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(NASA-CR-171870) ANALYSIS OF HEAD-DOWN TILT  
AS AN ANALOG OF WEIGHTLESSNESS USING A  
MATHEMATICAL SIMULATION MODEL (Management  
and Technical Services Co.) 66 p  
HC A05/MF A01

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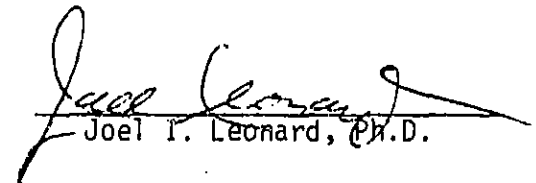
TIR 2114-MED-4003

<b>FROM</b> Joel I. Leonard, Ph.D.		<b>TO</b> Dr. Nitza Cintron-Trevino/SD4	
<b>DATE</b> 9/4/84	<b>CONTRACT NO:</b> NAS9-17151	<b>T.O. OR A.D. REF:</b>	<b>MIS OR OTHER NASA REF:</b>
<b>SUBJECT</b> Analysis of Head-Down Tilt as an Analog of Weightlessness Using a Mathematical Simulation Model			

Anti-orthostasis or head-down tilt of a moderate degree has been used as a ground-based analog of weightless space flight to study headward fluid shifts, decreased plasma volume, orthostatic intolerance and muscular skeletal degradation. In the present study, a mathematical model was used to help interpret these observations. The model which proved most valuable for these studies was originally developed by Guyton as a description of the major circulatory, fluid and electrolyte control systems. Two different experimental studies are employed in this paper to validate the model. The first is a 24-hour head-down tilt study and the second is a 7-day head-down bed-rest study. The major issues which were addressed included the reduction in plasma volume, the dynamic changes of venous pressure and cardiac output, the extent of central hypervolemia during long-term zero-g exposure, the existence of an early diuresis, the mechanisms which alter the renal-regulating hormones during the short-term and long-term periods, the significance of potassium loss on other zero-g responses, and the role of transcapillary filtration in adjusting fluid shifts. This study illustrates the use of mathematical models as an interpretive and analysis technique for experimental research for space life science.

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Attachment

  
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TIR 2114-MED-4003

ANALYSIS OF HEAD-DOWN TILT AS AN ANALOG OF WEIGHTLESSNESS  
USING A MATHEMATICAL SIMULATION MODEL

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September 1984

This work was supported by the following NASA contracts:  
NAS9-15487, NAS9-16328, NAS9-15850, and NAS9-17151

## ABSTRACT

Anti-orthostasis or head-down tilt of a moderate degree has been used as a ground-based analog of weightless space flight to study the major characteristics of headward fluid shifts, decreased plasma volume, orthostatic intolerance and muscular skeletal degradation. In the present study a mathematical model was used to help interpret the head-down tilt response and relate those physiological changes to those which occur in space flight. The model which proved most valuable for these studies was originally developed by Guyton and subsequently modified by ourselves to include the capability to respond to gravitational stresses. This versatile model is a detailed description of the major circulatory, fluid and electrolyte control systems. It has previously been used for simulating supine bed rest, water immersion and weightlessness itself. By using a common mathematical model to simulate both space flight and ground-based experimental analogs, it is possible to test hypotheses regarding mechanisms and control systems, and thus, discern the major characteristics of these stresses, their similarities and differences.

Two different experimental studies are employed in this paper to validate the model. The first is a 24-hour head-down tilt (-5 degrees) study and the second is a 7-day head-down bed rest (-6 degrees) study. The simulation of both of these maneuvers demonstrated changes in the fluid volume, hemodynamic, electrolyte, hormone and renal characteristics that were in good agreement with direct experimental observation. The fluid-shift hypothesis, that explains the reduction in plasma volume, was elucidated by studying model behavior. Other issues which were addressed, using the ability to study the model's reactions in detail, included the dynamic changes of venous pressure and cardiac output, the extent of central hypervolemia during long term zero-g exposure, the existence of an early diuresis which has yet to be measured, the mechanisms which alter the renal-regulating hormones during the short-term and long-term periods, the significance of potassium loss on other zero-g responses, and the role of transcapillary filtration in adjusting fluid shifts.

This study demonstrates the validity of the Guyton model in studying gravitational stresses, and the use of mathematical models in general as an interpretive and analysis technique for experimental research for space life science.

## ANALYSIS OF HEAD-DOWN-TILT AS AN ANALOG OF WEIGHTLESSNESS USING A MATHEMATICAL SIMULATION MODEL

In recent years, exposure of human subjects to a moderate degree of head-down tilt (anti-orthostasis or negative tilt) for several hours to more than a week, has been used as a ground-based analog of weightless space flight (Blomqvist et al., 1980; Volicer et al., 1976; Kakurin et al., 1976). Negative tilt has been shown to mimic the major characteristics of the weightlessness response, including headward fluid shifts, decreased plasma volume, and orthostatic intolerance. An anti-orthostatic animal has also been used with some success to study cardiovascular deconditioning and musculoskeletal atrophy similar to that which occurs in space-flight (Popovic, 1981; Morey 1979; Muscacchia et al., 1980). The hypogravic response, as it exists in head-down tilt or space flight, involves a redistribution of circulating blood and a consequent cascading or ripple effect on many elements of the fluid regulating system. These complex effects include changes in the circulatory and renal systems, in transcapillary fluid exchange, in the volumes of several major fluid compartments, and in the control of hormone secretion and autonomic activity. Musculoskeletal atrophy also exerts a known influence on these same systems when cellular fluid and electrolytes are transported and processed from the sites of tissue degradation. One of the few methods available for quantifying these physiological functions and for assessing their interrelationships is the computer simulation of a mathematical model.

Mathematical models have been used recently to study weightlessness and its one-g analogs, including water immersion and supine bed rest (Leonard et al., 1979; Leonard and Grounds, 1977; Leonard, 1982(a), 1982(b); Fitzjerrell et al., 1975). The model which proved most valuable for these studies, and the one currently employed for head-down tilt simulations, was originally developed by Guyton (Guyton et al., 1972) and subsequently modified by others (White, 1975; Leonard and Grounds, 1977). The major objective of this report is to demonstrate the capabilities of the Guyton model to simulate postural changes, and particularly, the short-term and long-term responses of head-down tilt. Further, because certain experimental responses to head-down tilt have been difficult to interpret, a secondary objective is to utilize the

fundamental relationships embodied in the model to resolve these problems areas. By so doing, the Guyton model could then represent a validated analytical tool to predict changes in weightless space flight and to test hypotheses which might account for those changes. The mathematical model, therefore, functions as an analog to zero-g physiology in the same way as animals are used as surrogates for human studies.

Although the primary interest in this report is the simulation of head-down tilt, it is natural to consider head-up tilt as well. The responses to orthostasis are well described (if not well understood), and this maneuver offers the opportunity to validate the model's newer gravitational elements. In addition, it can be argued that an understanding of the cardiovascular responses to orthostasis would contribute to an understanding of the responses to anti-orthostasis and the absence of gravity. Furthermore, in future research, head-up tilt studies may be useful for developing a model whose reference position would be the erect, rather than the supine, position. Preliminary modeling analyses of orthostasis and anti-orthostasis have been previously conducted with some success (Leonard and Grounds, 1977; Leonard, 1979). This report is a continuation of those earlier studies.

## 1.0 MODIFICATIONS TO THE GUYTON MODEL\*

In order to appreciate the manner in which simulations of weightlessness are performed, it would be useful to summarize the changes to the basic structure of the Guyton model. The original Guyton model was not capable of responding to postural maneuvers. Therefore, one of the first important modifications included the addition of leg vascular and extravascular compartments, so that the fluid redistribution characteristic of weightlessness could be reproduced and studied (Leonard and Grounds, 1977). At that point in time, however, the effects of gravity were not included and it was only possible to initiate headward fluid shifts by some artificial means (Leonard et al., 1977). In order to more realistically portray the shifts of fluid between the leg compartments and the head, it was necessary to

\* A brief description of the Guyton model is provided in Appendix I.

model both external forces (the gravity vector), and internal forces (tissue elasticity) with a high degree of fidelity. Therefore, the next logical stage of development of a model purporting to examine fluid regulation in zero-g included a representation of the gravity vector as it affects the fluid columns of the body.

The direct effect of gravity forces was introduced in three locations in the model: at the inflow to the leg arterial compartment, at the outflow of the leg venous compartments, and at the carotid baroreceptors. Hydrostatic forces were allowed to be a function of the vertical distance to the midpoint of the legs or to the neck baroreceptors as measured from the heart. By multiplying the hydrostatic pressures by the sine of the angle with respect to the horizontal, the vertical gravity component can be computed for any angle of tilt. These hydrostatic vectors are algebraically added to the usual dynamic pressures of the circulation. With the model so modified, it was possible to examine by simulation techniques the two postural maneuvers described above which have been most useful for studying fluid responses to gravitational disturbances: head-up tilt (orthostasis) and head-down tilt (anti-orthostasis). By simply specifying any angle of tilt, either head-up, supine, or head-down, it is possible to create a large range of hydrostatic forces in the model, from maximal (at the feet) in the erect position, to zero in the supine position, to minimal in the head-down position. Further modification of the model, as discussed below, was necessary during head-up tilt to account for orthostatic defense mechanisms which were not originally present in the model. Similarly, during head-down tilt it was found that a redesign of the pressure-volume relationships of the leg fluid compartments (both in the vascular and interstitium segments) was necessary to provide realistic simulation of fluid drainage from these compartments. Of particular interest were the effects of venous collapse, peripheral transcapillary fluid exchange, and tissue and venous tone. Problems in these areas were not apparent during previous simulations of simple supine bed rest. Validation of the model for each new situation, therefore, required structural changes in the model that eventually would enhance the range of model capabilities and lead to improved simulations of weightlessness.

## 2.0 CAPABILITY OF THE GUYTON MODEL TO PERFORM POSTURAL MANEUVERS

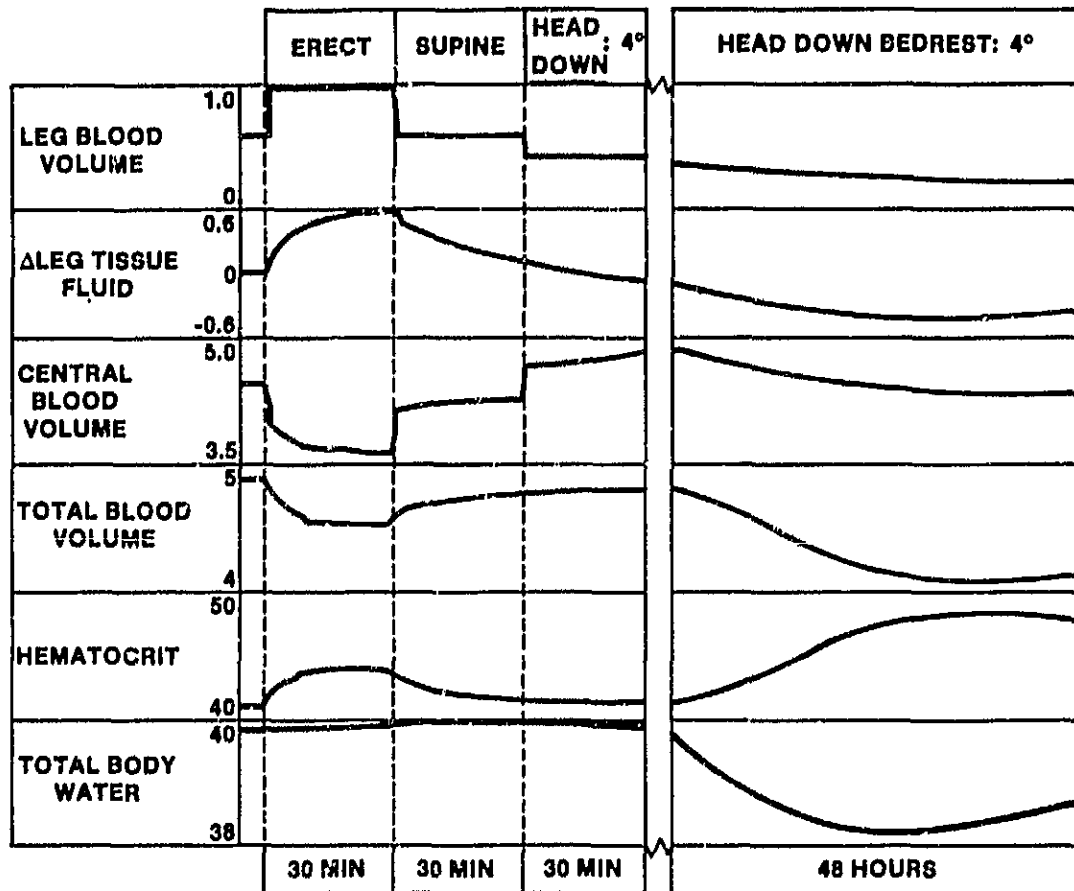
Although it may appear logical to believe that head-down tilt leads merely to opposite responses to that of a head-up tilt, this is not necessarily so. In the upright position the defense mechanisms must counter the tendency for loss of brain blood flow, while in the head-down position the physiological problem is that of reducing fluid pooling in the fragile thoracic regions which could lead to pulmonary congestion. The body appears better adapted for immediate protection against gravity in the orthostatic position compared to the anti-orthostatic position, where longer-term fluid adjustments must take place. Hampering the present analysis of these two stresses is the limited period of time that orthostatic subjects are usually studied (i.e., typically less than one hour) and the relatively infrequent number of studies conducted on anti-orthostatic subjects. Therefore, comparable measurements are not abundant during prolonged studies, and quantitative comparisons between these two postural maneuvers must await additional experimentation. Until that time, the mathematical modeling approach offers a means to integrate the available data and examine the underlying physiological regulatory behavior. Prior to describing a more detailed analysis of head-down tilt, it would be instructive to demonstrate the capability of the modified Guyton model to respond to postural maneuvers.

The capabilities of the modified model to predict fluid volume changes for a variety of ordinary postural changes in one-g are illustrated in Figure 1. In these simulations several consecutive short-term (30 minute) postural changes, including the erect, supine, and head-down positions, are followed by a longer term (48 hour) head-down bed rest. The angle of tilt used ( $-4^{\circ}$ ) for the anti-orthostatic maneuver is similar to that employed in experimental situations. Two important kinds of fluid shifts are examined in Figure 1: first, movement of blood between upper and lower body and second, plasma exchange between intravascular and extravascular compartments. The model realistically demonstrates the rapid blood volume shift of about 400 to 600 ml which occurs during normal short-term postural changes, and the somewhat slower shift of an additional 500 ml plasma which is normally pooled in the extravascular spaces of the legs when standing. Thus, in the erect position nearly one liter of fluid can be pooled in the legs, at the expense



FIGURE 1

**SIMULATED FLUID-SHIFTS DUE TO POSTURAL CHANGES**



(VOLUMES IN LITERS)

of decreasing the central blood volume and total blood volume. Tilting to the supine position returns fluid to the upper body and essentially reverses the previous changes. Tilting head-down to  $-4^\circ$  for a short period of time merely accentuates the magnitude of fluid shifts that were already observed in changing posture from erect to supine. However, longer exposure to head-down tilt (right half of simulation in Figure 1) dramatically reverses many of the short-term head-down shifts, except for drainage of fluid from the legs which becomes more severe. Therefore, although the model predicts that almost a liter of leg fluid has shifted cephalad by two days of anti-orthostasis (as measured from the supine), central blood volume has returned to nearly normal, due to the reduction in total blood volume. The loss of blood volume during prolonged head-down tilt is due primarily to feedback renal excretion pathways (as indicated in the simulation by loss of total body water), while blood volume loss in the short-term erect position arises from filtration into the leg interstitium. In both cases the loss of plasma is reflected by a hemoconcentration which is more severe in the anti-orthostatic position.

The simulations of Figure 1 also demonstrate that measurements of leg volume changes during bed-rest (or space flight) studies can be quite misleading, unless the reference posture is clearly defined. For example, at the end of 48 hours of head-down tilt, the simulation results indicate a decrement of total leg volume (leg blood volume plus leg tissue volume) of about one liter if measured from the supine position or about two liters if measured from the erect position. Also, the time at which the subjects remain either in the erect or supine position before the reference measurements are made is also crucial. Normally, the reference position is inadequately described in the experimental literature.

