extended to include and compare the three hormones of interest. All the stresses considered have the common characteristics of an acute reduction in hydrostatic gradients and a resultant headward shift of fluid, while longer-term, these maneuvers lead to reductions in body water, plasma volume, and electrolytes. Based on water immersion and head-down tilt studies, the plasma or urine levels of each hormone of interest demonstrate a suppression during the acute period where comparable space-flight data are lacking (Epstein, 1975; Greenleaf, 1980; Blomqvist, 1980).

HORMONAL CHANGES DURING HYPOGRAVIC STUDIES

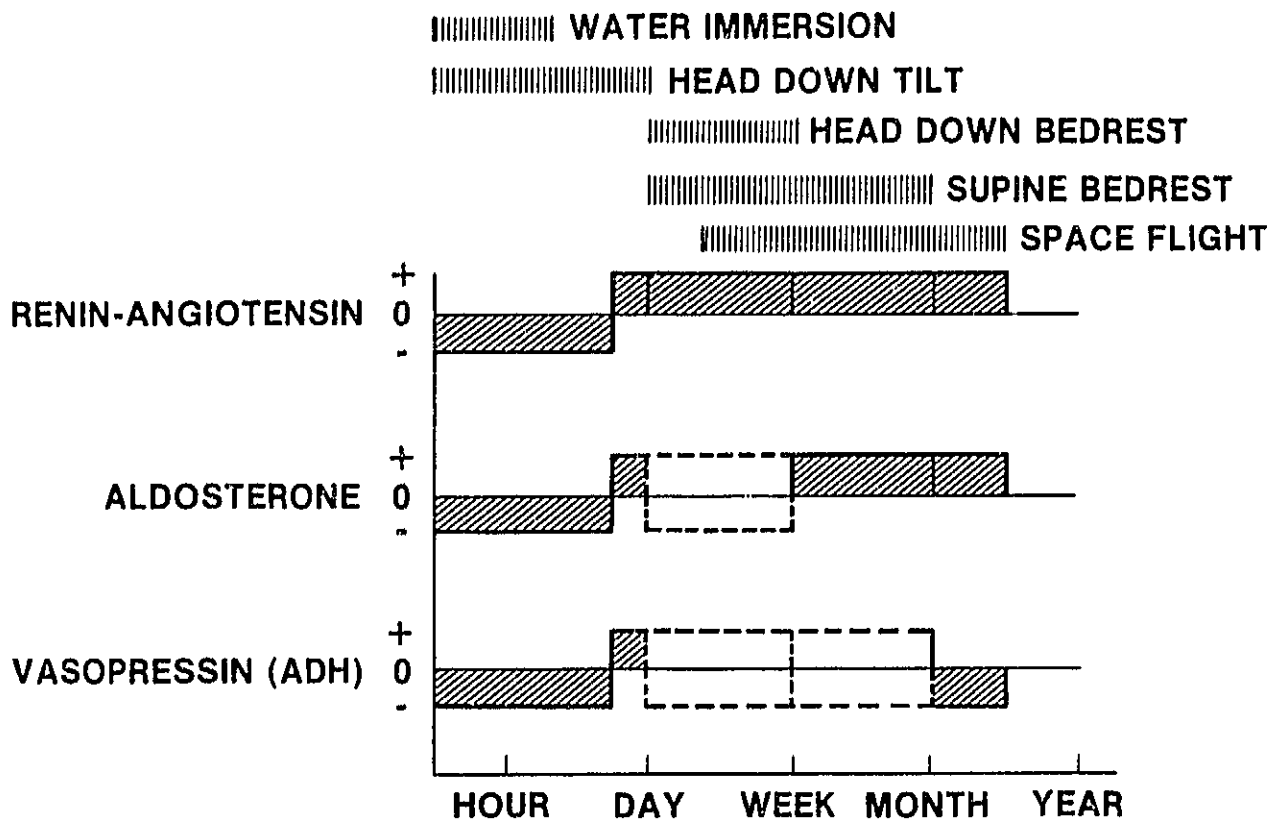


Figure 10

Following this acute phase, renin-angiotensin is the only hormone system which demonstrates a consistent behavior; i.e., in this case a significant elevation in plasma concentration. At the other end of the time scale, during space flights lasting more than one month, aldosterone was found to be elevated and ADH suppressed (Leach & Rambaut, 1977; see Appendix A-3). However, during intermediate periods, data from various bed-rest studies and space flight are not always in agreement (i.e., blank areas in Figure 10). It is the general behavior shown in Figure 10 that needs to be understood. In particular, it is desired to reconcile the differences between the acute and chronic responses as well as the differences among the separate experimental studies.

It should be of interest that previous computer simulation studies were successful in reproducing the experimental observations shown in Figure 10. The computer generated hormonal behavior during water immersion, head-down tilt, and space-flight simulations have been included in the Appendix as Figures A-5, A-6, and A-7. An additional set of model output for a 7-day bed-rest study is presented below (see Figures 13-15).

Analysis of Hormone Stimulating Factors

A schematic description of the factors which influence the three hormones in the Guyton model is depicted in Figure 11. This model is an extension of that previously shown in Figure 2 for ADH. As shown, each hormone is responsive to two general types of controlling stimuli: volume disturbances (as reflected by atrial, renal, or arterial pressures) and electrolyte disturbances (plasma sodium or potassium concentrations). The volume stimuli may provide control only during acute disturbances, either because of the existence of several types of adaptive mechanisms or because volume disturbances are fully corrected by various volume-regulating mechanisms. Three different types of pressure-related adaptive mechanisms are indicated in Figure 11, including receptor adaptation (i.e., adaptation of pressure receptors by increasing receptor tissue compliance or decreasing tissue tension), renal autoregulation (i.e., automatic adjustment of renal artery resistance to maintain blood flow reasonably constant), and baroreceptor resetting (i.e., adjustment of the set point to accommodate