The ability of the model to perform orthostatic simulations was examined in further detail. Orthostasis is characterized by a redistribution of blood volume toward the lower limbs and widespread responses in the cardiovascular, autonomic, and hormonal systems. A summary of the model results are shown in Table 1. (For further details, the reader is referred to the original study (Leonard and Grounds, 1977)). The most significant event during orthostasis is a shift of approximately 10 to 15 percent of the effective central blood volume from the thoracic cavity to the lower

TABLE 1

## SHORT TERM (30 MIN) HEAD-UP TILT RESPONSE OF THE MODIFIED GUYTON MODEL

<u>CIRCULATORY VARIABLE</u>	<u>CHANGE FROM SUPINE</u>
Mean Arterial Pressure	- 4%
Central Venous Pressure	-14%
Cardiac Output	-14%
Total Peripheral Resistance	+11%
Heart Rate	+ 6%
Stroke Volume	-18%
Blood Pressure in Legs	+55 mmHg
<u>FLUID VOLUMES</u>	
Blood Volume	-280 ml
Leg Interstitial Pooling	+470 ml
Leg Vascular Pooling	+410 ml
Central Blood Volume	-700 ml
Hematocrit	+ 6%
<u>LOCAL BLOOD FLOW</u>	
Blood Flow in Upper Body	-15%
Blood Flow to Kidneys	- 9%
Blood Flow to Legs	-18%
<u>NEURAL-ENDOCRINE</u>	
Sympathetic Activity	+ 15%
Angiotensin Level	+350%
Aldosterone Level	+ 15%

extremities, where it is pooled. The elevated pressures in the leg vasculature, created by the hydrostatic gradient, drive about 10 percent of the supine blood volume across the capillaries into the leg interstitial spaces. The loss of plasma, therefore, causes an elevation in hematocrit. The central blood volume losses are thereby approximately equally divided between pooling in the leg veins and in the leg tissues. In the model simulations, the fall in total blood volume due to extravasation of fluid from the legs is partially compensated by intravasation of fluid from the tissues of the upper body. However, no documentation exists to confirm this phenomena.

A major effect on cardiac pumping also occurs. The loss of central blood volume and total blood volume reduces venous return, stroke volume, cardiac output, and arterial and venous pressures. If it were not for compensatory mechanisms, which come instantly into play upon orthostasis, blood flow to the brain would be inadequate to maintain tissue oxygenation. These mechanisms, therefore, guard against insufficient cardiac pumping and orthostatic hypotension.

The defense of the body against orthostatic hypotension consists of both passive and active mechanisms (Guyton et al., 1973; Rushmer, 1961; Pierone, 1968). Table 2 describes most of these important mechanisms and categorizes them with regard to whether they existed in the original model, whether they were added to the model in temporary fashion for the present study, or whether they have not yet been tested. The most important physiological requirement of these mechanisms is to maintain central venous pressure, in order to promote adequate ventricular filling. While the exact mechanisms controlling this adjustment have not yet been established, certain factors are known to be important in preventing a debilitating fall in central venous blood volume and pressure. These factors include: contraction of large venous channels and venous reservoirs, such as those which exist in the visceral organs (reverse stress relaxation); external compression of veins by skeletal muscles in the legs (muscle pump); and an external pressure on the large abdominal veins exerted by both the weight of abdominal organs and an increase in abdominal muscular contraction (abdominal compression). The reduction in central blood pressure leads to a sustained increase in sympathetic activity and release of vasoconstrictor hormones (catecholamines,

TABLE 2

ORTHOSTATIC DEFENSE MECHANISMS USED IN GUYTON MODEL

<u>I. ELEMENTS PRESENT IN THE MODEL</u>	<u>PHYSIOLOGICAL EFFECT</u>
o Autonomic Stimulation	Falling arterial blood pressures elicit autonomic sympathetic signals from the baroreceptors, which increase heart rate to maintain cardiac output and increase peripheral resistance to maintain arterial blood pressure.
o Tissue Compliance	Plasma entering leg interstitium during tilt causes tissue pressure to increase and prevents excessive filtration and further loss of blood volume.
o Venous Valves	Helps to reduce instantaneous fluid pooling during tilt.
o Renin Release	Decreased renal pressure during tilt stimulates secretion of renin-angiotensin, a powerful vasoconstrictor which helps maintain blood pressure.
<u>II. ELEMENTS TEMPORARILY ADDED TO MODEL</u>	
o Abdominal Compression	A powerful reflex which causes abdominal muscle contraction upon standing. This action compresses splanchnic veins which helps to restore venous pressure and enhances venous return.
o Instantaneous Reverse Stress Relaxation	A local property of venous smooth muscle which allows a rapid decrease in unstressed vascular volume when veins partially empty during standing. This effect enhances venous return.
o Muscle Pump Effect	Contraction of leg muscles surrounding local blood vessels lowers leg venous and capillary pressure and increases venous return.
o Myogenic Reflex	A postulated local reflex which enhances vasoconstriction in response to high leg hydrostatic pressures. The effect is to increase arterial pressure and limit plasma filtration into the interstitium.
<u>III. ELEMENTS NOT PRESENTLY USED</u>	
o Cardiopulmonary Autonomic Response	The present model contains only high pressure baroreceptors. Still required are the potentially important cardiopulmonary volume receptors in the low pressure side of the circulation. This will permit arterial pressure to return to normal during tilt without exaggerating baroreceptor response.

angiotensin) (see Table 1). As a result, there is an increase in total peripheral resistance and heart rate which diminishes the tendency of arterial pressure to fall. Ultrafiltration into the tissues is minimized by increasing tissue fluid pressure and lymph flow, reducing the hydrostatic columns in veins by "pumping" blood past leg venous valves, transient venoconstriction of the extremity venules, and an effective decrease in the filtration permeability. In spite of the influence of these orthostatic defense mechanisms, the net result is a reduction in central blood volume by leg fluid pooling, a decrease in cardiac output due to reduced stroke volume (in spite of an increase in heart rate), and a fall in venous pressure. However, mean arterial pressure is usually maintained and perhaps elevated.

The general agreement between the experimental observations and the model simulations of a number of physiological parameters in response to passive tilting attests to the basic soundness of the original Guyton formulation and the new modifications in leg and gravity elements. Although these validation studies demonstrate a short-term tilt capability (i.e., about 30 minutes), additional modification of the model is required to extend this time period.

### 3.0 SIMULATION OF HEAD-DOWN TILT

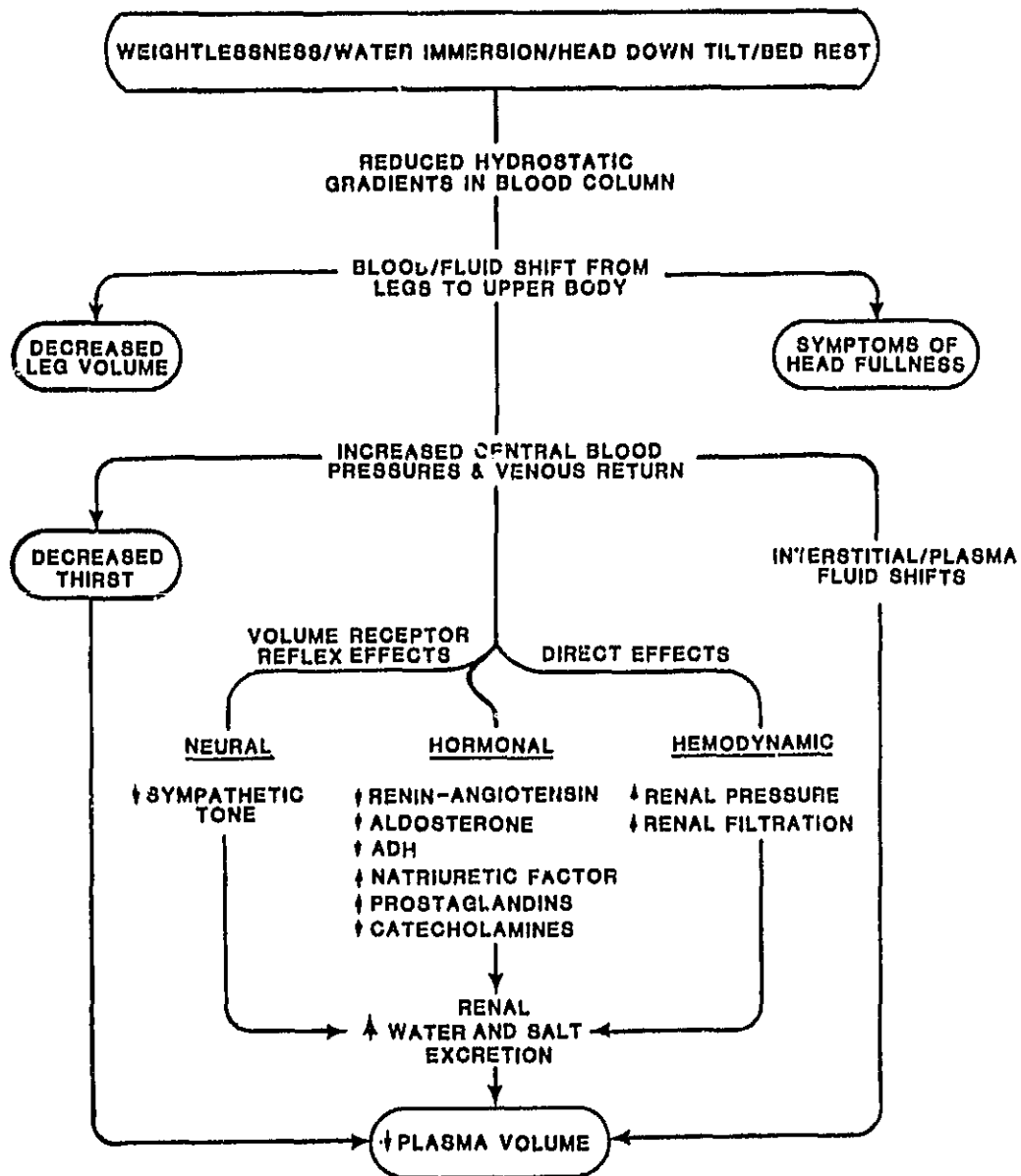
Although the head-down tilt maneuver appears highly promising as a zero-g analog, there have been few such studies reported using human subjects. Two of these investigations were examined with the objective of validating the technique for simulating head-down tilt. The first of these (Nixon et al., 1979; Blomqvist et al., 1980) concerned a 24-hour tilt stress ( $-5^\circ$ ) and in the second study (Joint Soviet-American Experiment on Hypokinesia, 1980) the subjects maintained the head-down position ( $-6^\circ$ ) for seven days. Thus, it was possible to study both a short-term and long-term anti-orthostatic bed rest response by comparing model behavior with experimental data. All of the results shown here were performed with the modified version of the Guyton model.

#### A. The Fluid Shift Hypothesis

One of the most significant and invariable findings from exposure to weightlessness, bed rest, water immersion, or head-down tilt has been a decrease in plasma volume. It is reasonable to believe that this stress response has a common etiology which involve the pathways responding to headward fluid shifts and central hypervolemia. In order to establish a context for discussing the model and experimental results, it would be useful to briefly describe these pathways in terms of the so-called "fluid-shift" or "fluid-redistribution" hypothesis (Figure 2). Most of the mechanisms described below and illustrated in Figure 2 have been described in one form or another by other investigators of ground-based studies (e.g., Gauer, 1975; Leach et al., 1969; Epstein, 1978).

Simply stated, the fluid-shift hypothesis is the concept that explains how a reduction of hydrostatic gradients in the blood columns causes fluids to shift from the legs (where they normally tend to pool during orthostasis) to the central circulation and results in an effective volume overload. Further, this central hypervolemia activates sensitive volume receptors and other mechanisms which then act to eliminate the excess fluid by several available pathways. The three normal routes by which plasma volume can be diminished are shown in Figure 2. They include capillary filtration into the tissues, renal excretion, and a thirst mechanism. Of these, the renal mechanisms are the most complex and Figure 2 indicates most of the important renal-regulating mechanisms available that have been implicated in the acute response. They have been separated into three groups, mediated by neural, hormonal, and hemodynamic factors. Although the pathways connecting these factors are not indicated (each item is a separate mechanism), they are, in fact, highly interrelated (Leonard et al., 1977).

Theoretically, it is possible for a reduction in plasma volume to occur by any one of the three major pathways shown. In practice, it appears that each pathway's contribution depends on its unique characteristics and the circumstances of the experimental study. For example, with regard to the thirst mechanism, deficit drinking appeared to account for the entire plasma volume loss in the Skylab crew. Previous modeling studies have suggested that



## FLUID - SHIFT HYPOTHESIS

FIGURE 2



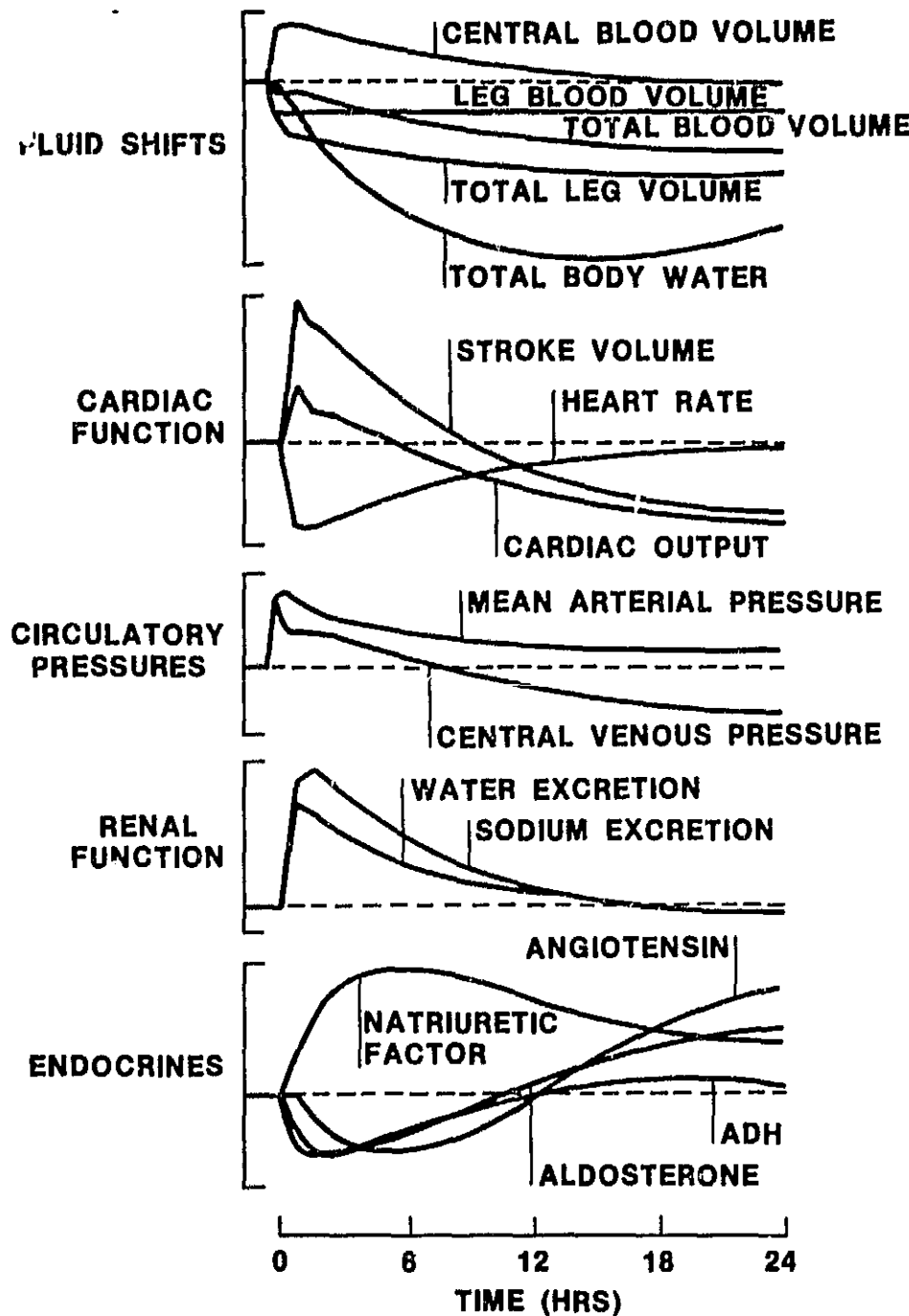
when fluid intake is restricted, an acute diuresis can be obscured in a 24-hour urine collection by a subsequent anuresis, thus accounting for the reduced values of pooled urine output during the first day of the Skylab missions (Leonard, 1982(a)). Ad libitum drinking is also diminished during bed rest. However, in water immersion subjects are often required to remain hydrated by consuming fluids at regular intervals. In those cases a significant diuresis is observed (Epstein, 1978). Our modeling studies have indicated that while diminished intake contributes to a reduction in body fluids, it does not abolish the diuresis effect completely (Leonard et al., 1977; Leonard, 1982).

There is scant experimental information regarding the extent of plasma filtration into the interstitial spaces during the fluid redistribution phase of hypogravity. Computer simulation analysis has revealed that this mechanism may be important only during the first few hours of weightlessness. Thereafter, lymph flow or inward filtration (i.e., absorption) eventually may restore interstitial volume of the upper body to normal (Leonard, 1982(a)). If fluid intake also returns to normal, as it does in long-term space flight, only the renal mechanisms remain as a potent pathway for preventing the restoration of plasma volume throughout months of weightlessness.

The renal pathways responding to volume overload have been intensely studied (Epstein, 1976; 1978), but there is still a lack of general agreement as to which mechanisms predominate in hypogravic stress. At one time it was believed that the reduction in ADH due to volume receptor stimulation (i.e., the Henry-Gauer reflex) was totally responsible for the diuresis of hypogravity. However, this view is no longer tenable in view of the large number of pathways which are available to participate in the fluid-shift response.