INFLUENCE OF VOLUME (————) AND ELECTROLYTE (-----) CONTROLLERS ON HORMONAL SECRETION

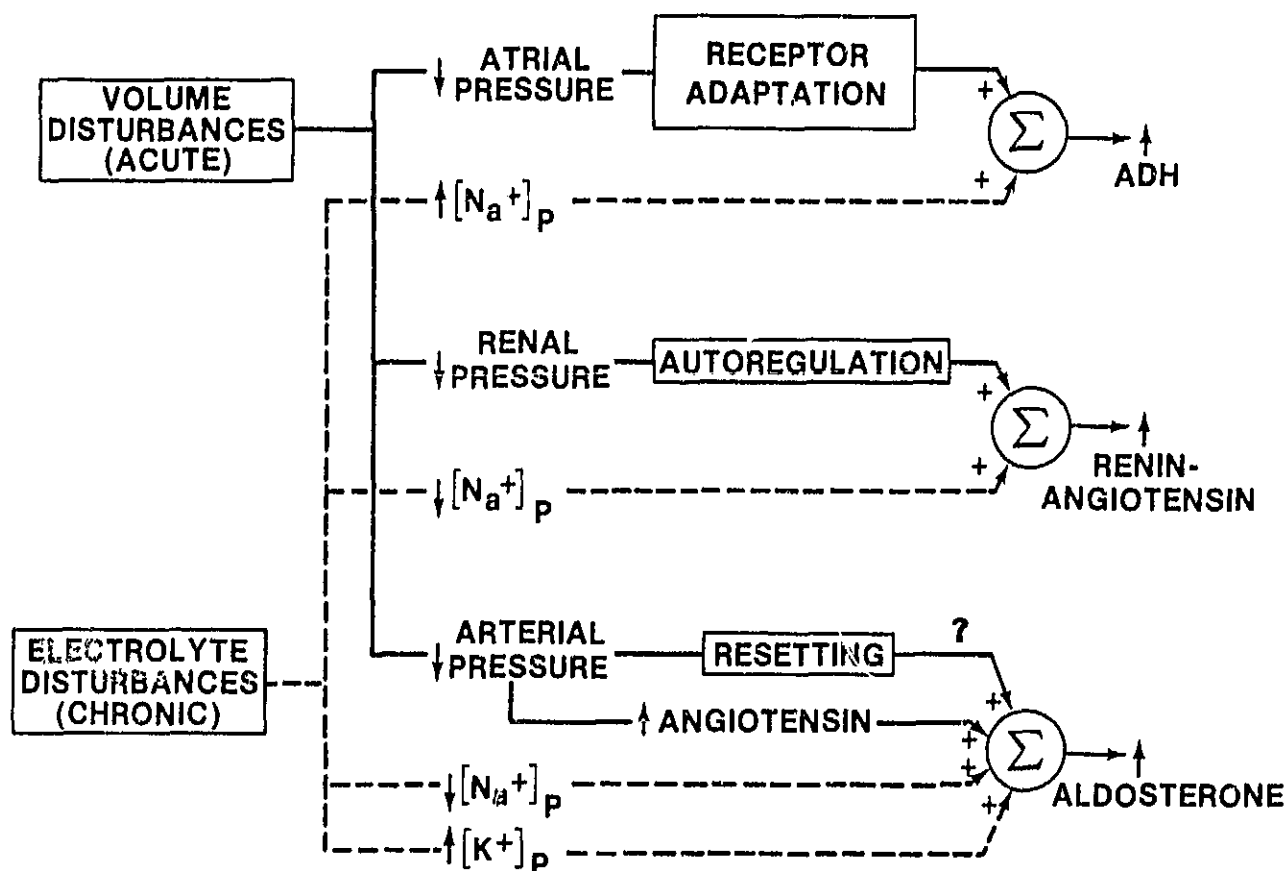


Figure 11

chronic changes in pressure). The influence of the electrolyte disturbances are not known to adapt, however, and it has been proposed that they are the primary long-term controllers of these hormones (Guyton et al., 1975).

As indicated in Figure 12 these hormones are part of a much larger feedback system that can apparently regulate circulatory and extracellular disturbances of various kinds. This diagram illustrates three distinct types of control mechanisms, including hormones, autonomies and hemodynamics which act to maintain extracellular volume and composition, as well as blood pressure and renal output. (More will be discussed about the control of renal output at the end of Section 3.0.)

All of the hormone stimulating factors shown in Figure 11 and 12 are known to change at one time or another during hypogravic maneuvers. For example, during the onset of weightlessness, blood pressures likely become elevated. (Unfortunately, the long-term responses of either venous or renal pressures have not been measured.) Also, plasma sodium is frequently reported to be depressed sufficiently to suppress ADH secretion, while plasma potassium is variable, dependent in part on muscle atrophy, metabolic intake, and excretion.

The hypothesis that is proposed, therefore, considers that all of these renal-regulating hormones are responsive to pressure influences during the acute stages of weightlessness and to electrolyte disturbances in the chronic state. In order to test this hypothesis, a simulation of a 7-day head-down bed rest was performed as described below.

Simulation Behavior of Hormone Response

Figure 13 illustrates the hormonal responses obtained in the mathematical simulation of a 7-day head-down (-6°) bed-rest study (Leonard, 1984a). The dynamic behavior of these responses reflects the presence of multiple and competing pathways and the interactive nature of the renal-endocrine and fluid-electrolyte systems. This simulation of head-down tilt was accomplished by imposing the hydrostatic forces associated with -6° on the appropriate circulatory elements. The model automatically responds to this stress by redistributing fluid to the upper body volume segments and