#### B. 24-Hour Head-Down Tilt

Computer simulations of the first 24-hours of head-down tilt, as shown in Figure 3, demonstrate the behavior of fluid volumes, hemodynamics, and renal-endocrine function that is expected from the fluid-shift hypothesis. The immediate or acute response occurs within the first several hours beginning with a decrease in leg volume. The change in leg fluid volume has



**SIMULATION OF HEAD DOWN TILT (-6°)**

**FIGURE 3**

two components, consisting of a rapid decline in blood volume and a more gradual decrease in interstitial fluid. Associated with this change are increases in central blood volume, circulatory pressures, stroke volume, and cardiac output, a decrease in heart rate (demonstrating the altered sympathetic outflow and suggesting an acute decrease in peripheral resistance), suppression of the renal-regulating hormones (including ADH, aldosterone, and angiotensin) and an increase in natriuretic factor. The increase in renal excretion of water and salts (resulting from a complex interplay between neural, hormonal, and hemodynamic factors) is ultimately expressed as a decline in extracellular fluid, represented in Figure 3 as decrements in blood volume and total body water.

Following these acute responses, which are essentially in agreement with the hypothesis diagram of Figure 2 (with the exception of certain factors such as prostaglandins, catecholamines and head fullness that are not represented in the model), most of the hemodynamic, renal, and endocrine indices return to their normal values before the end of the 24-hour period. However, this occurs at the physiological cost of a permanent shift of blood and leg fluid volumes. Thus, the reduction in blood volume leads to relief of central hypervolemia as reflected by restoration of the central blood volume and the circulatory and cardiac indices. At the same time, endocrine levels and renal output values return to normal, secondary to normalization of the blood pressures. Therefore, except for fluid volume changes which remain depressed, all other variables examined exhibit a transient biphasic behavior, with a return to baseline. It is particularly noteworthy that in several instances these quantities are predicted to eventually overshoot baseline conditions. Thus, venous pressure, stroke volume, cardiac output, ADH, angiotensin, and aldosterone appear to reverse direction at the end of the 24-hour period compared to their values during the acute stress phase. Therefore, after about 12 hours, one would find a reduced blood volume in accord with the fluid-shift hypothesis, but most of the other elements of that hypothesis would show measured values in opposite directions to that indicated in Figure 2.

This simulation analysis, therefore, demonstrates the importance of considering the dynamic properties of regulatory systems in order to explain

otherwise unexpected or counterintuitive results. For example, if measurements during head-down tilt were performed only after 12 hours, the model predicts that an investigator would find angiotensin levels elevated, renal excretion stable, or venous pressures below normal. These results might appear paradoxical in the face of presumed central hypervolemia and at odds with the concepts outlined earlier. Such "paradoxical" findings have in fact been observed in bed rest studies and during space flight (Hyatt, 1971; Leach and Rambaut, 1977). However, the simulation analysis suggests that rather than invalidating the theoretical expectations, these types of results merely indicate that earlier measurements should have been performed in order to capture the expected acute phenomena. In other words, the hypothesis diagram of Figure 2 (typical of those found in the literature) is really a static picture representing only the acute primary responses to headward fluid shifts; a more realistic dynamic analysis would allow for secondary changes that may cause a reversal of direction in various parameters. It is obviously important to make measurements continuously and early in time, in order to appreciate the dynamic feedback characteristics of hypogravic-induced headward fluid shifts.

In this same context it is useful to observe that the event which is common to the three major pathways shown in the fluid-shift hypothesis diagram (i.e., thirst, interstitial/plasma exchange, and renal pathways) is the reduction of plasma volume. Therefore, this event more than any other can be considered to be a test of the hypothesis. Furthermore, failure to demonstrate any of the particular mechanisms such as reduced ADH or a diuresis during the acute stress phase does not necessarily invalidate the overall theory, because alternative pathways can be activated to achieve the desired plasma volume loss. The simple fact that plasma volume fails to return to normal even after days or weeks of bed rest or months of space flight, and even after fluid intake and transcapillary exchange has returned to normal, is presumptive evidence that the renal mechanisms for controlling blood volume are indeed operative and responding to the tendency toward central hypervolemia.

### C. Comparison of Model and Data for 24-Hour Head-Down Tilt

The validity of the computer simulations shown in Figure 3 were assessed by comparing the model responses with the experimental studies of Blomqvist and co-workers (Nixon et al., 1979). Results from that experimental study are shown in Figure 4 (Hemodynamic Responses) and Figure 5 (Endocrine Responses). Table 3 lists changes observed in both model and human subjects at the end of 24 hours. A graphical schematic summary of this study has been reported by Blomqvist et al. (1980) and is reproduced in Figure 6. With few exceptions, the behavior of the model's responses was remarkably similar to the experimental findings.

As was discussed earlier, head-down tilt causes a significant central fluid shift and produces transient changes in major hemodynamic parameters which return to control levels before the end of the 24-hour period. It appears that cardiovascular and blood volume regulation was achieved in the human subjects in a similar manner as suggested by a more detailed analysis of the model; that is, by a combination of renal diuresis, transcapillary filtration, accommodation by vascular capacitance elements, and a reduction in blood volume, associated with a transient suppression of volume-regulating hormone levels (Figures 4 and 5). At the end of the experimental period many of the observed quantities exhibited a deviation from control values and these changes were similar to those predicted by the simulation (see Table 3). Several examples include the changes in total body water (-1.3 vs. -1.1 liters; experimental vs. model), leg volume (-0.9 vs. -0.7 liters), blood volume (-0.43 vs. -0.56 liters), and cardiac output (-7.8 vs. -11.1 percent). The early rise in urinary excretion noted in the experimental study was also observed in the simulation. Also, the model succeeded in differentiating between the eventual fall below control in venous pressure versus the elevated arterial pressure. (However, the transient dip in arterial pressure and the failure of cardiac output to rise, during the first several hours in the human subjects, is not currently explicable and was not predicted during the simulation.) Finally, the interesting biphasic behavior of the ADH, aldosterone and angiotensin endocrines, whereby there was a clear trend with a transient initial suppression of all plasma hormone levels and a return to

FIGURE 4

# **HEMODYNAMIC RESPONSES OF HUMAN SUBJECTS TO HEAD-DOWN TILT** (DERIVED FROM NIXON, et al, 1979)

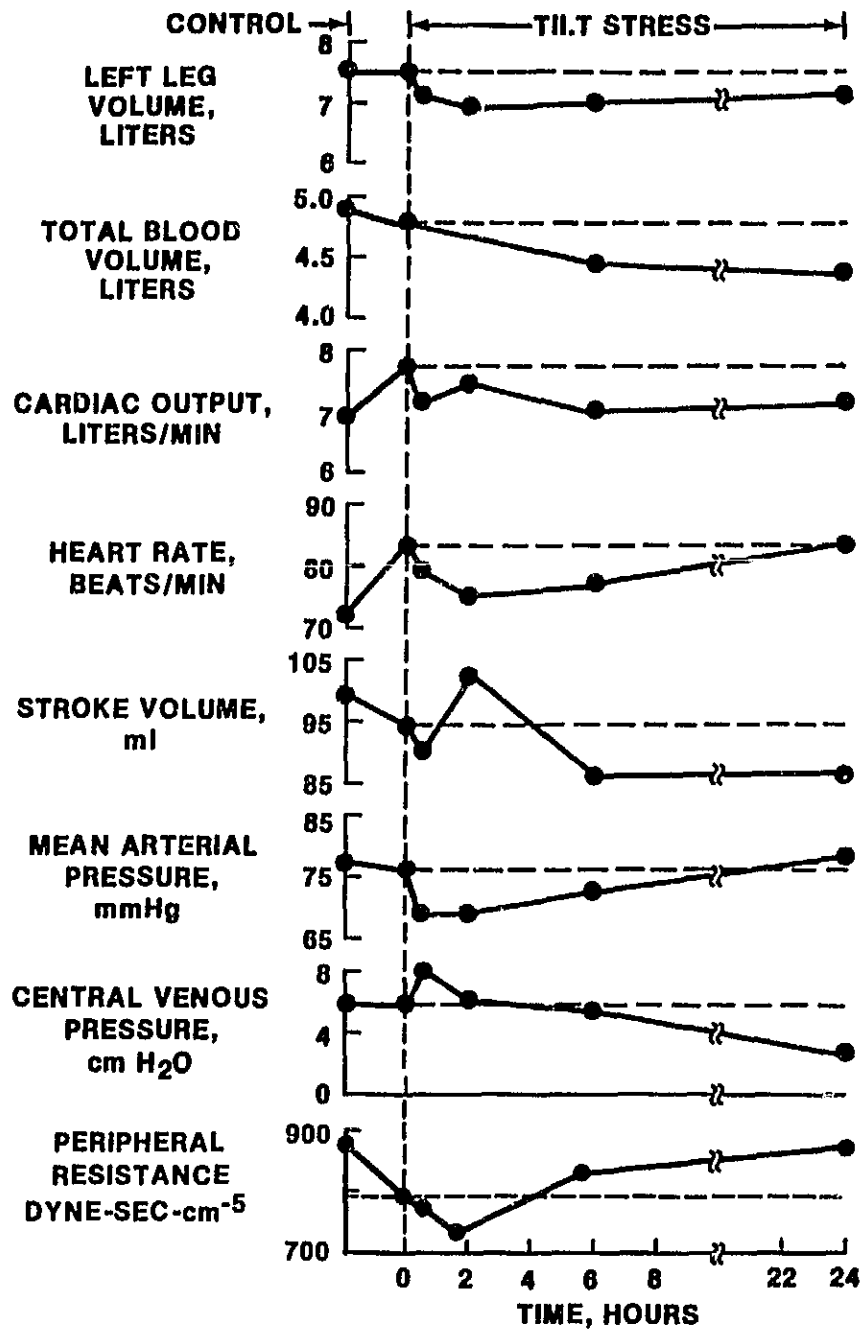


FIGURE 5

ENDOCRINE RESPONSES OF HUMAN SUBJECTS  
TO HEAD DOWN TILT

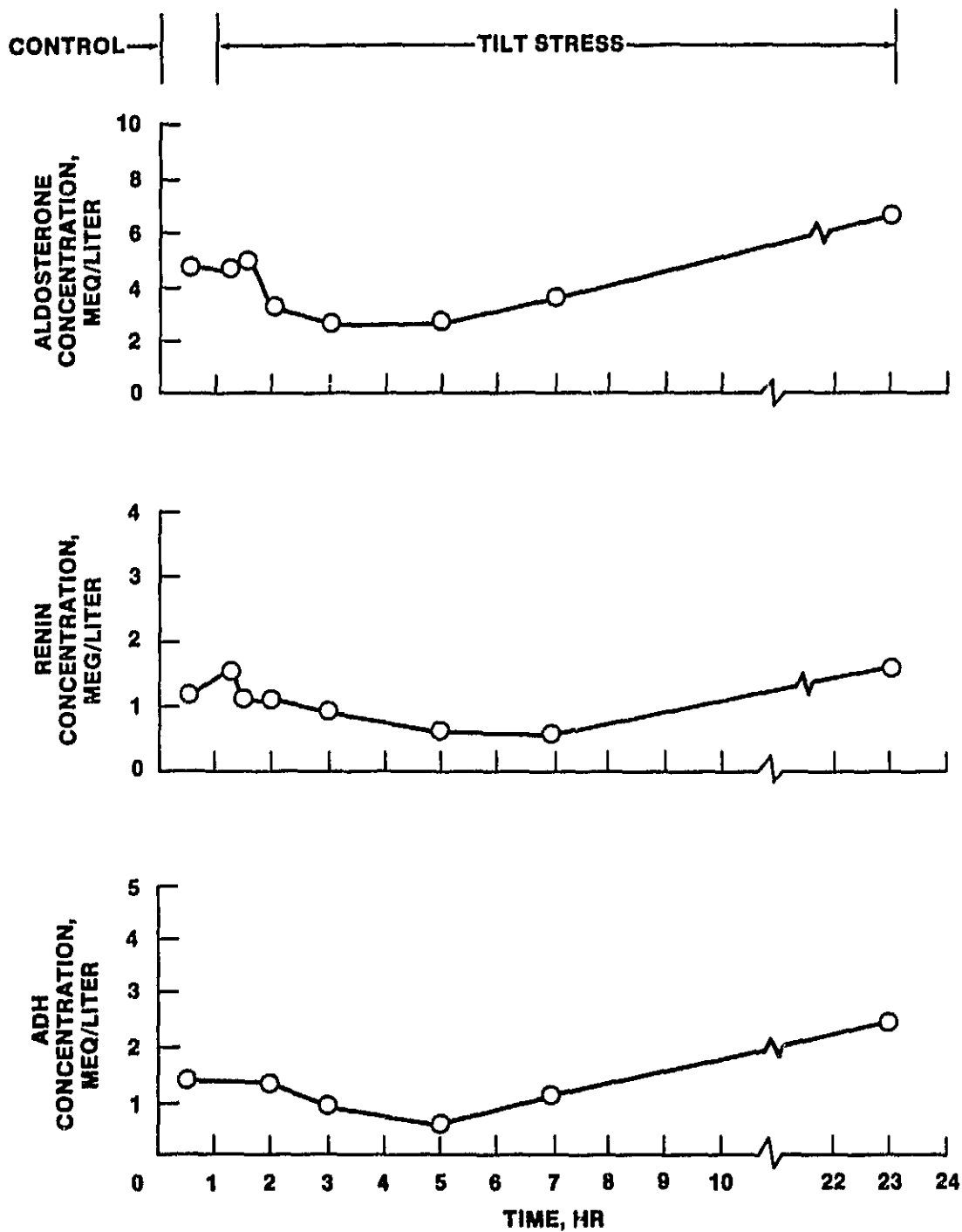


TABLE 3

# COMPARISON OF SIMULATION AND EXPERIMENTAL RESPONSE FOR 24-HOUR HEAD-DOWN (-5°) TILT STUDY

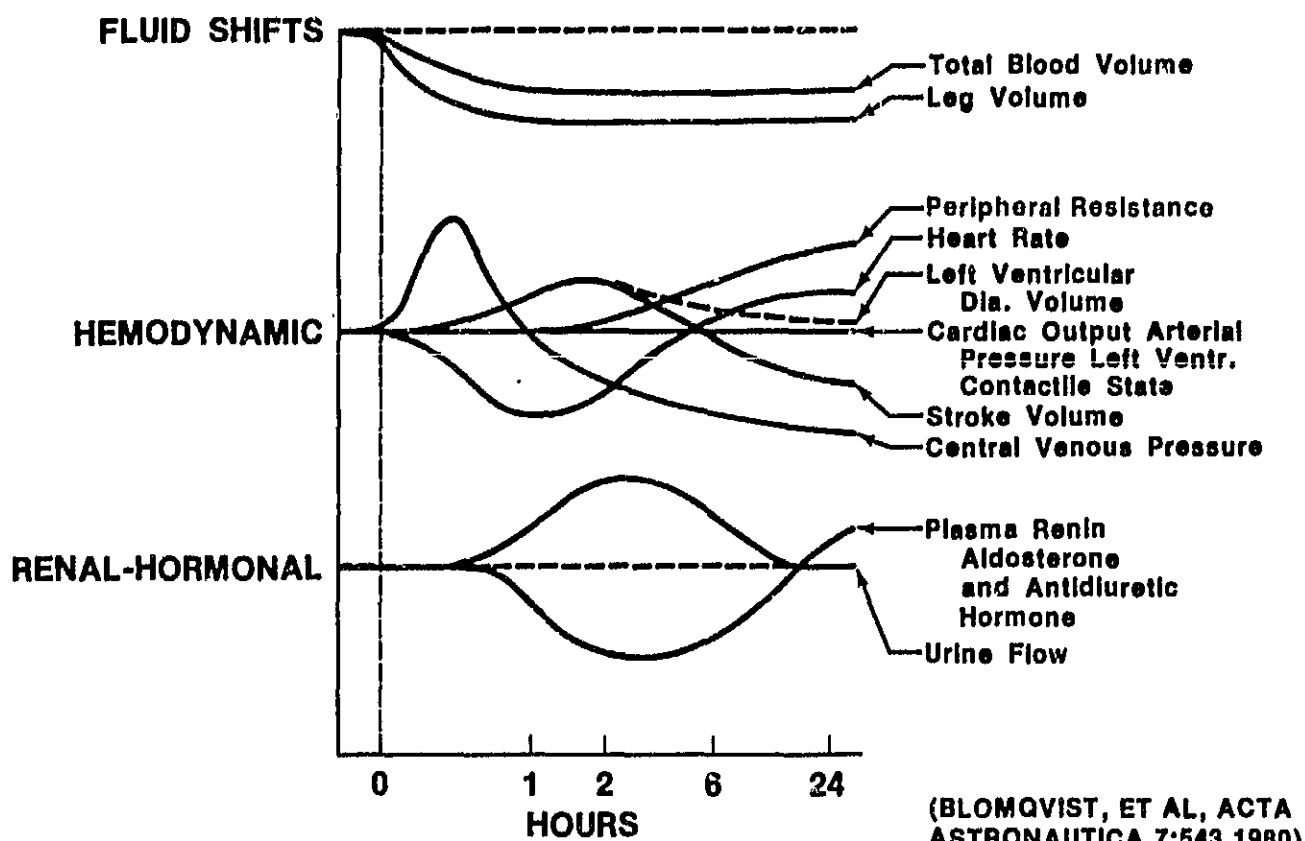
<u>QUANTITY</u>	<u>VALUE @ 24-HOURS COMPARED TO CONTROL</u>	
	<u>HEAD-DOWN TILT</u>	<u>MODEL</u>
<b>FLUID SHIFTS</b>		
TOTAL BODY WATER	-1300 ml	- 1130 ml
LEG BLOOD VOLUME	ND	- 256 ml
LEG INTERSTITIAL VOLUME	ND	- 454 ml
TOTAL LEG VOLUME	- 900 ml	- 710 ml
TOTAL BLOOD VOLUME	- 425 ml	- 563 ml
HEMATOCRIT	+ 7.5%	+ 12.5%
URINE RATE, 1ST 8 HR/24 HR	127%	190%
<b>HEMODYNAMICS</b>		
CARDIAC OUTPUT	- 7.8%	- 11.1%
STROKE VOLUME	- 8.5%	- 9.8%
HEART RATE	0%	1.4%
ARTERIAL PRESSURE	+ 3%	+ 3%
CENTRAL VENOUS PRESSURE	- 49%	- 9%
LEFT ATRIAL PRESSURE	ND	- 50%
PERIPHERAL RESISTANCE	+ 11.3%	+ 16.0%
<b>HORMONES</b>		
ANGIOTENSIN	+ 25%	+ 27%
ALDOSTERONE	+ 35%	+ 17%
ADH	+ 57%	+ 3%
NATRIURETIC FACTOR	ND	+ 13%

ND = NOT DETERMINED



FIGURE 6

# IDEALIZED RESPONSE OF HUMAN SUBJECTS TO HEAD-DOWN TILT



control levels, was seen in both experimental and simulation studies. The enhanced activity of a natriuretic factor, predicted by the simulation, was not measured experimentally.

### Analysis of Renal-Endocrine Response

An initial suppression of the major renal-regulating hormones - ADH, aldosterone, and renin-angiotensin - has been previously observed during various water immersion studies (Epstein, 1978) and in computer simulations of water immersion (Leonard, 1982(a)). Thus, it was not unexpected that the studies of Blomqvist and co-workers verified this finding for head-down tilt (see Figure 5) and in so doing supported the concept that headward fluid shifts, whether produced by head-down tilt or water immersion, are accompanied by decreased secretion of this hormone system. Current knowledge of hormonal action suggests that this response would augment the diuresis and natriuresis observed during these stresses. For example, increased urine volume flow rate is enhanced by decreased levels of ADH, while sodium excretion is elevated by decrements in aldosterone and angiotensin. (Whether or not non-hormonal factors may be involved or play an even more significant role in the renal response is currently not settled (Epstein, 1978). This computer analysis suggests that hemodynamic factors, specifically an increase in glomerular pressure, contributes significantly to the initial diuresis. Support for this view comes from recent water immersion and head-down tilt studies (Stegemann and Skipka, 1977; Leach et al., 1982).

Of equal importance in the Blomqvist studies, however, was the first reported observation that these hormones return to, and overshoot, their pre-tilt control values during the latter part of the 24-hour experimental period. This phenomena of suppression, recovery and overshoot was predicted by computer-model simulations several years before these validating experiments were performed (Fitzjerrell et al., 1975). At that time, as now, it was believed that understanding such a transitory response to central hypervolemia is essential to reconcile data from short-term and long-term hypogravic studies (Leonard et al., 1979). Specifically, short-term studies such as water immersion indicate hormone suppression, while results from Skylab and certain longer-term bed-rest studies demonstrate that angiotensin and

aldosterone become elevated over days or weeks. One can predict a transition between these two states by assuming that there are common physiological mechanisms involved in these various stresses (Leonard, 1982(c)). Although the cause(s) for the hormone "overshoot" are not yet known, the computer analysis has suggested a number of factors which may be involved. These include alterations in plasma volume, plasma electrolyte concentrations, and diet, and will be discussed subsequently in this report.

In our preliminary simulations of head-down tilt, ADH suppression was short-lived (i.e., less than 30 minutes) before increasing above control in response to a rising plasma sodium concentration. An elevation in either ADH or sodium concentration is unrealistic during acute hypogravic stress in light of more recent studies (Epstein et al., 1975; Greenleaf et al., 1980; Khosia and DuBois, 1979; Nixon et al., 1979) which indicate that both quantities diminish, for at least a number of hours. A more accurate simulation was obtained by two modifications to the model. First, a renal-natriuretic factor was introduced which permitted plasma sodium concentration to be maintained near or below normal levels during the first day of hypogravity exposure (Leonard et al., 1977). Natriuretic activity was determined as a linear function of arterial pressure and permits excess sodium excretion during hypertensive states. Secondly, the sensitivity of ADH to venous pressure was increased by a factor of 15 relative to the sensitivity of ADH to plasma osmolarity (i.e., sodium concentration). The evidence for a natriuretic factor is becoming increasingly stronger (Epstein, 1978; DeWardener and Clarkson, 1982) and evidence for enhanced sensitivity of the volume-pressure control of ADH during central hypervolemia is also available from recent studies (Guyton et al., 1975; Dunn et al., 1973). As a result of these model modifications, ADH secretion diminishes during acute headward fluid shifts (Figure 3), and following reflex normalization of central blood volume ADH returns to, or above, normal, agreeing quite well with Blomqvist's experimental data.

#### Analysis of Circulatory Response

The longer-term changes in cardiac output, and arterial and venous pressure (i.e., those observed at about 24-hours) are particularly intriguing. At this point in time, both the experimental data and model results

demonstrate an elevated arterial pressure and a diminished cardiac output and venous pressure. The cause of these changes is not immediately apparent. Consider first the decline below normal venous pressure. In the model and in the experimental findings of Blomqvist and co-workers, this change is associated with a fall in blood volume, an increase in unstressed venous volume (i.e., an effective increase in compliance), and an increase in peripheral resistance. Each of these factors is individually capable of reducing the venous pressure, but whether each factor is truly involved in causing venous pressure to fall below normal in human head-down tilt subjects is not known. This was the subject of a special modeling study discussed next.

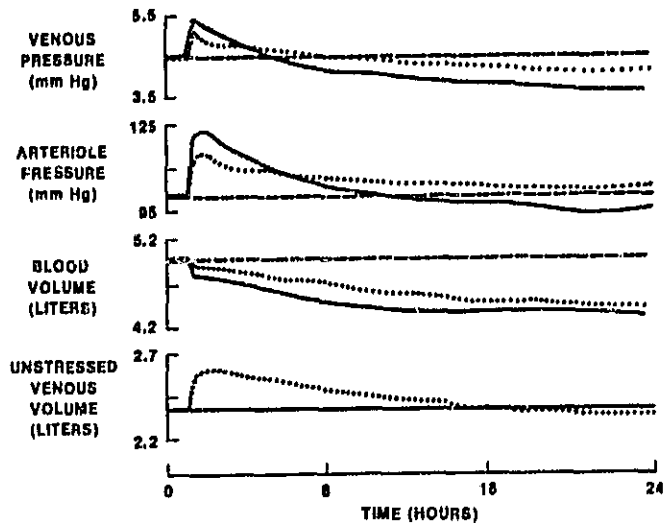
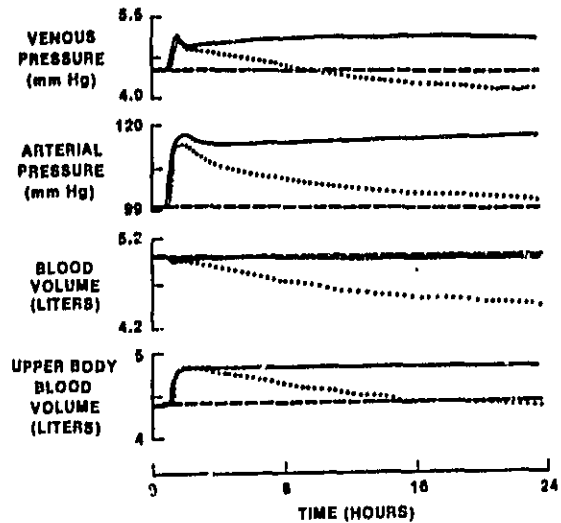
The general approach for studying this problem was to remove the influence of each of the above variables (blood volume, unstressed venous volume, and peripheral resistance) in an attempt to reveal the importance of each variable in controlling venous pressure. Therefore, these variables were clamped at their normal values, one at a time, during a head-down tilt simulation. If venous pressure was thereby prevented from declining below normal, the clamped variable would then be a likely candidate for having caused the venous pressure decline in the intact system.

As shown in Figure 7, four different simulations of head-down tilt were performed. These included: (a) A normal simulation (shown as a dotted curve) identical to the simulation shown in Figure 3; (b) Clamping the renal output and transcapillary filtration. As expected, this action prevented the loss of body fluids and reduction in blood volume, and resulted in high venous pressure throughout the simulation. This demonstrates that the loss of blood volume is a necessary condition for a net reduction in venous pressure; (c) Clamping the unstressed venous volume at normal (but allowing the kidneys and capillaries to function normally). This allowed blood volume loss but prevented stress relaxation in the model. (Stress relaxation increases the unstressed venous volume.) Preventing a change in unstressed volume had the effect of causing venous pressure to be higher than normal at the start of the simulation and lower than normal at the latter part of the run, but it did not prevent venous pressure from declining below normal. This rules out unstressed venous volume as a candidate factor; (d) Clamping total peripheral resistance at normal. This variable was thus prevented from rising as it did

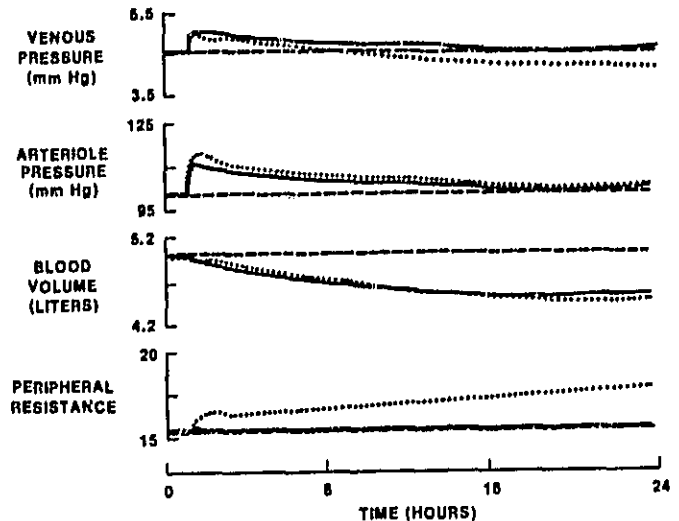
FIGURE 7

# **SIMULATION STUDY OF FACTORS CONTROLLING BLOOD PRESSURE DURING HEAD-DOWN TILT**

(B) ——— RENAL EXCRETION CLAMPED  
..... NORMAL SIMULATION



(A) ——— UNSTRESSED VOLUME CLAMPED AT NORMAL  
..... NORMAL SIMULATION



(C) ——— PERIPHERAL RESISTANCE CLAMPED  
..... NORMAL SIMULATION

in the normal simulation. As a result, venous pressure fell towards normal, but not below normal. This study, therefore, suggests that in the model, at least, blood volume loss and elevated peripheral resistance are primarily responsible for the chronic decline in venous pressure. Unstressed venous volume (or compliance) changes had only a temporary effect.

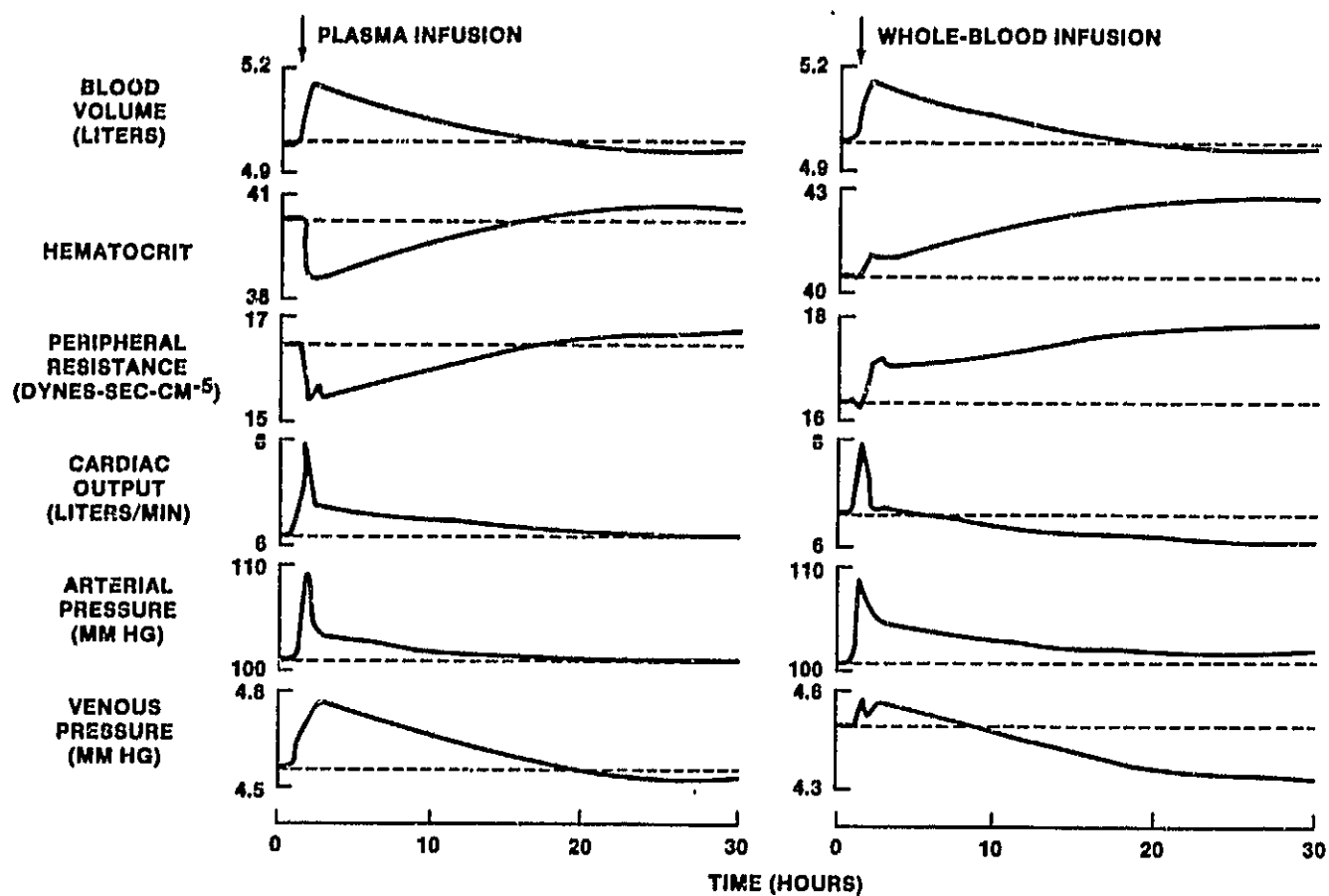
An additional analysis was performed to distinguish between the effects of blood volume loss and elevated peripheral resistance in causing a lowering of venous pressure. Rather than simulating the effects of head-down tilt in producing central hypervolemia, blood infusion simulations were performed. From the viewpoint of the central circulation, both tilting and infusions would appear to have similar effects; i.e., head-down tilt can be considered to be an autogenic infusion from the lower limbs. While total blood volume increases only in the case of infusions, central blood volume increases in both cases.

Two different types of infusions were simulated: an infusion of plasma (water + iso-oncotic proteins + iso-osmotic electrolytes) and an infusion of iso-hemoconcentrated blood (plasma + red cells). In both cases 250 ml were administered in a period of 10 minutes. The simulation response to these two infusions over a period of 30 hours is shown in Figure 8. Although the blood volume and arterial pressure responses are nearly identical in both cases, i.e., an increase and then a decline toward normal (or slightly below normal), the venous pressure and cardiac output responses are quite different. These quantities (flow and pressure) both increase as a result of the extra infusion volume; but, in the case of the plasma infusion there is a return to baseline, while in the case of the whole-blood infusion there is a decline below baseline. In the latter case, the flow and pressure responses are reminiscent of computer simulation results of normal head-down tilt (Figure 3).