MODEL REGULATION OF EXTRACELLULAR AND CIRCULATORY DISTURBANCES

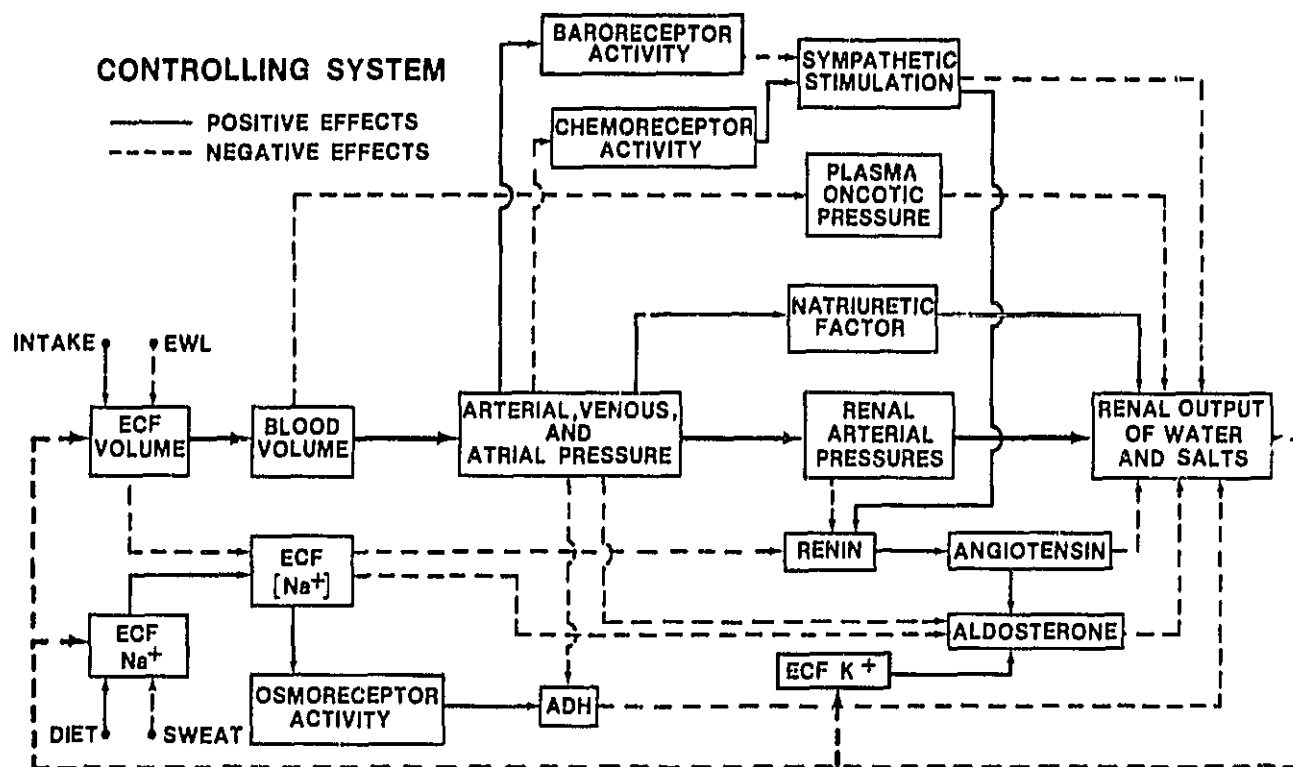


Figure 12

HORMONE RESPONSES DURING SIMULATION OF HEAD-DOWN BED REST

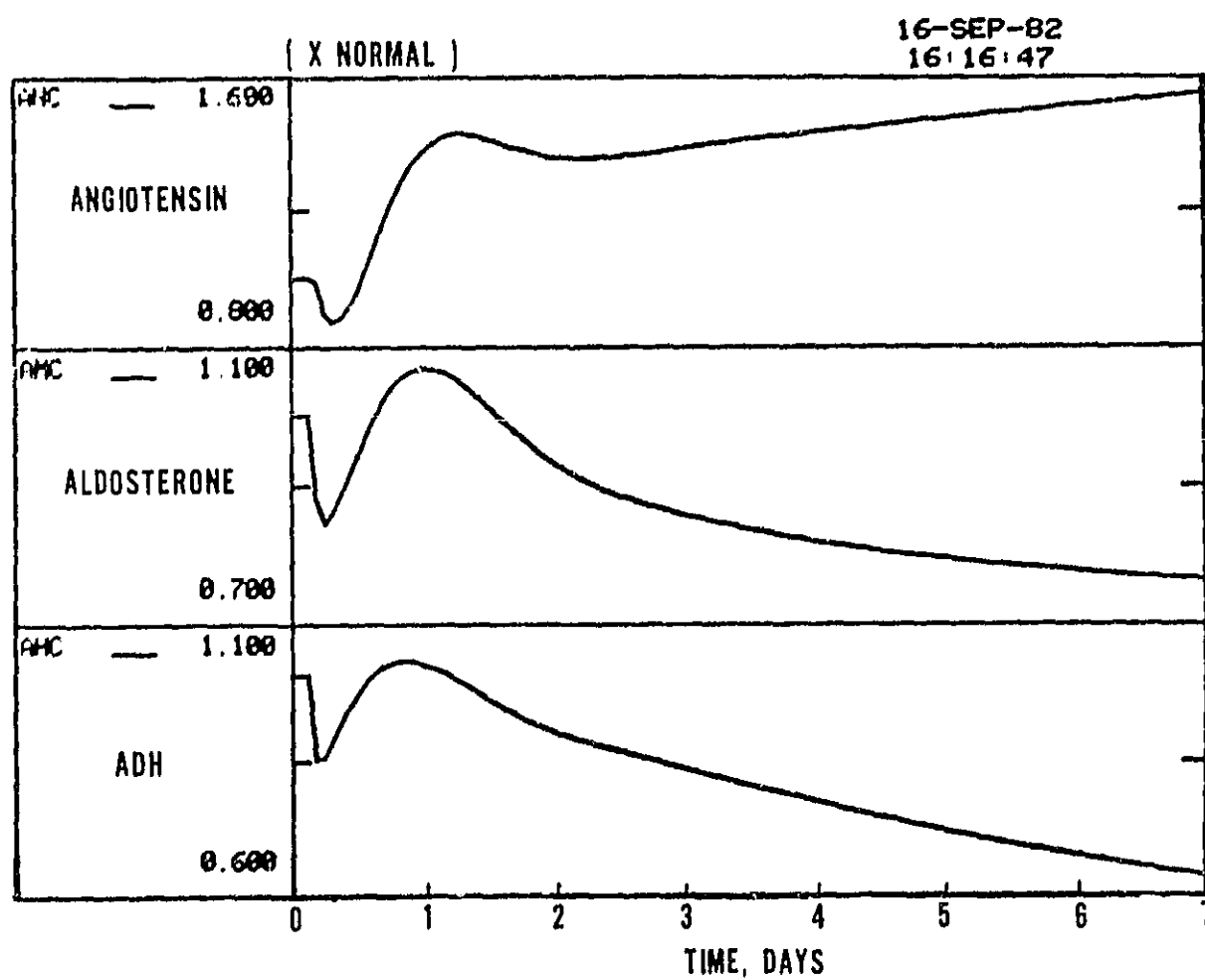


Figure 13

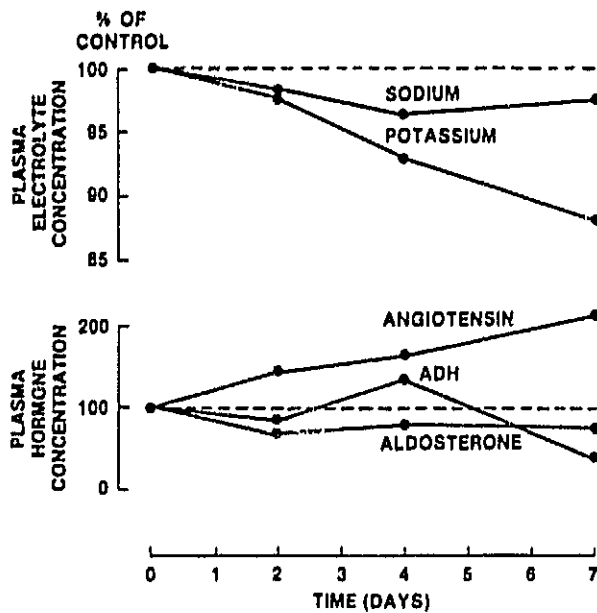
initiating compensatory reactions to alleviate the central hypervolemic condition. Renal excretion of the "excess fluid" has been considered to be a significant element of the physiological response to zero-g and hormone readjustments are important mechanisms in the renal response.

The most notable characteristic observed in Figure 13 is the triphasic nature of each response. The behavior of aldosterone and angiotensin appears to be similar to the ADH response that was discussed earlier and described in Figures 8 and 9. The simulation exhibited a significant decrease in all three hormone levels during the first several hours of head-down tilt, in agreement with the data summarized in Figure 10 and Appendix Figure A-4. This acute suppression of hormone level is a homeostatic response to elevated blood pressures. Subsequent to the decrease in hormone level was a rebound which, in turn, was followed by a long-term trend that demonstrated either higher plasma concentrations in the case of angiotensin, or lower concentrations in the case of aldosterone and ADH. The long-term trend was clearly not due to pressure effects because at seven days venous pressure was depressed and arterial pressure was nearly normal (see Leonard 1984², for model results). According to the diagram of Figure 11, these pressure changes should not evoke the simulated hormone behavior shown in Figure 13. Rather, it appears that the electrolyte concentrations alone could be responsible for chronic hormone conditions. This is demonstrated more conclusively as discussed below.

Figure 14 depicts the plasma electrolytes (sodium and potassium) and hormone changes during the 7-day head-down tilt study; the measured amounts on the left and the computer simulation on the right. (The hormone time profile of Figures 13 and 14 are the same.) Both the plasma electrolytes, which we are hypothesizing are responsible for the long-term hormone levels, decreased in this study. It was possible to duplicate the experimentally observed electrolyte alteration by imposing on the model the same dietary reduction in water, sodium, and potassium that was recorded for the bed-rested subjects. (Dietary intake was intentionally reduced to about 30 percent below normal during bed rest to account for lowered metabolic demand.) The dietary influence on the overall response was significant as Figure 15 indicates.

PLASMA ELECTROLYTES AND HORMONES DURING HEAD DOWN BED REST

JOINT US/USSR EXPERIMENT (1979)