The underlying cause of these differences in model responses can be traced to the quite different alterations in hematocrit and resistance which are also shown in Figure 8. Plasma infusions quite logically lead to a lower hematocrit than that caused by whole-blood infusion. (In both cases there is a tendency for a relative hemoconcentration to occur over time as plasma is

FIGURE 8

# **SIMULATED EFFECT OF PLASMA OR WHOLE-BLOOD INFUSIONS ON HEMODYNAMIC RESPONSES**



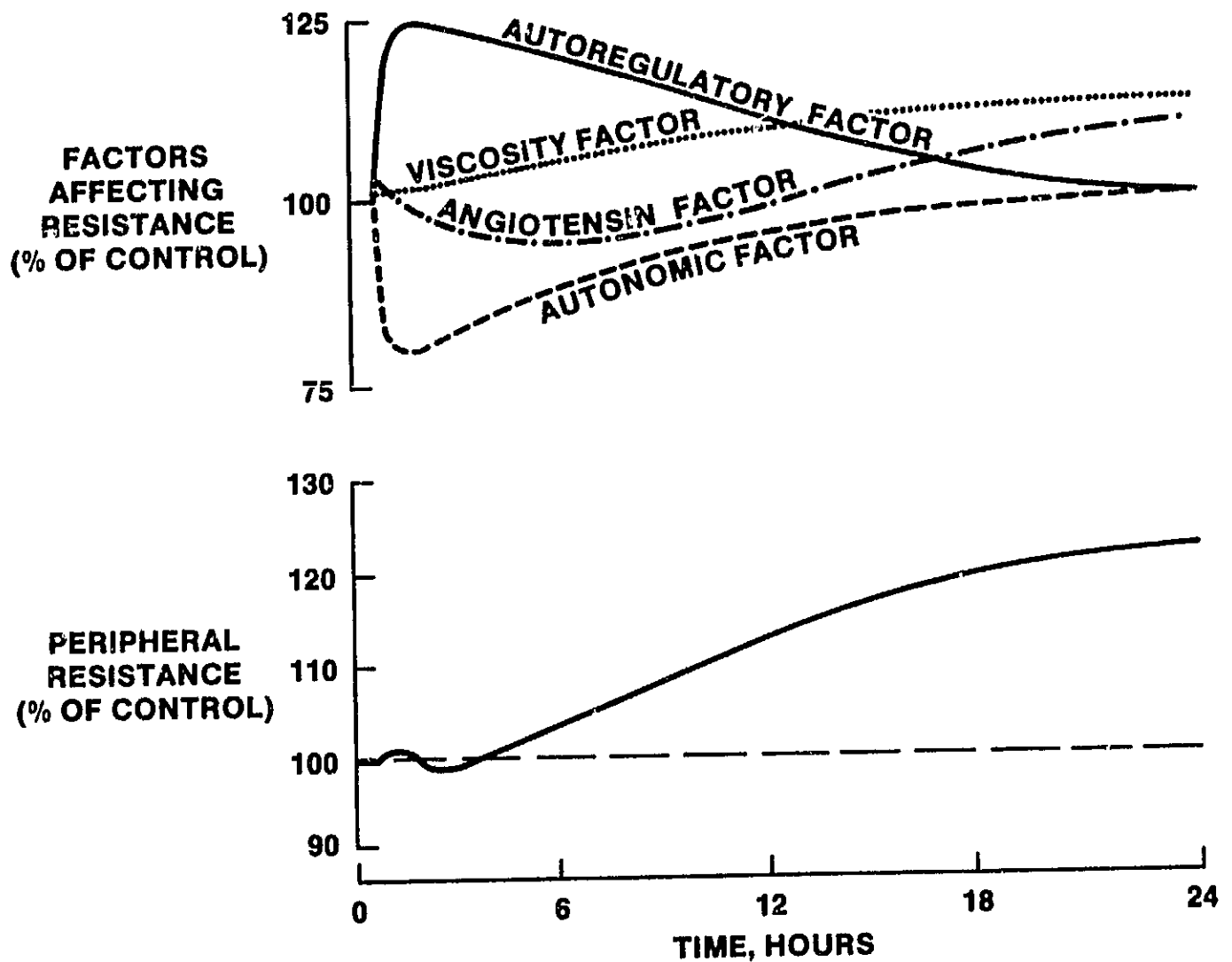
forced from the over-expanded vasculature, but an absolute hemoconcentration occurs only in the case of blood infusions). In the model, resistance to flow is directly related to hematocrit (as well as other factors discussed below). The difference in peripheral resistance between the two infusion responses accounts for the differences in venous pressure and cardiac output. This simulation, therefore, demonstrates that even when blood volumes are normal (latter half of simulation period of Figure 8), venous pressure can be below normal (and arterial pressure above normal), if blood is hemoconcentrated. If hemoconcentration is accompanied by an absolute blood volume loss, as occurs in head-down tilt, then venous pressure could fall even lower.

If the longer-term changes in circulatory flow and pressure can be traced to an increase in systemic resistance, as suggested in the simulations discussed above, the next questions to ask are "what are the factors which cause resistance to rise during a head-down tilt model simulation?" and "how well do these results regarding resistance changes compare to experimental findings?" In the model, one of the factors having a profound effect on resistance is an autoregulatory mechanism which adjusts local flow according to the oxygen needs of the tissue. The hemoconcentration which develops during head-down tilt, secondary to rapid plasma volume losses, alters the oxygen supply-demand balance at the tissue level to favor tissue hyperoxia. This in turn causes an autoregulatory increase in resistance, thereby reducing blood flow and returning the tissue oxygen supply toward normal. An additional factor which can produce an increase in autoregulatory resistance is a decrease in oxygen demand (or oxygen uptake), which has long been known to occur in bed rest (Detrick et al., 1945). However, in these simulations, the assumption of lower metabolic demand was not imposed upon the model. Hemoconcentration has influence on resistance, not only via the autoregulatory factor described above, but also due to a viscosity effect which increases frictional resistance. Another major influence on resistance is the vasoconstrictor effects of angiotensin; angiotensin increases above normal following 12 hours of simulated head-down tilt. The dynamic influence of these various factors on resistance is shown in Figure 9. Note that different factors appear to dominate the control to resistance at different time periods.



FIGURE 9

## FACTORS CONTROLLING PERIPHERAL RESISTANCE



Whether or not these quantitative dynamic responses are strictly correct is not of major concern at this juncture. However, it is certainly relevant that increases in hemotocrit, angiotensin, and total peripheral resistance have been noted in supine bed rest and head-down tilt (Nixon et al., 1979 and Joint Soviet-American Experiment, 1979). Peripheral resistance has been measured to increase about 15 to 20 percent in these cases (i.e., see Figure 4), in excellent agreement with model predictions. Although no definitive explanation for the resistance changes has been offered, it is well known that exercise conditioning decreases total peripheral resistance (and by implication one would expect deconditioning or hypokinesia to increase TPR). Studies of hypokinesia in humans and rats have suggested that resistance may increase because of a closure and atrophy of blood capillary networks, especially in the muscles (Cureton, 1969; Saltykova, 1982). Another explanation comes from Stegmann and Skipka (1977) who have shown that untrained subjects have a greater closed loop carotid pressure-arterial pressure gain compared to trained subjects. This can be interpreted as an increase in sensitivity of peripheral resistance elements to incoming central neural signals.

These model studies of a 24-hour head-down tilt experiment have demonstrated the basic validity of the numerous feedback control mechanisms embedded in the model as well as the numerical techniques employed to simulate the anti-orthostatic position. The analysis has demonstrated that it is insufficient to merely consider either the acute primary stress reaction or the long-term secondary responses as distinct events. Rather, it is important to examine the system's dynamic behavior in order to understand the full range of hemodynamic, renal, endocrine, and volume responses to fluid-redistribution in zero-g. Although it is not yet known which mechanisms are ultimately responsible for the loss of body fluids, it was suggested that only the renal pathways are capable of maintaining plasma volume at reduced levels appropriate for hypogravity. Several other important questions remain to be answered, including the issue of whether central blood volume returns to normal levels as predicted by the model. In addition, this reflex response appears to occur at the expense of a diminished central venous pressure, the etiology of which is not known but was suggested to involve peripheral resistance effects. The establishment of a model which is valid for acute changes to head-down tilt

can now be used as a basis for predicting early changes during space flight (which are as yet unknown), as well as providing a point of comparison for other space flight analogs such as supine bed rest and water immersion.

D. Seven-Day Head-Down Bed Rest

It appears obvious from the above study that many of the physiological disturbances and regulatory influences have not stabilized at the end of 24 hours. What is the behavior of these parameters during longer exposure to head-down tilt? In order to provide an answer to this question, simulations of seven-day head-down tilt were performed and were then compared to the findings of the Joint US/USSR Hypokinesia Study (1979). Simulations of the seven-day bed rest study were performed in a nearly identical manner to the 24-hour study. That is, the angle of tilt with respect to the horizontal was set to  $-6^\circ$  and the responses to this stress were observed over the seven-day simulated period. In addition, a decrease in dietary intake was imposed. In contrast to the normal eating and drinking patterns reported for the subjects of the 24-hour head-down tilt study, the subjects of the seven-day study were provided a calorically reduced diet, and drank ad libitum water also at diminished levels. The average reduction in food weight and fluid volume was very close to -30 percent. Consequently, the model parameters which control dietary water, sodium and potassium were also reduced by similar amounts. Other than the dietary changes and length of study, all aspects of the model simulations were identical for both the 24-hour and the basic seven-day simulations. Additional simulations were performed which tested other hypotheses, and the specific effects of these tests (including the effects of a reduced diet) will be examined in detail in a later section. In Table 4 are listed a number of important physiological parameters (similar to those presented in Table 3 for the short-term study) and their simulated changes (from control) measured at the end of seven days. Also shown, by way of comparison, are the corresponding experimentally measured changes. These data will be discussed next.

TABLE 4

# **COMPARISON OF SIMULATION AND EXPERIMENTAL RESPONSE FOR 7-DAY HEAD-DOWN (-6°) BED-REST STUDY**

## VALUE @ 7-DAYS COMPARED TO CONTROL

	<u>BED REST</u>	<u>MODEL</u>
<b>FLUID SHIFTS</b>		
TOTAL BODY WATER	- 600 ml	- 805 ml
LEG VOLUME	- 460 ml	- 650 ml
BLOOD VOLUME	- 8%	- 13%
HEMATOCRIT	+ 7%	+ 9%
RED CELL MASS	- 9%	- 5%
<b>HEMODYNAMICS</b>		
CARDIAC OUTPUT	- 9.5%	- 10.7%
ARTERIAL PRESSURE	+ 9.5%	0%
VENOUS PRESSURE	- 2% (EDV)	- 8.6%
PERIPHERAL RESISTANCE	+ 14.0%	+ 11.0%
<b>RENAL FUNCTION</b>		
WATER EXCRETION	- 39%	- 31%
SODIUM EXCRETION	- 39%	- 33%
POTASSIUM EXCRETION	- 13%	- 16%
<b>ELECTROLYTES</b>		
PLASMA [Na <sup>+</sup> ]	- 3.0 meq/l	- 6.7 meq/l
PLASMA [K <sup>+</sup> ]	- 0.5 meq/l	- 0.5 meq/l
TOTAL BODY POTASSIUM	ND	- 4%
<b>PLASMA ENDOCRINES</b>		
ANGIOTENSIN	+ 116%	+ 55%
ALDOSTERONE	- 28%	- 24%
ADH	- 65%	- 37%
<b>END DIASTOLIC VOLUME</b>		
ND = NOT DETERMINED		

### Fluid Volumes and Hemodynamics

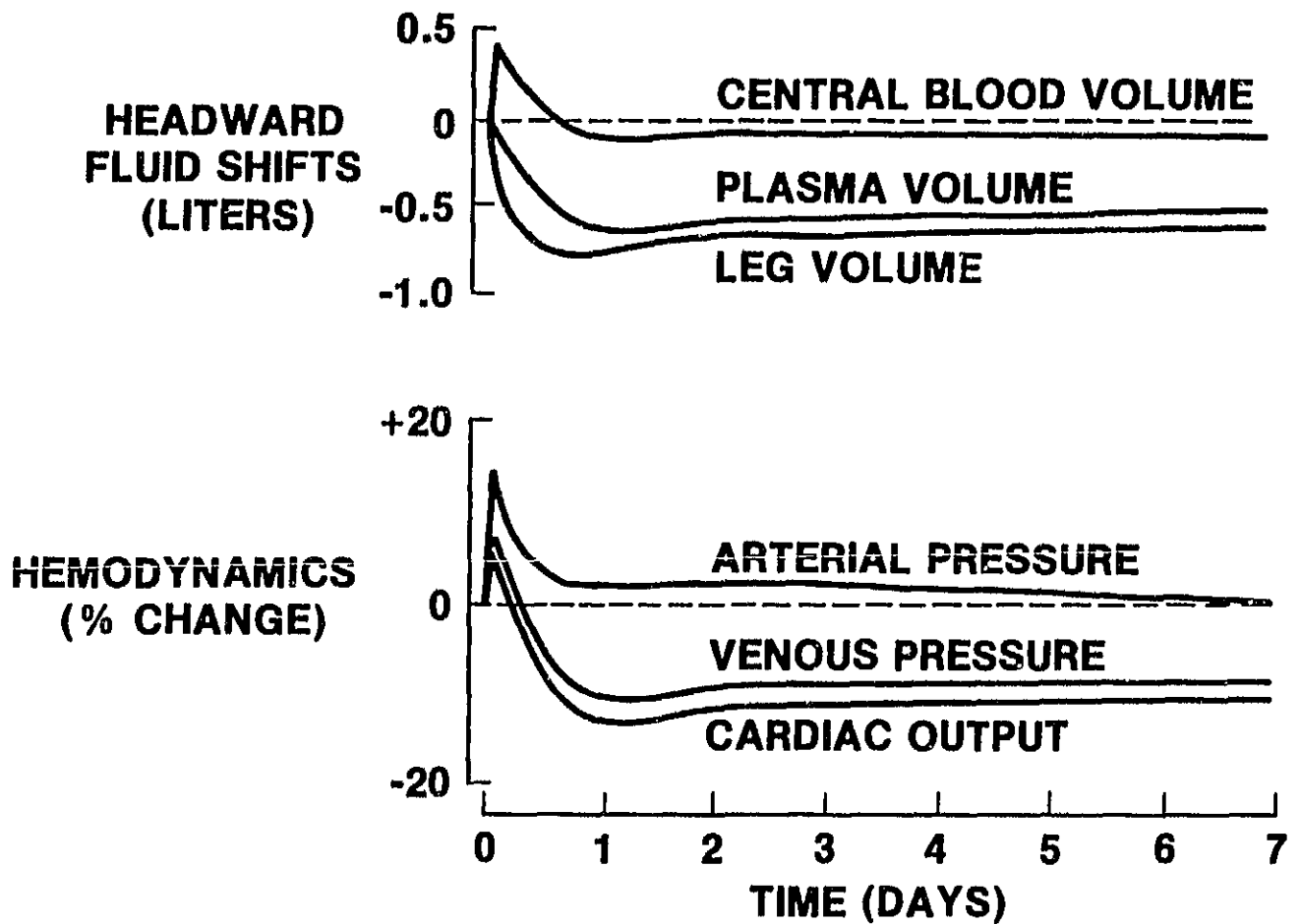
As would be expected, the initial response of the model was nearly identical for both the short-term 24-hour study and long-term seven-day study. Head-down tilt caused an acute shift of blood and tissue fluid from the legs to the central circulatory regions leading to reflex changes having long-term fluid and hemodynamic consequences. These responses can be observed in Figure 10, where the model predicts that most of these disturbances stabilize after the second day of head-down bed rest. At this time the legs have lost approximately 700 ml fluid from both intravascular and interstitial sources while the plasma volume decreases by about 550 ml. Associated with these fluid losses is the almost complete correction of central blood volume toward its normal value. The reduction of cardiac output and venous pressure to stable levels, which are about 10 percent below control, is a continuation of the trend observed at the end of the 24-hour head-down tilt study (compare Figures 3 and 10). At the same time, arterial pressure has a tendency to remain slightly elevated as it returns toward normal.\* These simulated responses are in reasonable qualitative agreement with observations in the human subject (Table 4).\*\* Also, the analysis of circulatory responses discussed in Section 3C (i.e., the influence of increasing peripheral resistance) would apply here and tentatively explain the hemodynamic responses.

### Endocrine Behavior

Of primary interest in this study was the interpretation of renal-endocrine function and electrolyte metabolism. Alterations of these systems have been the subject of various space-flight investigations because they provide important clues to fluid volume control during weightlessness. Some of the quantities which reflect the status of these systems, and which were

\* Fluid and hemodynamic responses of the model to long-term (two months) space flight are shown for comparison in Appendix B. The results indicate that there is a strong tendency for the hemodynamic variables to return to normal after several weeks of zero-g adaptation.

\*\*Although measurements of CVP were not performed in the seven-day bed rested subjects, the end-diastolic volume, which can be taken as a measure of CVP, was measured and demonstrated a slight reduction (see Table 4).