COMPUTER SIMULATION

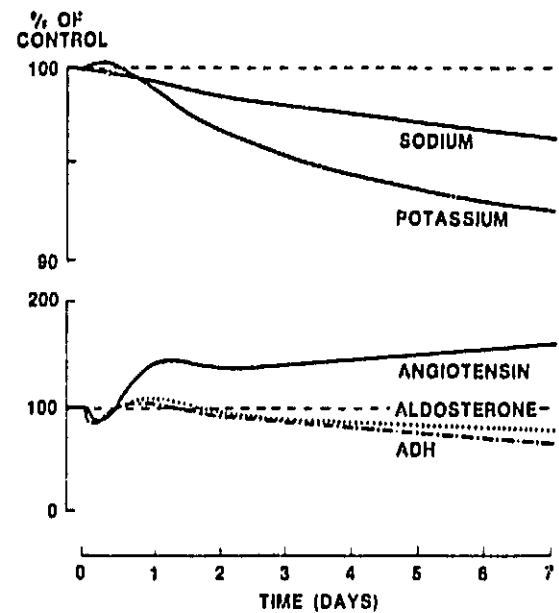


Figure 14

SIMULATED HORMONAL RESPONSES DURING 7-DAY HEAD DOWN BED REST

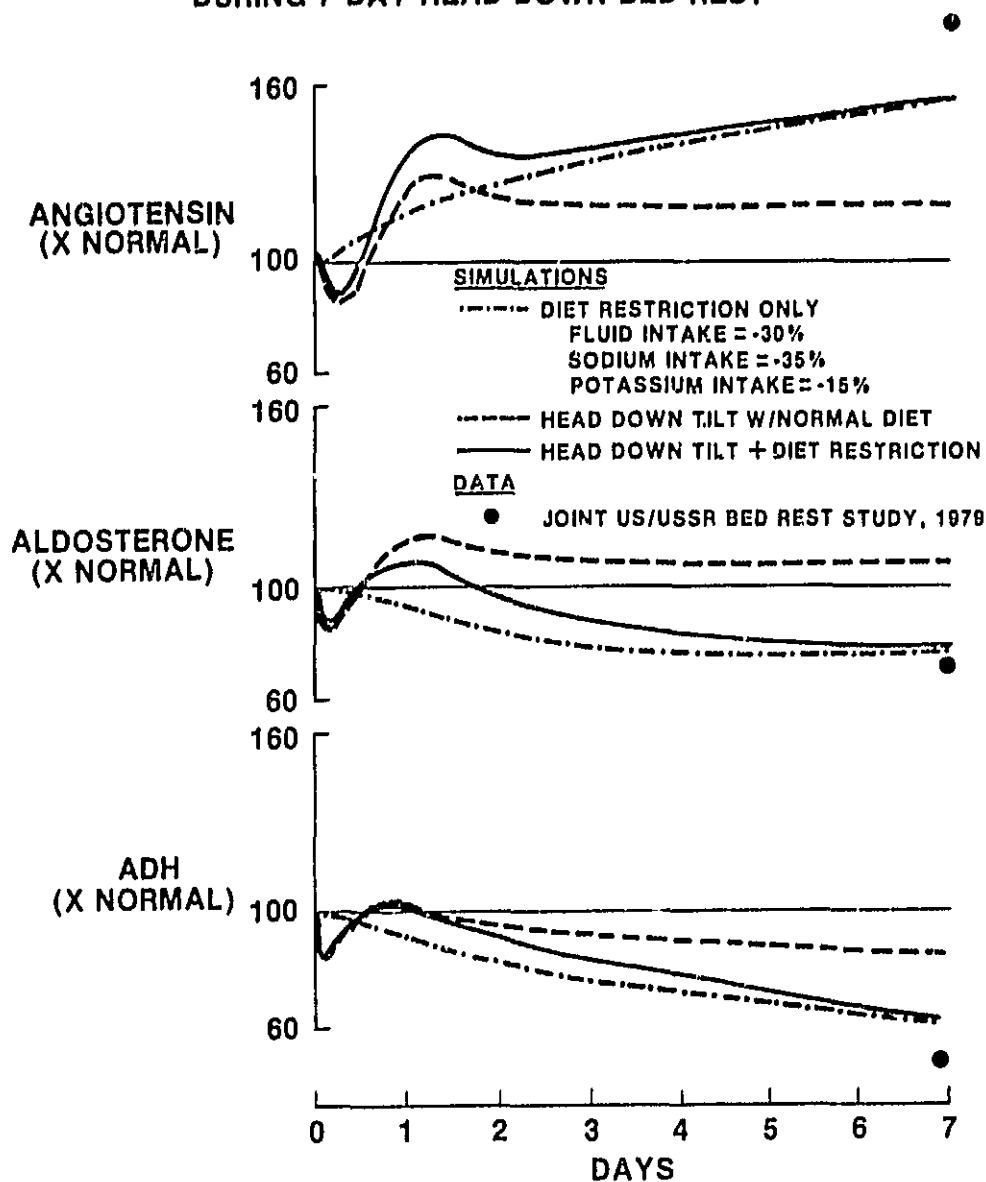


Figure 15

The solid line of Figure 15 depicts the same simulated hormone changes shown previously in Figures 13 and 14, and represents the case of head-down tilt, plus a dietary restriction of water and salts. Using a computer model, it is comparatively easy to determine the relative contribution of either diet or head-down tilt to the overall response. For example, the dashed line shows the results of a head-down tilt with a normal diet and the dotted line depicts the simulation of dietary changes by themselves without head-down tilt. It is clear that the model's long-term responses of head-down tilt, plus dietary changes are primarily a result of the dietary impact on the plasma electrolytes. In all cases the addition of the dietary effects improves the agreement between model responses and data (data are indicated by the solid circle at Day-7). On the other hand, the acute changes are relatively independent of dietary effects and are, in fact, due to volume disturbances resulting from the initial headward fluid shifts. In these simulations, pressure disturbances had nearly normalized, and had only a minor effect after the second day.

Space-flight Endocrine Responses

In the light of the model hypotheses presented in Figure 11, it is possible to explain the long-term behavior of ADH, aldosterone, and angiotensin in space flight as chronic adaptation to metabolic factors. Specifically, the measured decrements in plasma sodium probably contributed to suppression of ADH, as well as elevations of aldosterone and angiotensin. More important to the control of aldosterone, however, was the observation that plasma potassium and angiotensin, both potent stimulators of aldosterone, were elevated. It appears that these stimulating factors (i.e., sodium, potassium, and angiotensin) may have changed sufficiently to quantitatively account for ADH and aldosterone levels. However, the magnitude of the increase in angiotensin levels in space flight (as well as in bed-rest studies) seems to be much greater than can be explained by the measured decrements in sodium. The entire reasons why angiotensin increases in hypogravity over longer periods of time have probably not been entirely explored. If renal pressure is found to be depressed, this could be an important clue to help resolve this issue, as renal hemodynamics play a significant role in determining angiotensin release.

Renal-Endocrine Behavior

It is not the major purpose of this report to assess the potency of the hormonal mechanisms on renal excretion. There are many other non-hormonal pathways available as suggested in Figure 12, and little information exists as to their relative effectiveness during conditions of weightlessness. However, it would be useful to assess whether changes in renal excretion observed during hypogravic stresses are in accord with theoretical expectations based on hormonal behavior.

During space flight an increase in urine fluid volume, sodium and potassium excretion has been measured (Skylab averages over a 3-month period). (Acute changes which occurred during the first day in space were not consistently measured). The increase in urine volume is in agreement with overall decrements in ADH, and the increase in potassium excretion is expected from elevated aldosterone levels. However, aldosterone is a sodium-retaining agent and based on changes in aldosterone one would expect a decrease rather than the measured increase in renal excretion of sodium. The presence of a still-unidentified natriuretic factor has been proposed as a hormonal mechanism to aid excretion of sodium. Angiotensin was increased in Skylab, and this agent is a stimulating factor of aldosterone, a fact which helps explain the measured increase in aldosterone.

The response of ADH during Skylab has come under particular question because of the varied responses of each Skylab mission (see Appendix, Fig. A-1). On the 28-day flight, ADH was elevated throughout the flight while the crewmen on the 59-day and 84-day flights exhibited a decline in ADH. This paradoxical response was never fully explained. Just as important as it is to explain the factors influencing ADH, it is useful to assess if ADH induces the appropriate renal response. That is, it would be useful to show if ADH and urine volume are inversely related in zero-g as one would expect from physiological theory in one-g. This has never been demonstrated previously. Figure 16 illustrates the average of the nine-man Skylab crewmember response for urinary ADH and urine volume. The time period considered is the first 28 days of flight (the common period for all flights) and the 20 days following flight. One can observe that a good inverse correlation exists between ADH and urine volume.

URINARY ADH AND DAILY URINE VOLUME SHOWN AS PERCENT CHANGE FROM PREFLIGHT LEVELS

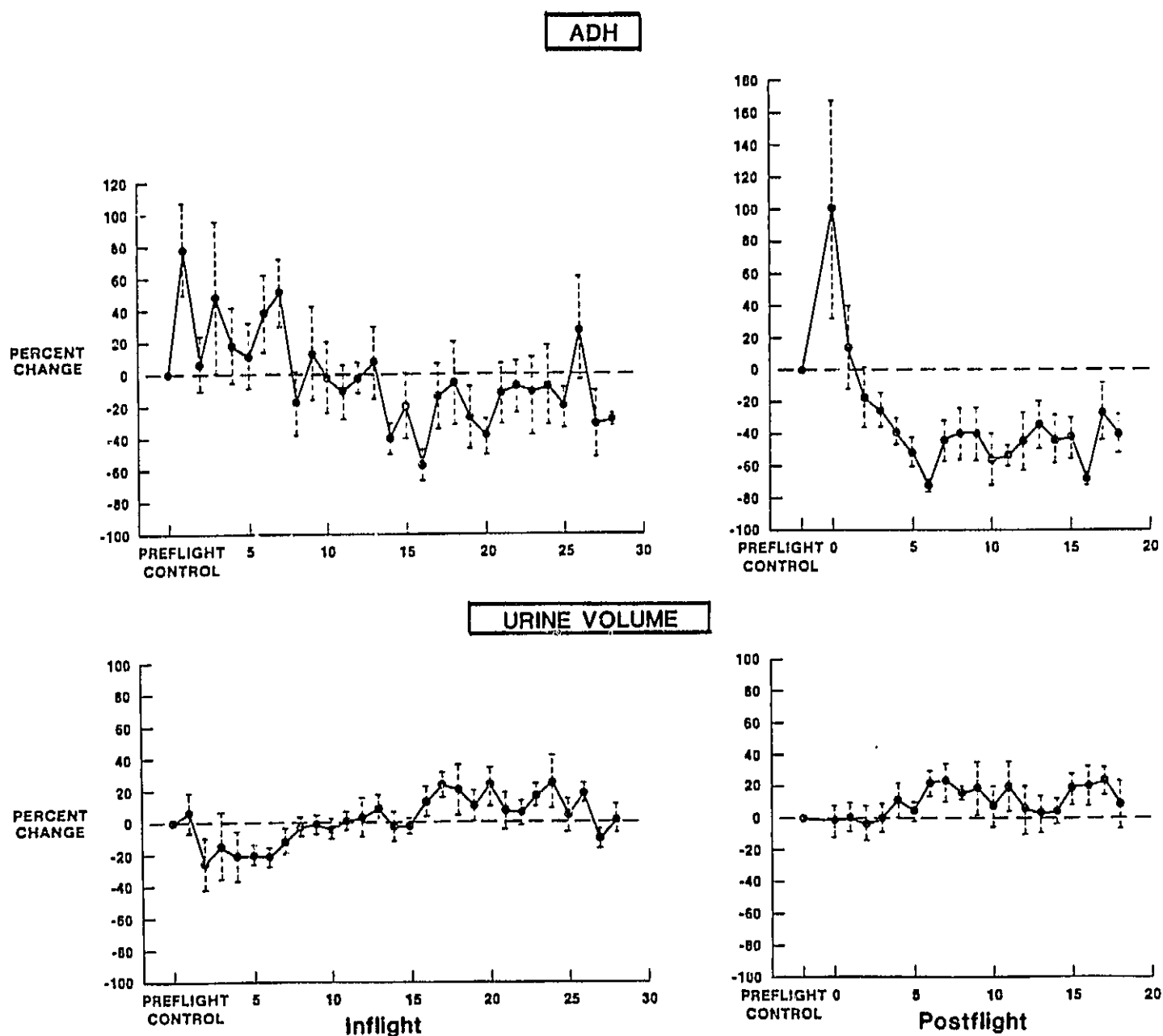


Figure 16

During the first week of flight (Fig. 16), for example, ADH is elevated and then decreases below control for the remainder of the month; urinary volume follows an opposite behavior showing a crossover at the same time as ADH (at the end of the first week). Similar behavior is shown for the postflight period (Fig. 16).

The space-flight data, discussed above, involves long-term exposure to hypogravity; there is not sufficient data for the first day of flight. On the other hand, water immersion and some bed-rest studies provide an opportunity to examine shorter term hypogravity. Table 1 indicates the general direction for the variables of interest, hormones and renal excretion. As we have shown previously using the computer simulation and has been confirmed in experimental water-immersion and head-down tilt studies, for the case of less than one-day exposure, there is an increase in renal excretion and a decrease in hormone levels, as expected. Intermediate periods of exposure, such as the one-week head-down tilt study, show a more confounding picture. It appears that urine volume cannot be predicted, in this period, based on ADH levels, nor is sodium excretion in accord with aldosterone behavior.

Urine output can be positively correlated, however, with net fluid intake (Leonard, 1984a). For example, during the 7-day head-down bed rest, fluid and food intake diminished approximately 30 percent, as did urine excretion. However, in Skylab, evaporative water loss was shown to be diminished by approximately 10 percent (Leach et al., 1978) which translates into an effective increase in net fluid intake; as may be expected in such cases, urine output also increased a corresponding amount.

This brief analysis indicates that only in the acute stress of hypogravity (as exemplified by water immersion and head-down tilt) does renal excretion consistently correlate with hormone behavior. In the intermediate and long-term cases which were considered, it appears that other mechanisms predominate. For at least one of these hormones, however, we have shown a qualitatively good correlation; that is, between ADH and urine volume during long-term space flight.

TABLE 1
CHANGES IN HORMONE LEVELS AND URINE EXCRETION

	<u>WATER IMMERSION</u>	<u>7-DAY HEAD-DOWN BED REST</u>	<u>1-3 MO. SPACE FLIGHT</u>
PLASMA HORMONES			
ADH	↓	↓	↓
ALDOSTERONE	↓	↓	↑
ANGIOTENSIN	↓	↑	↑
URINE EXCRETION			
WATER	↑	↓	↑
SODIUM	↑	↓	↑
POTASSIUM	↑	↔	↑

↑ INCREASE

↓ DECREASE

↔ NO CHANGE

SUMMARY

An understanding of hormonal behavior is one key to understanding fluid volume regulation during space flight. Although hormonal research in the space life sciences has produced a reasonable amount of data, there are many inconsistencies between crewmen, between space-flight and ground-based studies, and between acute and chronic measurements. This study has attempted to resolve these conflicts by considering a wide range of data and a computer model system for integrating these data with principles of hormonal regulation. An important result of the analysis is a generalized theory that explains the overall behavior of the major renal-regulating hormones.

This analysis suggests that the renal-regulating hormones represent a tightly coupled system that responds acutely to volume disturbances and chronically to electrolyte disturbances. During hypogravic maneuvers this leads to an initial suppression of hormone levels and a long-term effect which varies depending on metabolic factors. These factors, such as diet, sweat loss, physical activity, and muscle atrophy, can alter the plasma electrolytes and thus influence hormone behavior. This shift toward osmo-control may be postulated to derive from an inherent sensitivity of hormones for electrolyte stimuli and/or from a gradual adaptation of pressure disturbances. In addition, the simulations reveal that if pressure effects rapidly normalize, a transition phase may exist which leads to a dynamic multi-phasic endocrine response. The directional changes of these hormones found during Skylab and specific ground-based analog studies can be qualitatively accounted for by these mechanisms in most cases. However, the discrepancies between the different studies may be a result of competing and time-varying stimuli which differ between subjects and test conditions. These discrepancies may be particularly evident during the transition phase (after the first several hours and continuing for several days).

Confirmation of the above hypotheses is confounded by the lack of crucial data which can only be acquired during space flight. The presence of a number of competing factors makes the interpretation of hormone data quite difficult unless these factors are measured concurrently. For example, it is clear from this analysis that careful measurements of blood pressure, serum

electrolytes, and volume shifts must be obtained simultaneously with endocrine levels. In addition to mean arterial pressure, pressure at other specific sites such as renal pressure and venous pressure have been identified as particularly significant. These measurements are often equally lacking in ground-based studies such as water immersion and bed rest. Secondly, it would be useful to perform metabolic balance studies including dietary intake and excretion for fluids and electrolytes. Presently there is an absence of endocrine measurements during the important first mission day of space flight. This information would complement similar information obtained during the first few hours of water immersion and head-down tilt and would be essential to the theoretical understanding of the system. Similarly important is the need for measurements to be performed on the same subjects during both the acute and chronic phases of flight.

Without the proper ground-based controls, it is easy to mask the true effects of weightlessness. It appears that dietary factors can have a strong modifying effect on hormone behavior. In the same vein, it would be reasonable to believe that other metabolic factors such as the degree of fluid and salt loss via sweating, muscle atrophy, etc. would also alter hormone response. Unless non-gravitational factors are carefully controlled and monitored, it would make the interpretation of hormone changes quite difficult. We have shown that, in theory, some of these effects can be accounted for using mathematical models.

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TABLE A-1

SOURCES OF ZERO-G ANALOG DATA USED FOR COMPOSITE STUDY

<u>STRESS</u>	<u>HORMONES</u>	<u>CENTRAL VENOUS PRESSURE</u>	<u>ELECTROLYTES</u>
Water Immersion	Greenleaf Epstein	Echt Arborelius	Greenleaf Epstein Dubois
Head-Down Tilt	Blomqvist	Blomqvist	N/A
Head-Down Bed Rest	Joint US/USSR	*Joint US/USSR	Joint US/USSR
Supine Bed Rest	Various (see Table A-2)	N/A	Leach Chobanian
Space Flight	Leach & Rambaut	*Kirsch	Leach & Rambaut