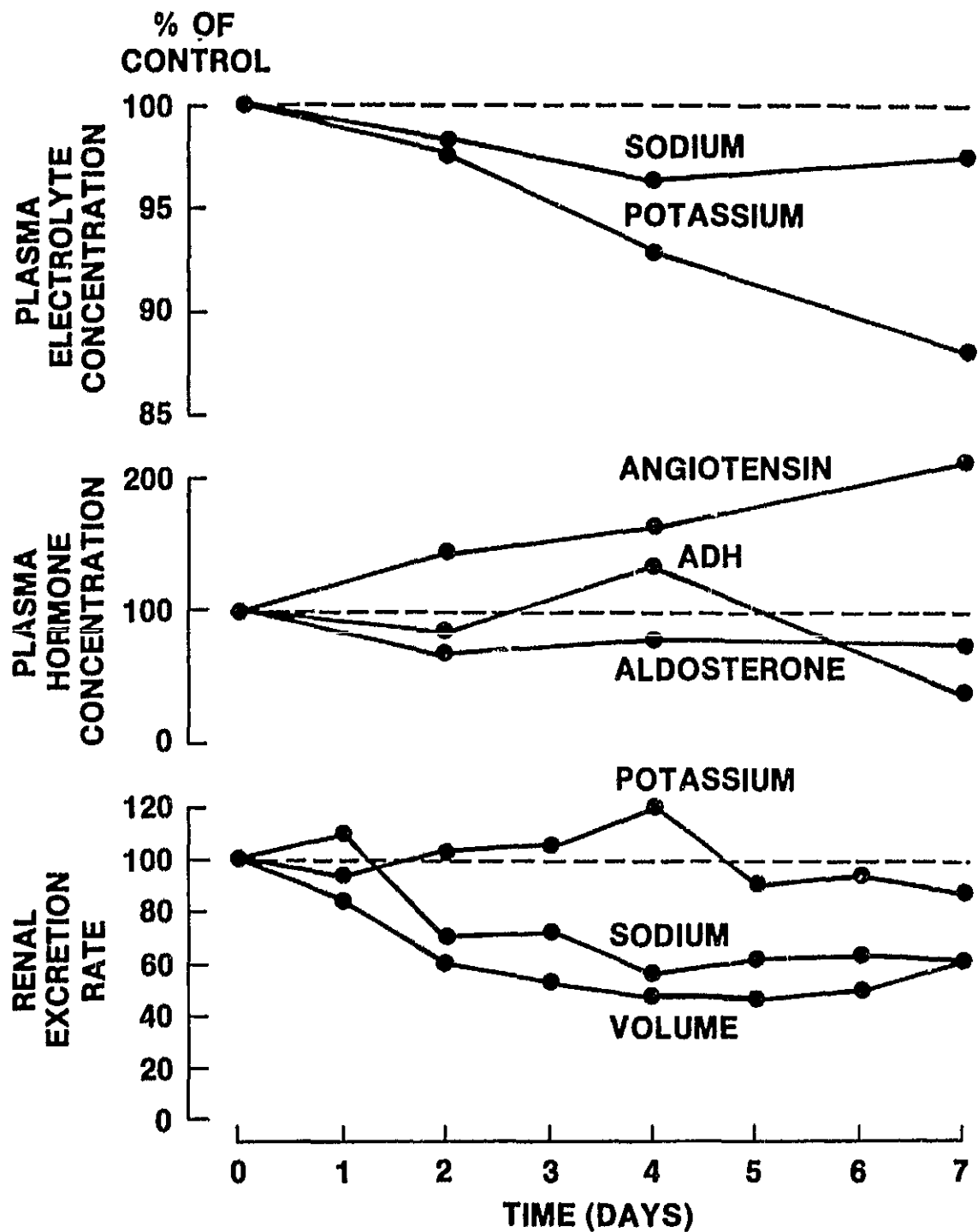
**FLUID SHIFTS AND HEMODYNAMICS  
DURING HEAD DOWN BED REST  
— SIMULATION RESPONSE —**

FIGURE 10

measured during the joint US/USSR study, are illustrated in Figure 11. The three groups of data shown are physiologically related by some well-defined pathways. For example, it is known that the plasma electrolyte concentrations can be important determinants of the secretion rates of endocrines such as ADH, aldosterone, and angiotensin. In turn, this particular group of hormones exerts a powerful influence on the renal excretion of fluids and electrolytes. Thus, by feedback regulation, ADH is influenced by, and provides renal control of plasma sodium concentration; the same is true regarding the control of plasma potassium levels by aldosterone (Guyton et al., 1975).

The data shown in Figure 11 indicates several changes which, at first glance, appear paradoxical. For example, there is a decrease in aldosterone which is associated with a diminished plasma sodium concentration and with a significantly elevated angiotensin level. In addition, urine flow is diminished in spite of a reduced level of ADH. There is also a reduction in sodium excretion which is associated with a decrease in aldosterone. In each case the normal relationships between hormone, electrolyte, and renal excretion appear to be violated, in the light of current theory. Nevertheless, these effects, observed in the human (Figure 11 and shown again in Figure 12), have all been reproduced in the simulation of head-down bed rest (Figure 12).

When a model is able to predict an unexpected event, it is desirable to determine the factors in the model that produced the outcome. Examination of the relationships embedded in the model reveals the factors that influence each of the hormones of interest. Figure 13 illustrates, in rather simplified fashion, that the secretion of renal-regulating hormones are influenced by only three factors: blood pressure, plasma electrolytes, and other hormones. By assessing these pathways in conjunction with the experimental data (quantities measured at the end of seven days are indicated by check marks in Figure 13), it is possible to discern which is the most likely event underlying the observed change in hormone level. Thus, of the two factors which can reduce ADH, it appears that the most plausible candidate during head-down bed rest is the measured decline in plasma sodium. An increase in venous, atrial pressure or end-diastolic volume was not observed in head-down tilt except for the first hour or so (Blomqvist et al., 1980). Similarly, the disturbances in plasma sodium can also, at least partially, explain the



**ELECTROLYTES, HORMONES AND RENAL EXCRETION  
DURING HEAD-DOWN BED REST  
— EXPERIMENTAL DATA (LEACH, 1979) —**

FIGURE 11



FIGURE 12

ELECTROLYTES, HORMONES AND RENAL EXCRETION DURING HEAD-DOWN BED REST

— JOINT US/USSR EXPERIMENT (1979) —

— COMPUTER SIMULATION —

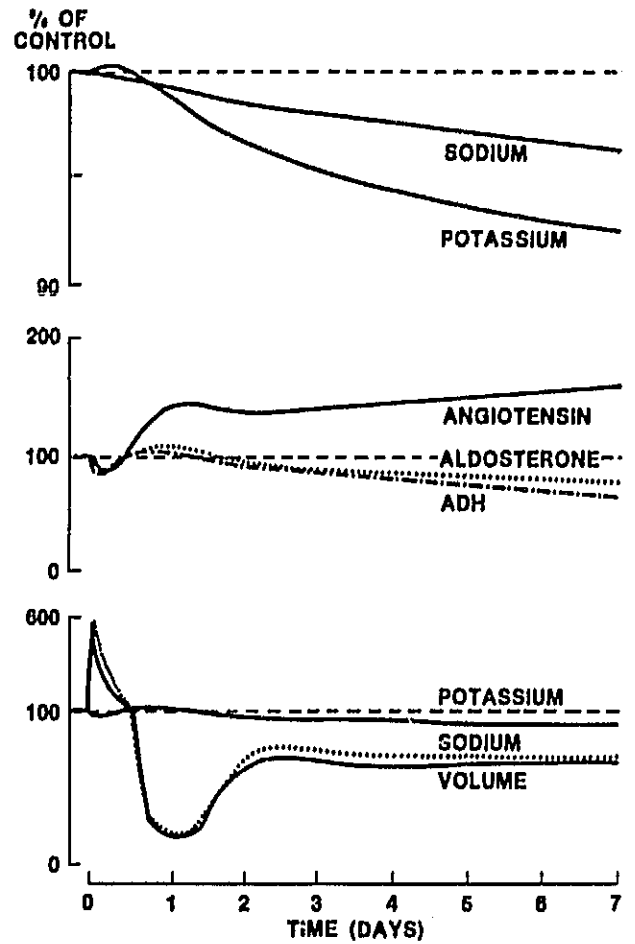
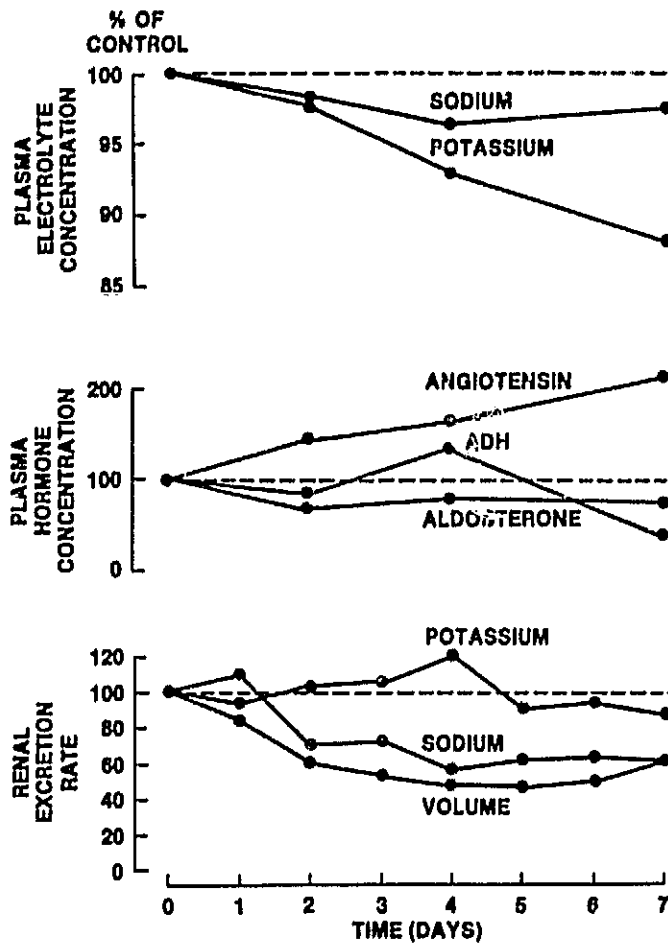
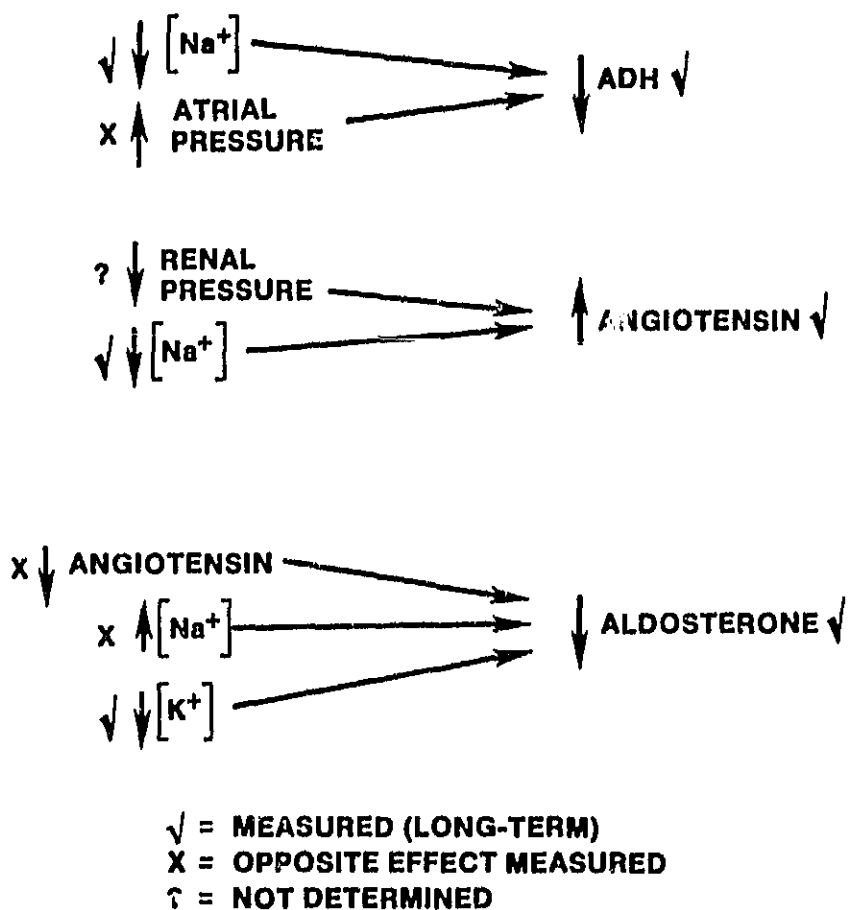


FIGURE 13

# DETERMINANTS OF PLASMA HORMONE LEVELS OBSERVED DURING 7-DAY HEAD-DOWN BED REST



increases of angiotensin observed in the seven-day head-down tilt studies. Renal pressure was not measured; thus, its role is not yet firmly established. Not shown in Figure 13 is the model prediction that a decrease in plasma volume has a more than proportional effect on increasing the plasma concentration of angiotensin. Finally, plasma potassium was the only one of three aldosterone-controlling factors in the model to change in the appropriate direction; this perhaps explains the decline in aldosterone. The influence of diminished plasma potassium on aldosterone must have been powerful enough to counter the opposing influences of plasma levels of sodium and angiotensin. Thus, this analysis is able to demonstrate how changes in plasma electrolytes can account, both qualitatively and quantitatively, for the changes in renal-regulating hormones which were observed during one week of head-down bed rest. These interpretations, based on analysis of the model and its behavior, do not prove that the same mechanisms are operative in the human as they are in the model. However, this does provide a rational basis for proposing new hypotheses and for designing new experimental studies.

### Renal Excretion

The fluid and sodium renal output responses of the model, as shown in Figure 12, can be conveniently separated into two distinct phases, an acute response and a longer-term response. (Potassium excretion will be discussed in a separate section.) The acute phase, lasting about 2 days, is characterized by a highly dynamic behavior consisting of a distinct diuresis and natriuresis, a subsequent reduction in excretion and a rebound towards normal. The longer-term phase indicates that a nearly steady-state plateau is reached after the second day of bed rest at a reduced level. Whether the highly variable acute response predicted by the model occurs in the human subject is unknown. Urine voids were pooled during the 24-hour periods of bed rest and such pooling tends to obscure the instantaneous changes suggested by the model. However, it is possible to integrate the model's renal response and obtain an effective 24-hour value for comparison with the data. Such results indicate that the model predicts a net increase in both urine volume and sodium on the first day. In comparison, the data reveal for the same time period that although sodium excretion increases, fluid excretion decreases; thus, the model's behavior is in only partial qualitative agreement with the

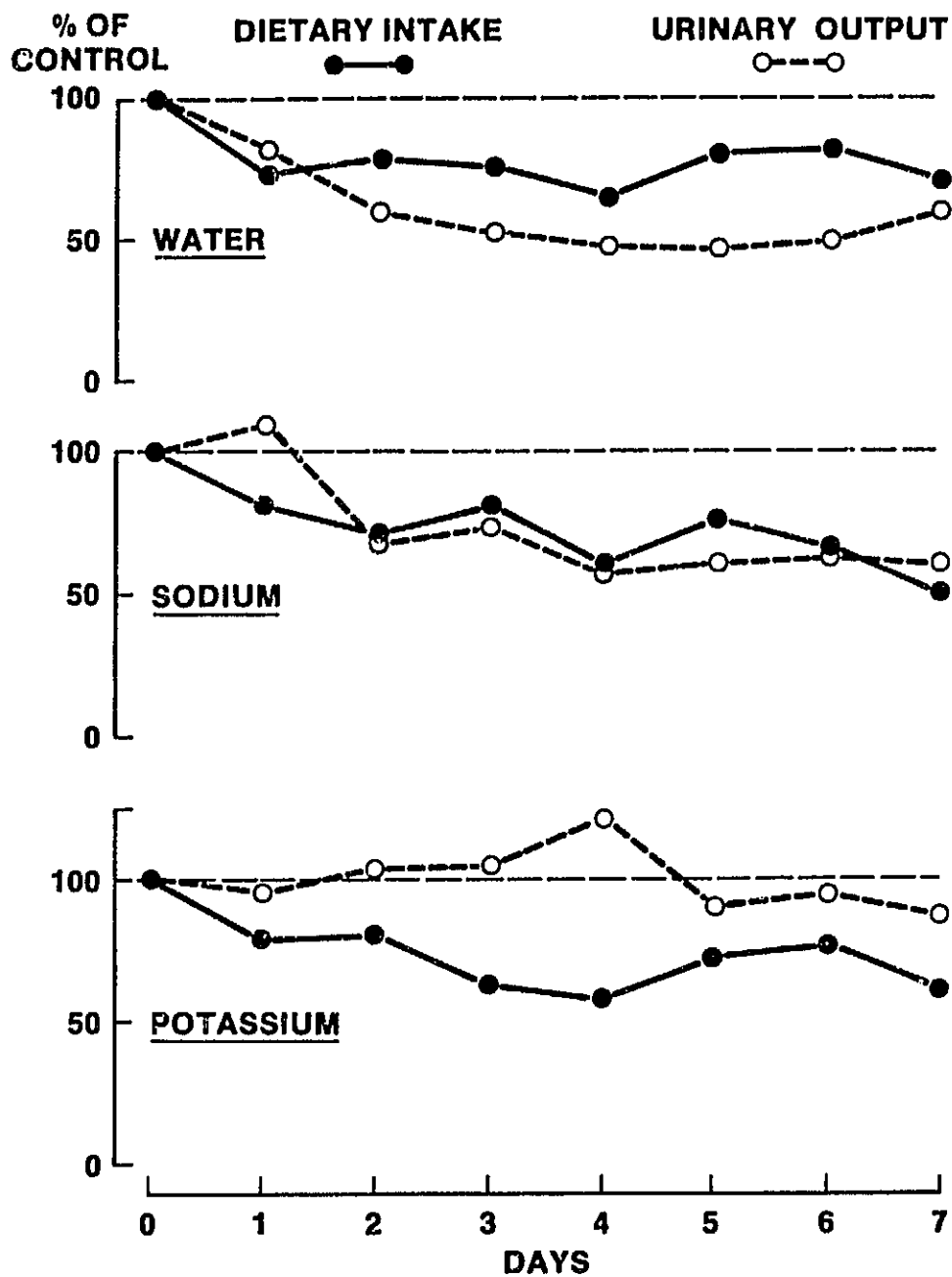
data. Agreement between model and data improves considerably after the third day. By these criteria, the model's prediction of the acute response does not appear as valid as its prediction of the longer-term response.

It appears that over the long-term, renal excretion cannot be explained on the basis of hormonal mechanisms. Decreases in both ADH and aldosterone would normally be expected to enhance the excretion of water and sodium, and not the reverse as shown in Figure 12. Apparently, these renal-regulating hormones are not always able to exert their "normal" influence at renal sites, especially in chronic situations when dietary factors have been altered. The dietary factors in this case refer to the intake of fluid, sodium, and potassium consumed by the human subjects which were diminished by 24, 29, and 30 percent, respectively, during bed rest. It was necessary to impose these dietary disturbances on the model in order to correctly simulate the experimental plasma electrolyte, hormone levels, and renal excretion data. Not surprisingly, renal excretion diminishes with diminished intake. This relationship is shown more clearly in Figure 14 where the changes in diet and urine, measured during the seven-day head-down study, both exhibit similar downward trends for water and sodium. Renal regulation of these substances in the mathematical model results in similar behavior (Figure 12). That is, at steady-state renal excretion exactly balances dietary intake (the model does not normally account for other metabolic losses such as fecal or sweat). Non-hormonal mechanisms, including changes in plasma electrolyte levels and renal hemodynamics, are apparently responsible for determining this balance in both the human subjects and the model.

#### Effect of Diet<sup>\*</sup>

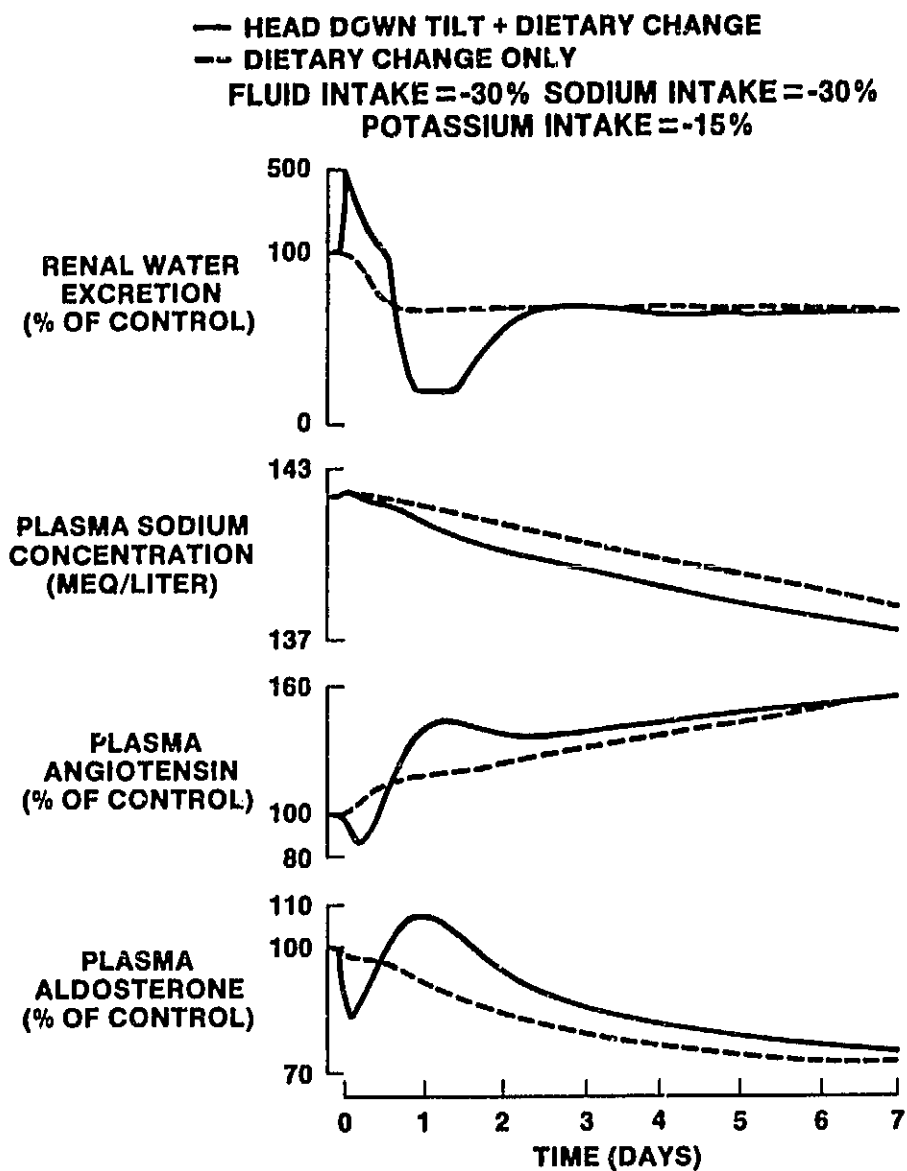
The model results have therefore suggested the importance of dietary intake in causing the observed changes in renal-endocrine behavior and fluid-electrolyte metabolism during the bed rest study. Figure 15 demonstrates this effect more clearly. Two types of simulations are illustrated. One of these

\* In order to validate the ability of the model to respond to simple dietary restriction stimuli, two classical cases were simulated: water restriction and sodium restriction. The results, shown in Appendix C, indicate an appropriate model response.



**FLUID AND ELECTROLYTES IN DIET AND URINE  
DURING HEAD DOWN BED REST STUDY**

FIGURE 14



EFFECT OF DIETARY CHANGE  
ON HEAD-DOWN BED REST

FIGURE 15

(solid line) is the response to head-down tilt plus the additional effect of dietary reductions of water, sodium, and potassium. (These results are identical to those that have been previously shown in Figure 12.) The second simulation (dashed line) was performed by simulating only the effect of identical dietary changes without head-down tilt. Only a few physiological quantities are shown here for convenience, but they are representative of the effects on plasma electrolyte concentration, plasma hormone levels, and renal excretion. As can be observed, the effect of diet alone can account for the changes seen at the end of seven days of head-down tilt with diet restriction. On the other hand, the acute effects (Days 1 and 2) predicted by the model are peculiar to head-down tilt and are not apparently affected by alterations in diet. Some of the other quantities which were examined, such as hemodynamic indices or circulatory blood volumes, were not significantly affected by diet. It appears that the major effects of diet, as predicted by the model, occur primarily via alterations in plasma electrolyte concentrations with secondary changes occurring in hormone secretion and renal excretion. (In addition, disturbances of plasma electrolyte concentrations would be expected to have osmotic consequences on intracellular hydration. This will be discussed subsequently.) It is common to find significant reductions in diet allotment during bed rest studies, so that this conclusion, if true, may be applicable to a wide range of investigations.

#### Potassium Metabolism

The striking feature of the renal excretion data shown in Figure 14 (which was reproduced by the simulation of Figure 12) is that renal potassium losses are relatively unaltered in comparison to water and sodium excretion. This occurs in spite of the fact that the dietary intake of all three substances was reduced in the human subjects by approximately the same amount (i.e., 25 to 30 percent). During the last three days of the study, potassium excretion is somewhat less than normal but is still less than one-half of the decrement in water or sodium excretion.

What can be responsible for this difference in behavior of potassium and sodium excretion? One likely possibility is that intracellular stores of potassium have been mobilized and contribute to extracellular potassium which

partially compensates the dietary depletion of this electrolyte. If this is true, the sum total of potassium in the extracellular fluid which is available for renal excretion would be greater than occurs with dietary reduction alone. An obvious mechanism that would permit intracellular potassium to become available in this situation is the phenomenon of muscle atrophy due to disuse immobilization, and hypogravity. Although muscle atrophy leads to losses of many intracellular electrolytes and nitrogenous compounds, potassium is the predominant intracellular cation of the body.

Figure 16 is a diagrammatic view of potassium metabolism, accounting for each major extracellular pathway in both the human and the mathematical model. In this representation, the major difference between the model and real system is that the model does not account for fecal and sweat pathways. It is assumed that a steady-state condition exists so that the sum of all inputs to the extracellular fluid are equal to all outputs. Values for input and output potassium fluxes in Figure 16 were derived from the seven-day bed-rest study. For convenience, the daily dietary intake has been normalized to 100 meq potassium. Four pathways into and out of the extracellular fluid are considered for the human subjects: diet, cellular potassium, renal, and fecal-sweat. Under normal control conditions (Figure 16A) potassium in the fecal-sweat pathway can be estimated from the algebraic difference,  $K_{\text{diet}} - K_{\text{renal}}$ , so that strict balance is maintained. If it is assumed that the fecal-sweat pathway does not change in magnitude during bed rest (Figure 16B), then the changes in magnitude of the  $K_{\text{cell}}$  pathway can be estimated by solving the following equation for  $K_{\text{cell}}$  at steady-state:

$$K \text{ Balance} = 0 = K_{\text{diet}} + K_{\text{cell}} - K_{\text{renal}} - K_{\text{fecal-sweat}}$$

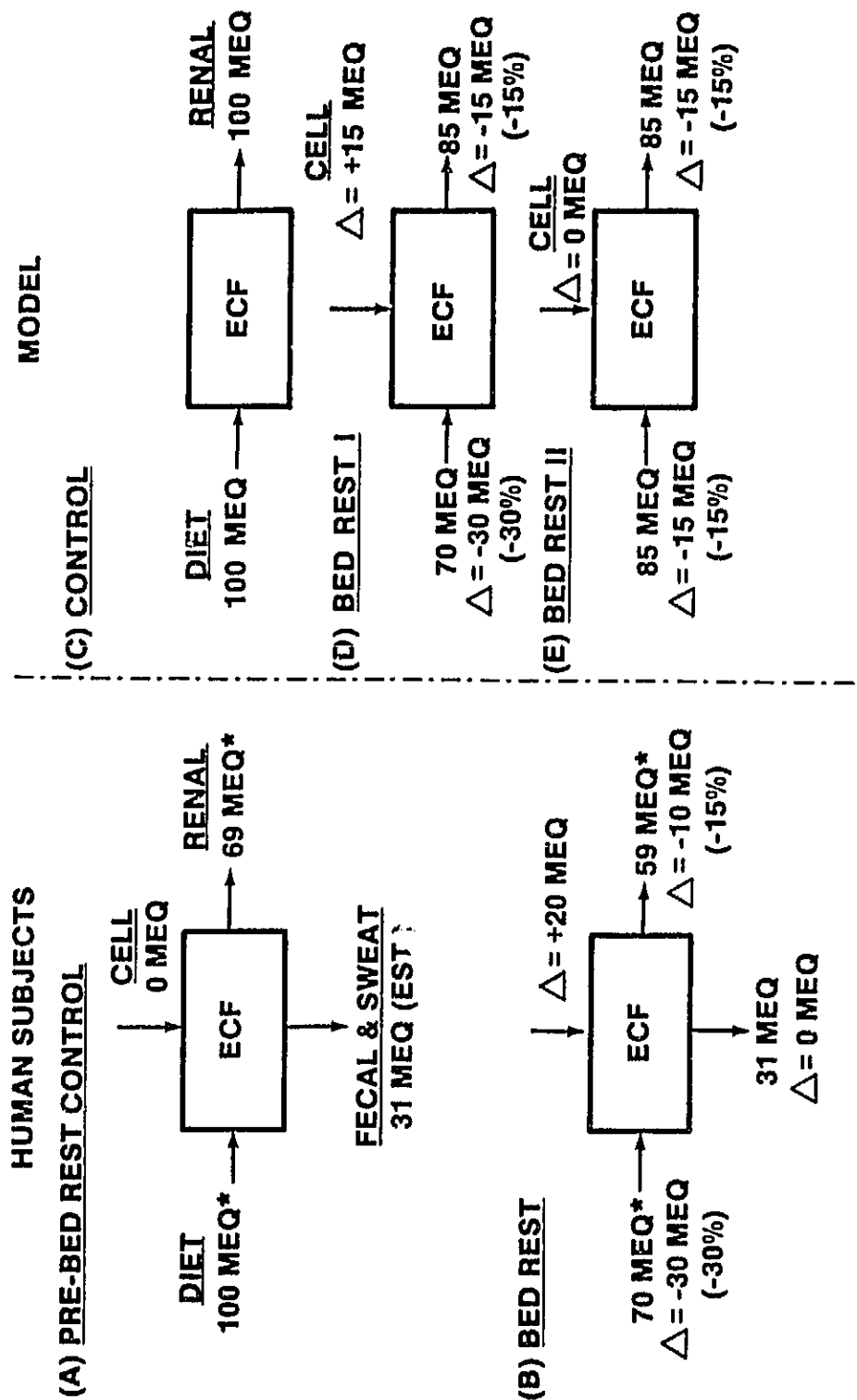
Thus, it is estimated that the intracellular potassium compartment contributes 20 meq/day. The values used for diet and renal excretion in Figure 16B were obtained from average experimental values for the last several days of bed rest.

There is no fecal-sweat route contained in the model; so, for the steady-state control condition (Figure 16C), the diet and renal values are equivalent. In order to simulate bed rest, two alternative cases are



FIGURE 16

# EXTRACELLULAR POTASSIUM METABOLIC PATHWAYS AT STEADY-STATE DURING HEAD-DOWN BED REST



\* MEASURED  
 ALL VALUES ARE EXPRESSED AS DAILY AMOUNTS.  
 $\Delta$  = CHANGES FROM CONTROL

considered, noted as Bed Rest I and Bed Rest II. In Bed Rest I (Figure 16D), the percentage decreases of diet and renal output found in the human subjects during bed rest (i.e., -30 and -15 percent) are used in the above equation to find a value for  $K_{\text{cell}}$  (assuming  $K_{\text{fecal-sweat}} = 0$ ). The decrement in net potassium input found in this case; i.e.,  $K_{\text{diet}} + K_{\text{cell}} = -15 \text{ meq}$ , can be expressed as an equivalent "effective" dietary intake of -15 meq as shown in Bed Rest II (Figure 16E) whereby the value for  $K_{\text{cell}}$  is zero.

The two cases, Bed Rest I and II, are equivalent in the sense that they will both result in similar changes in body potassium turnover, plasma potassium concentration, and renal potassium excretion. While the Bed Rest I configuration was more realistic because it accounts for cellular losses of potassium, the Bed Rest II case was more convenient to use. For convenience, the simulations of the seven-day bed-rest study which have been described above (i.e., Figures 10, 12, and 15) were performed using the "effective" dietary change in potassium of -15 percent (i.e., Bed Rest II) rather than the true change measured in the human subjects of -30 percent. As can be observed from Figure 12, using an "effective" dietary change for potassium resulted in realistic trends in potassium excretion. Using the true change in potassium intake, without accounting for cell potassium loss, led to reductions in potassium excretion that were unacceptably low.

An additional study was performed based on the more realistic concept of Bed Rest I. The results of that study demonstrated that for all practical purposes, all of the computer responses shown previously (i.e., fluid shifts, circulatory indices, plasma electrolytes, hormonal levels, and renal excretion) were not altered when the "effective" dietary input was divided between the diet and cell pathways as suggested in Figure 16. However, accounting for cellular loss of potassium did result in a number of transient changes and two long-term changes that are of general interest and will be discussed next.

First, the effects of a simple intracellular potassium loss on other systems of the body were studied independent of any other effects of bed rest or zero-g adaptation. This was accomplished by permitting 70 meq potassium to be released from the cellular compartment of the model in the manner shown in

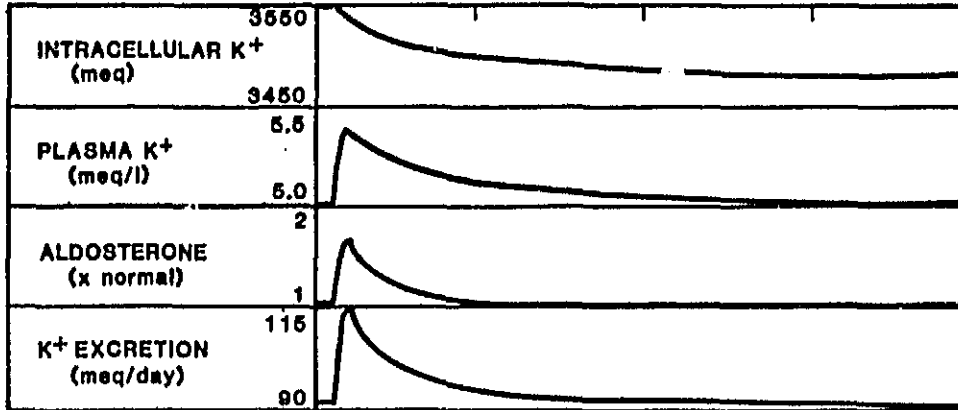
Figure 17. The illustration in Figure 16D can be used to trace the path of intracellular potassium as it leaves the cell, enters the extracellular space and the circulation, and ultimately is excreted by the kidneys. The release of cell potassium into the extracellular fluid has the immediate effect of elevating plasma potassium concentration and secondarily stimulating secretion of aldosterone. Intracellular water osmotically follows potassium from the cell and temporarily increases extracellular fluid volume before renal correction occurs. Because aldosterone has a dual renal effect of eliminating potassium and conserving sodium, plasma potassium returns to normal levels while plasma sodium increases slightly. An increase of plasma sodium in turn has a suppressant effect on angiotensin. The net long-term effect of this sequela is a permanent loss of body potassium, and a reduction of intracellular water. All the other responses shown in Figure 17, which permit potassium to leave the cell without creating dangerous levels in plasma, are short-lived. Therefore, by accounting for cellular loss of potassium it is possible to predict both decrements in total body potassium and intracellular fluid. Body potassium was not measured during the head-down tilt study, but it was possible to calculate from the available data a loss of about 400 ml fluid volume from the intracellular compartment.