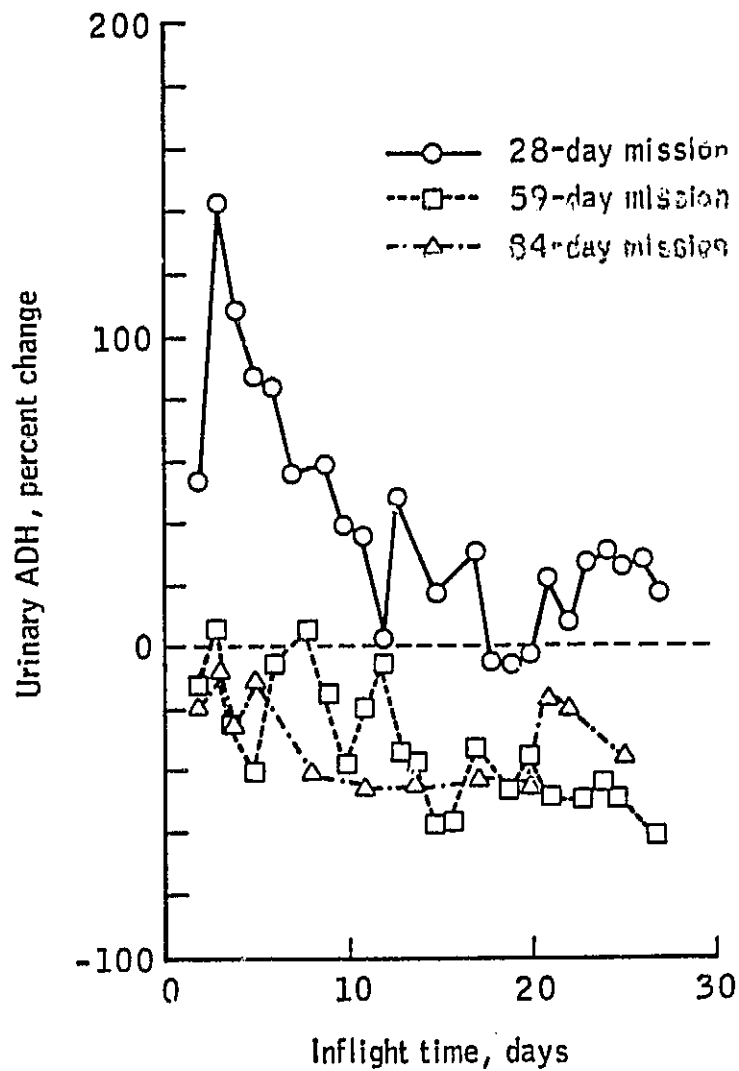
* - Indirect measurement only

N/A - Not available

TABLE A-2

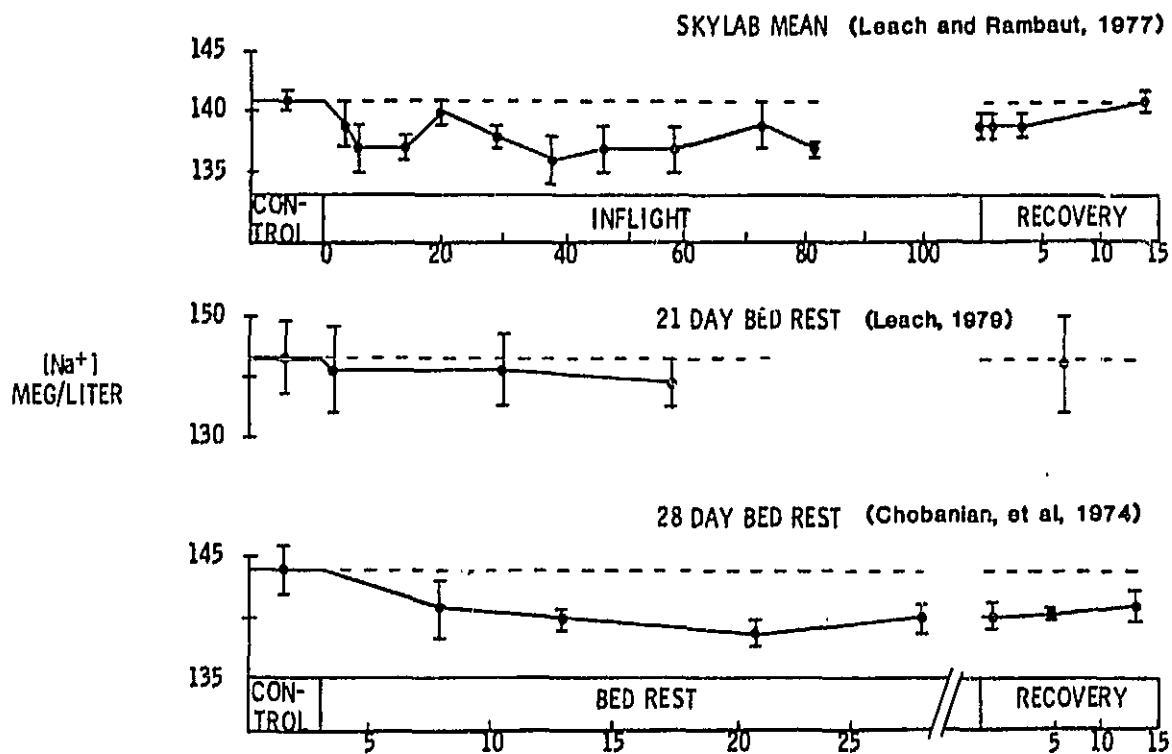
HORMONAL CHANGES DURING SUPINE BED REST

<u>HORMONE</u>	<u>BR DURATION</u>	<u>PERCENT CHANGE</u>	<u>INVESTIGATOR</u>
URINARY ALDOSTERONE	1 WK	+ 44%	GUROVSKIY ET AL., 1979
	2 WK	0%	MELADA ET AL., 1975
	2 WK	+ 37%	LEACH, 1976
	4 WK	0%	HYATT, 1971
	4 WK	+ 20%	LEACH, 1977
	1 WK	+ 6% (Urine) - 28% (Plasma)	LEACH, 1979 "
PLASMA RENIN ACTIVITY	1 WK	+100%	BUROVSKIY ET AL., 1979
	2 WK	+ 43%	LEACH, 1976
	2 WK	+250%	MELADA ET AL., 1975
	2-1/2 WK	+ 91%	KEIL & ELLIS, 1976
	4 WK	+132%	LEACH, 1977
	5 WK	+100%	FASOLA ET AL., 1970
	1 WK	+ 32%	LEACH, 1979
ADH	2 WK	+17% 1ST WK - 8% 2ND WK	LEACH, 1976
	2-1/2 WK	- 33%	KEIL & ELLIS, 1976
	4 WK	+ 56%	LEACH, 1977
	1 WK	+ 38% (Urine) - 18% (Plasma)	LEACH, 1979



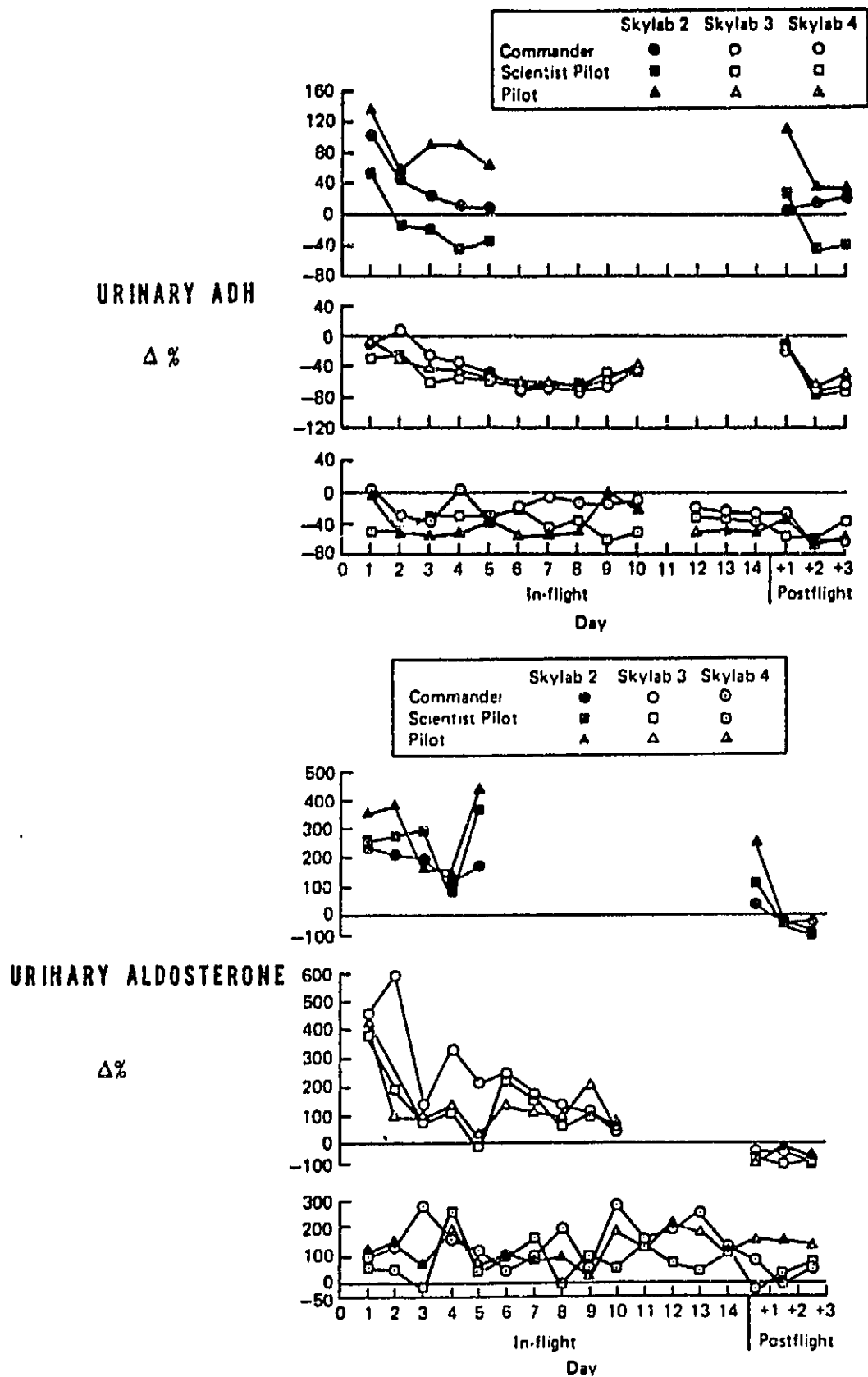
URINARY ADH OF EACH SKYLAB CREW (N=3)

Figure A-7



EFFECT OF SPACEFLIGHT AND BED REST ON PLASMA SODIUM CONCENTRATION

Figure A-2

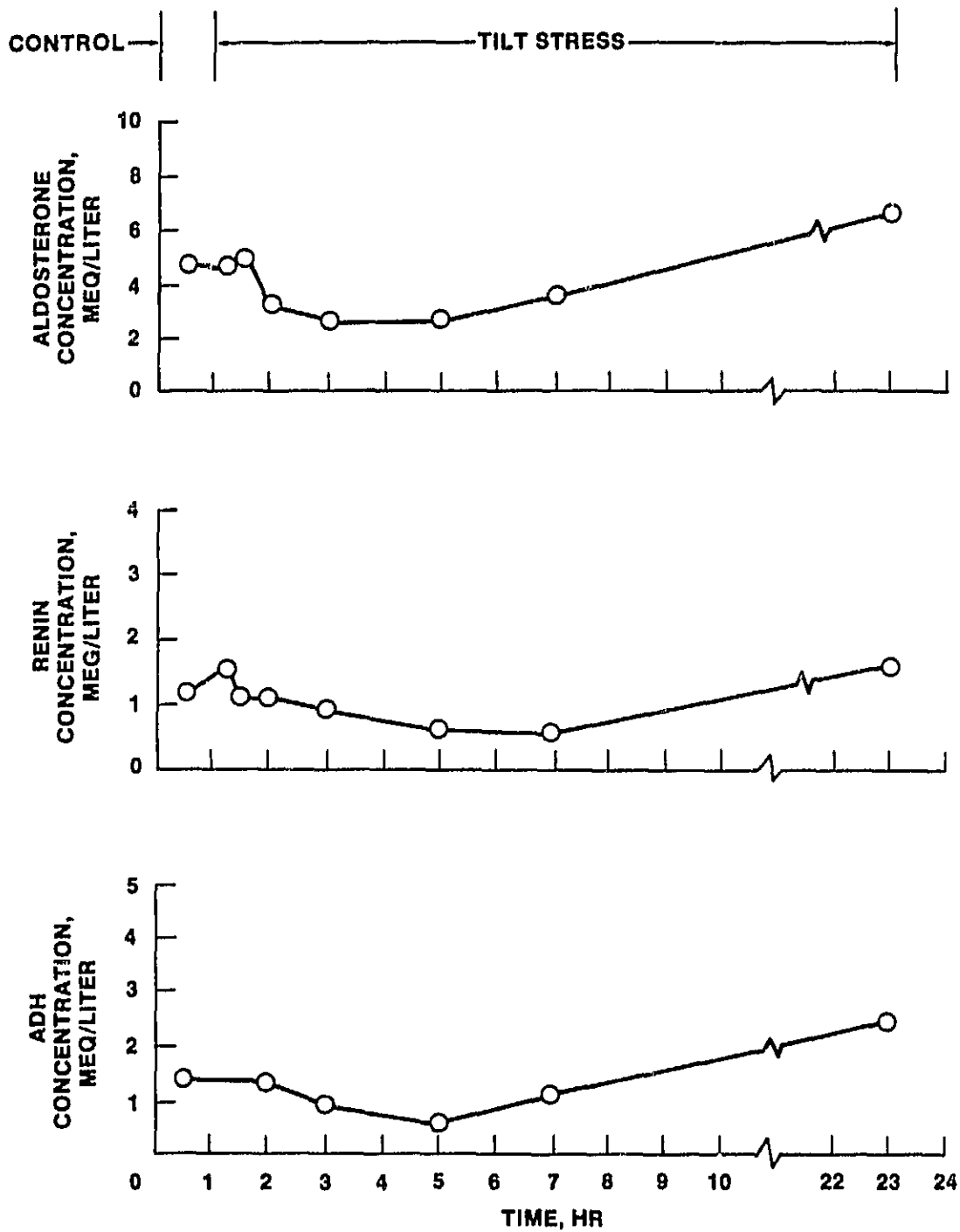


(Leach & Rambaut, 1977)

Figure A-3

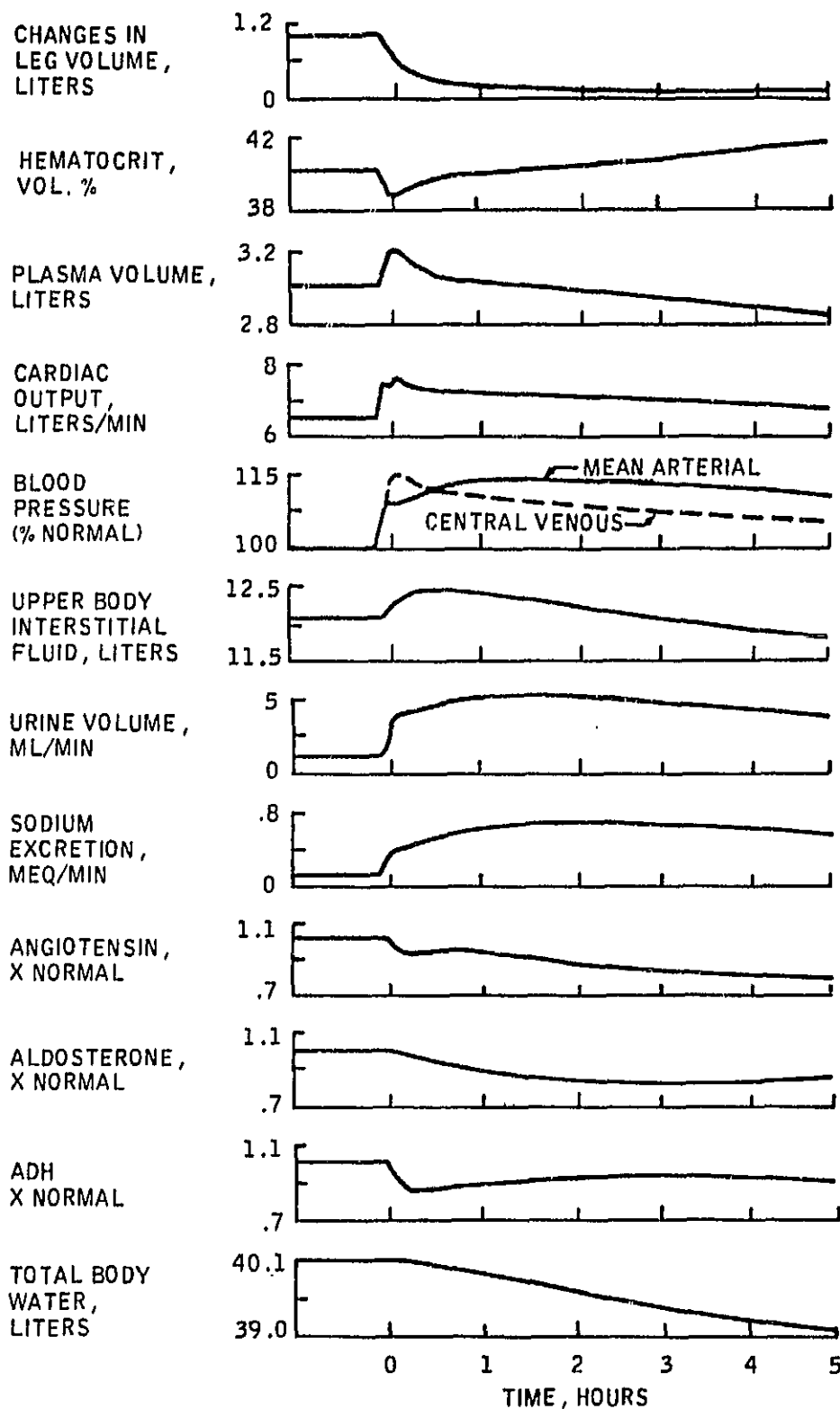
ADH AND ALDOSTERONE CHANGES DURING SKYLAB MISSIONS

ENDOCRINE RESPONSES OF HUMAN SUBJECTS TO HEAD DOWN TILT



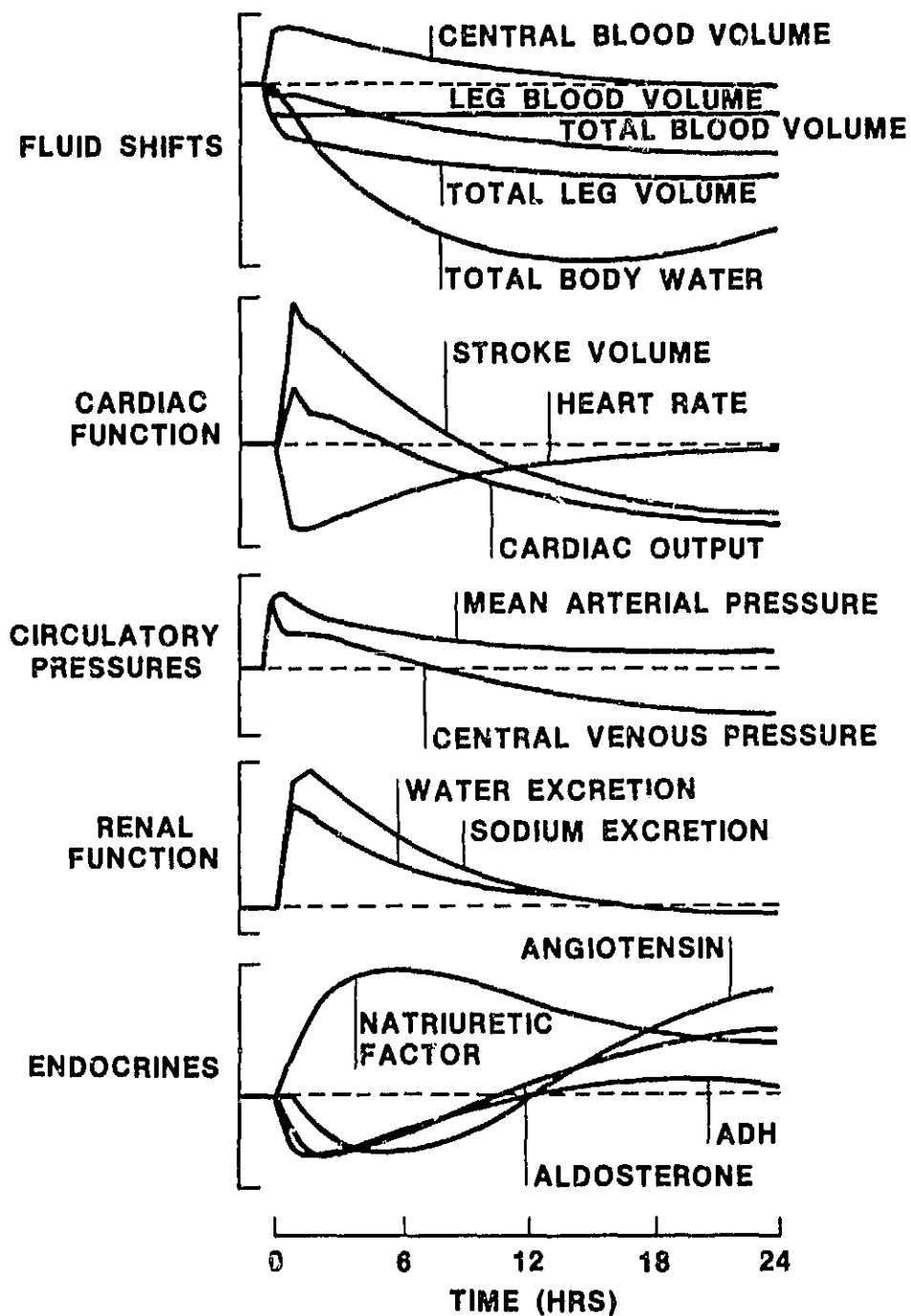
Drawn from
Blomquist, et al 1980

Figure A-4



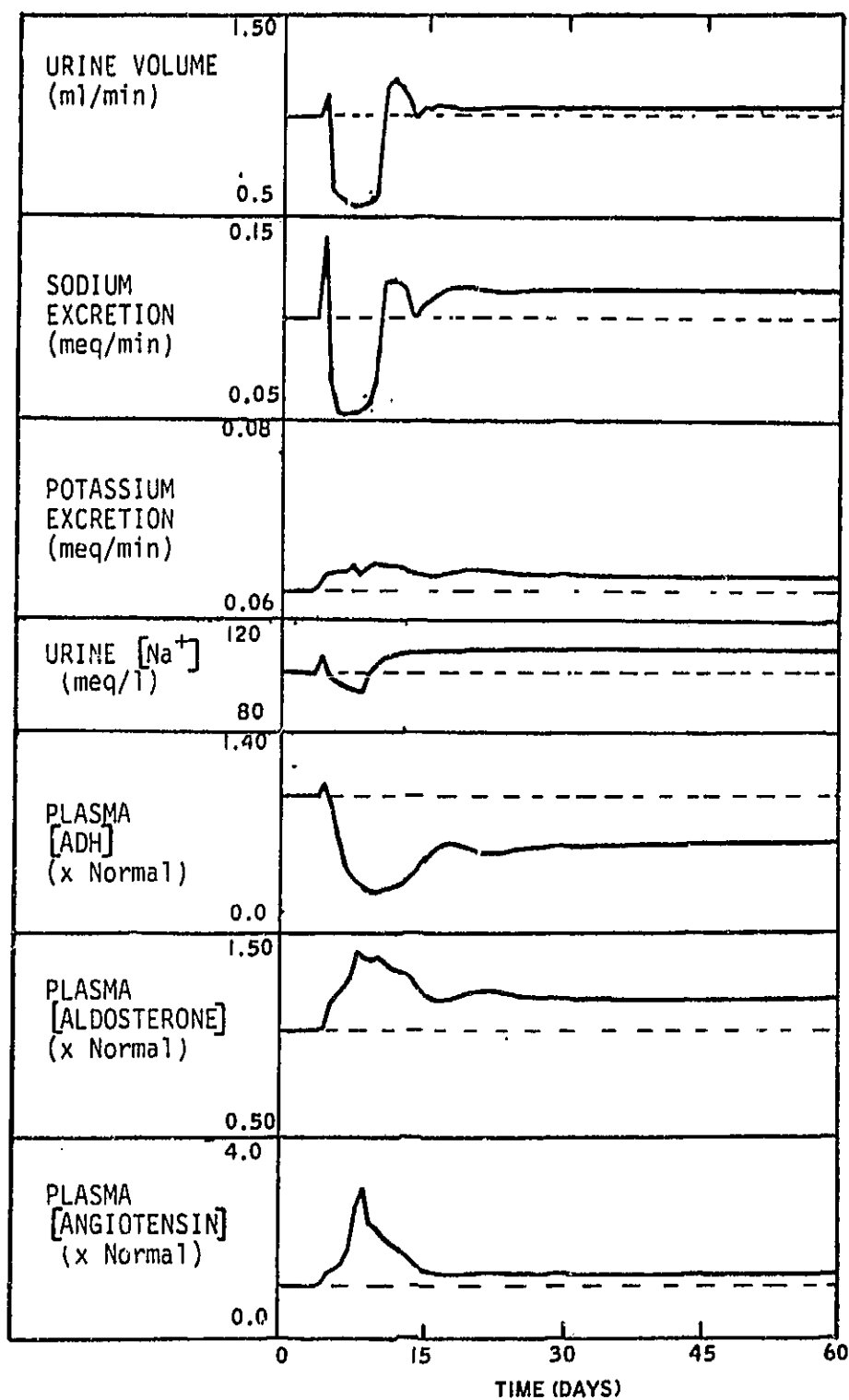
SIMULATION OF WATER IMMERSION

Figure A-5



SIMULATION OF HEAD DOWN TILT (-6°)

Figure A-6



SIMULATION OF COMPOSITE SKYLAB MISSION

RENAL-ENDOCRINE FUNCTION

Figure A-7