The effects of cellular potassium loss on body fluid volumes during a simulation of head-down tilt are shown in Figure 18. Two different simulations are illustrated, one with and one without a potassium leak from the cellular compartment (i.e., Figure 16, Bed Rest I and Bed Rest II). For the case that assumes no unusual loss of cell potassium (i.e., the case, Bed Rest II, that is represented in Figures 10, 12, and 15), intracellular fluid volume exhibits a mild but steady increase throughout the bed-rest simulation. The underlying cause of this event is a simple osmotic transfer of fluid from the extracellular compartment which has become hyponatremic (see Figure 11) and, therefore, hypo-osmotic. The increase in intracellular fluid is also reflected by the upward slope of the long-term total body water response. (The acute changes in total body water during the first two days arise for reasons not related to potassium metabolism and will be discussed in the next section). The case of potassium loss (Bed Rest I) was simulated by permitting 100 meq potassium to be removed from the cell compartment over the seven-day period in the exponential manner shown in Figure 18. As a result of this

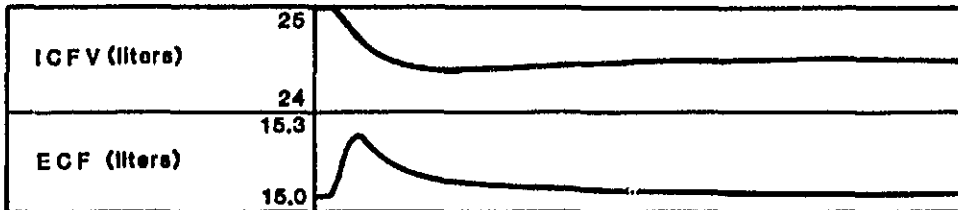
FIGURE 17

# SIMULATION RESPONSE TO RELEASE OF CELL POTASSIUM

## POTASSIUM



## FLUID VOLUMES



## SODIUM

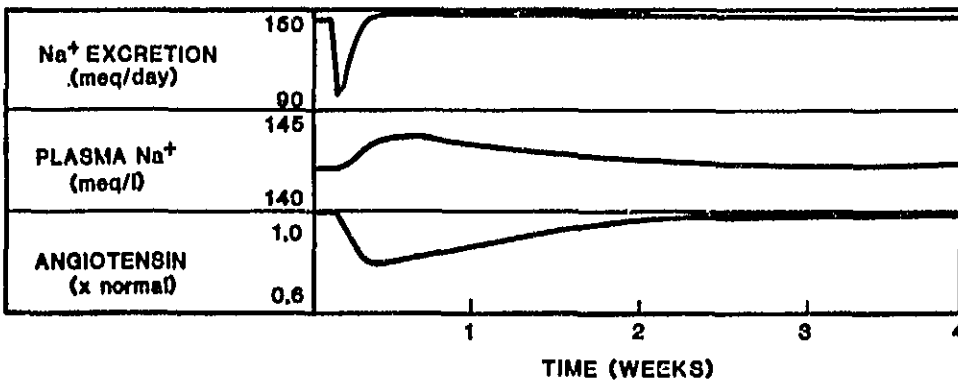
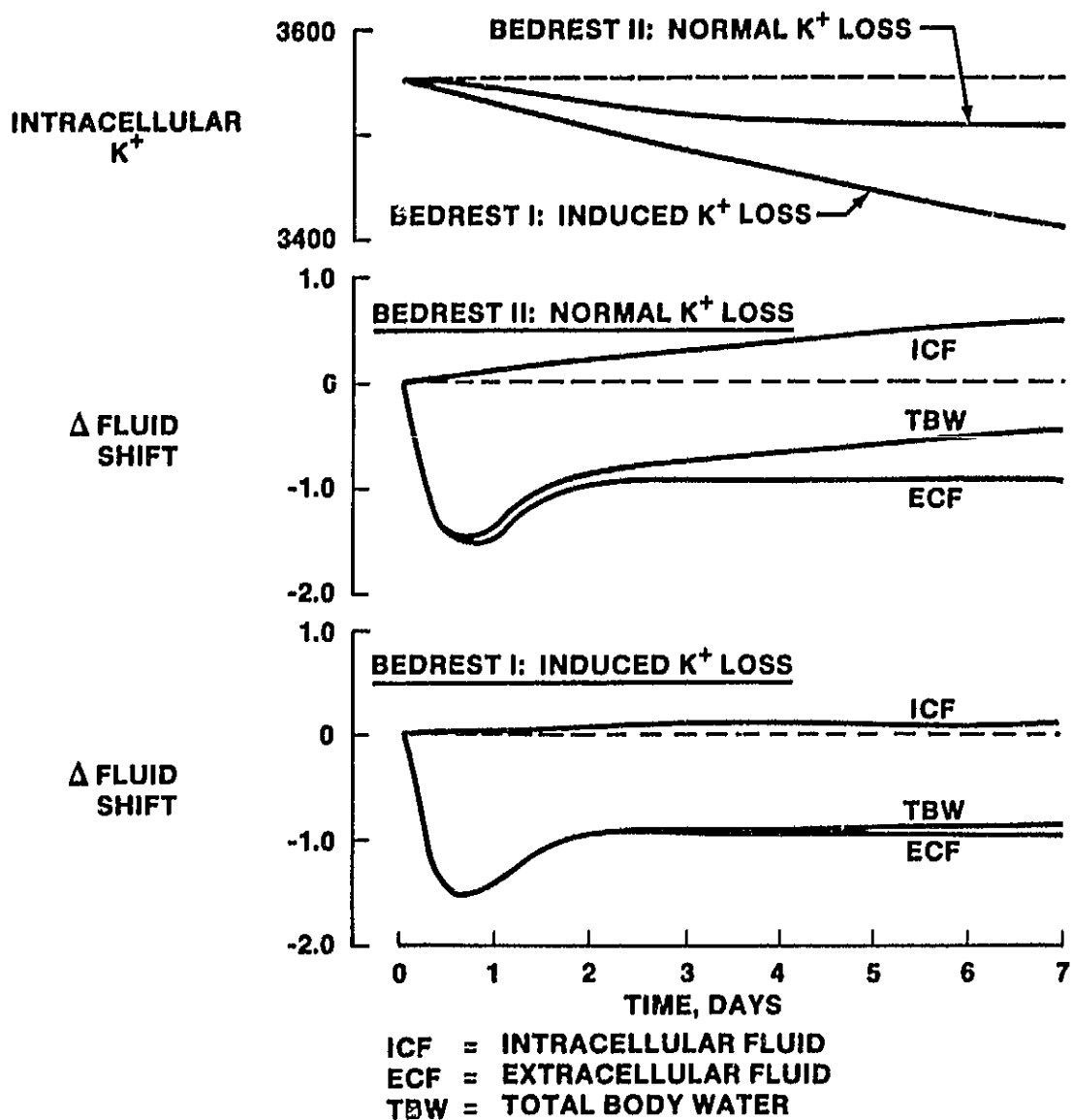


FIGURE 18

## EFFECT OF POTASSIUM LOSS ON FLUID COMPARTMENTS DURING SIMULATED HEAD-DOWN TILT



maneuver, fluid osmotically follows potassium from the cells. However, cell water does not deplete below normal because the water loss due to potassium extrusion is compensated by water entering the cell under the influence of the extracellular hypo-osmotic forces. The particular mathematical function which is used to transfer potassium from intracellular to extracellular compartments was adjusted so that the extracellular concentrations of sodium and potassium were similar to that for the case where intracellular potassium is not lost. These concentrations have been previously described (Figure 12).

It should be obvious that the final change in cell water (and also a portion of the change in total body water) is determined by the osmotic gradient across the cell membrane. This gradient, in turn, is a function of the rate at which potassium is extruded from the intracellular compartment and the rate at which the kidneys remove sodium from the extracellular compartment. Subtle changes in these relative rates of electrolyte loss can cause cellular water to increase, remain the same, or decrease. As we stated before, a decrease in cell water was measured during the head-down tilt study, but no information is available regarding potassium loss. Therefore, additional data is required before further optimization of these computer responses is warranted.

In summary, then, the release of cellular potassium into the extracellular fluid pool is not only a reasonable method to account for muscle atrophy but also results in a more accurate simulation. It permits the dietary intake to be reduced to a more realistic level without significantly changing the plasma potassium levels or potassium excretion rates which were already realistic in the original simulations. More importantly, intracellular fluid volume becomes more stable in its dynamic behavior because the cell water which was removed with cell potassium acted to nullify the increase in cell water that occurs by osmotic exchange when plasma osmolarity is reduced.

#### Plasma Colloids and Interstitial/Plasma Exchange

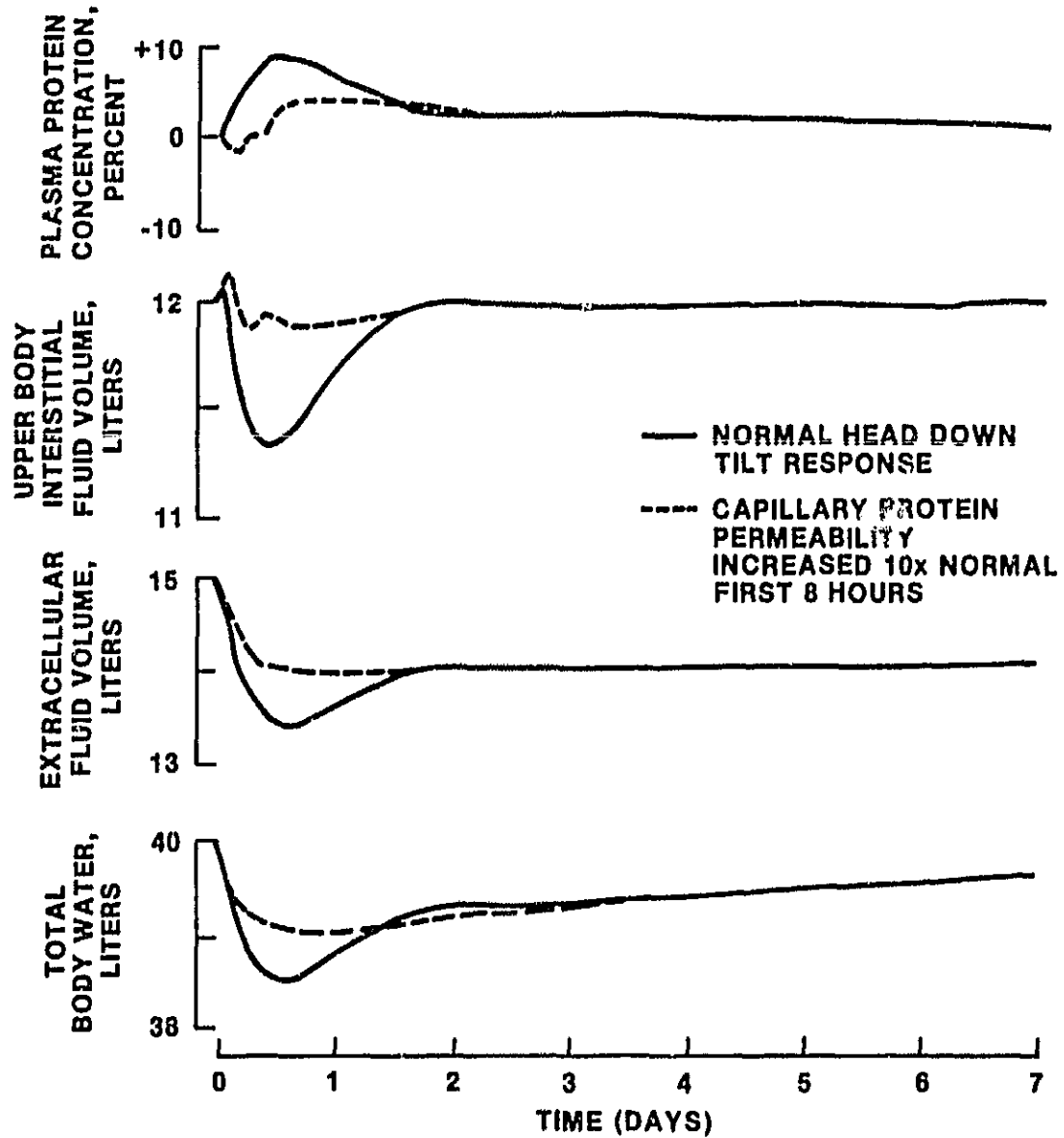
Earlier, it was shown that the simulated prediction of total body water (TBW) included a highly dynamic acute response (Figure 18). This facet

of the simulation was examined in more detail. As indicated in Figure 19 by the solid lines, a normal head-down tilt maneuver (with restricted diet but no cell potassium loss) results in a dramatic loss of 1.5 liters TBW followed by a rebound which has a rapid and slow component. The slower rebound component was accounted for by intracellular fluid and potassium shifts, as explained in the last section. However, the acute changes in total body water taking place during the first 36 hours appear to have extracellular origins, as shown by the solid tracings of interstitial fluid and extracellular fluid volumes. The initial loss of 1.5 liters TBW can be derived from a loss of plasma volume (-0.55 liters shown in Figure 10), a loss of upper body interstitial fluid (-0.65 liters), and a loss of lower body interstitial fluid (-0.3 liters, not shown). Of these losses, the only one which is unexpected is the loss in upper body interstitial fluid. Conventional wisdom suggests that headward fluid shifts should promote transcapillary filtration and thereby an increase in interstitial fluid. However, computer analysis of this event reveals that as plasma volume diminishes, plasma protein concentration becomes elevated which favors transcapillary fluid absorption from the interstitium. This is only partially offset by the tendency of the heightened blood pressure to filter fluids in the opposite direction. Following the initial fluid loss (at about 12 hours), interstitial fluid in the upper body is predicted to return to normalcy due to several factors: a reduction in lymph flow, normalization of plasma colloids, and readjustments of the pre/post capillary resistances to favor filtration. The steady-state plateau of the extracellular fluid volume after the second day is a reflection of a decrease in plasma volume and the return to normalcy of interstitial fluid.

Many of these predicted changes discussed in the above paragraph are unexpected and should be accepted only cautiously. However, there is little evidence at this time to disprove their veracity. In favor of the body water rebound effect are the decrements in body water of 1.3 liters at the end of 24-hours (measured by body weight changes in the Blomqvist experiment) and only a 0.6 liter loss at the end of seven days (measured by isotope dilution in the joint US/USSR study). Nevertheless, until the dynamic behavior can be verified in a single experiment, it is reasonable to question this phenomenon as well as the transient decrease in interstitial fluid. These events were subjected to further scrutiny as described below.

FIGURE 19

**EFFECT OF ACUTE INCREASE IN CAPILLARY PROTEIN PERMEABILITY ON HEAD DOWN BED REST RESPONSE**





It has been suggested above that the transient dip in interstitial fluid and total body water results entirely from concentration of plasma colloids in the circulation. There is no data available that indicate whether or not colloidal concentration takes place during the acute phase of bed rest. However, it has been shown that several hours of water immersion results in dilution of plasma colloids (Greenleaf et al., 1981). Therefore, an hypothesis was formulated that suggested plasma colloids would not concentrate, and interstitial fluid would not deplete, if transcapillary protein permeability were increased. An increase in permeability, allowing proteins to leak into the interstitium at a faster than normal rate, is plausible in the face of high distension pressures which accompany acute headward fluid shifts. Such changes have been demonstrated during massive fluid infusion in dogs (Manning and Guyton, 1980). This hypothesis was evaluated using computer simulation by permitting the capillary protein permeability to double from its resting value during the first eight hours of head-down tilt. The results are shown by the dashed lines in Figure 19. The most obvious consequence that this hypothesis has on fluid volume shifts is to eliminate the large changes in interstitial fluid, thereby reducing the magnitude of depletion of total body water. Although the permeability was only altered for a small fraction of the total simulation time (i.e., eight hours compared to seven days), the entire characteristic of the fluid volume responses was altered in a manner that appears quite plausible. Unfortunately, data do not exist to validate the "increased permeability" hypothesis during bed rest, but it should be noted that a similar hypothesis produced more realistic results during simulations of water immersion (Leonard, 1982).

#### 4.0 CONCLUSIONS

##### Modeling Strategy

Researchers use mathematical models for many different purposes and with different strategies in mind. It would be useful to discuss how modeling contributed uniquely toward resolving scientific issues in the present study. The power of the Guyton model lies not in the accuracy or fidelity of its mathematical descriptions; each element in the model is represented in only a gross manner. Neither is it true that the model will invariably and

faithfully simulate a series of experimentally determined measurements; quantitative accuracy is usually achieved only in a general and relative sense. Rather, the value of this model lies in its ability to simultaneously account for a large number of interactive and competitive pathways that connect a multiplicity of related systems. Feedback regulation of any of the body's important functions is usually achieved by a redundancy of mechanisms. If one fails, or is otherwise limited in its ability to effect proper control, another will exert its dominancy. The model, by mimicking this type of redundant control, has the capability to simulate a virtual panorama of responses to complex or unusual stimuli (such as head-down tilt with dietary disturbance and muscle atrophy) and still provide the stability and uniformity of control that exists in the real system. Thus, control of blood pressure or renal excretion following head-down tilt, is accomplished in the model by a combination of autonomic, hormonal, and hemodynamic mechanisms, each responding to an effective volume overload with a characteristic intensity and time constant. It is not only possible to study the net result of this process, that is, the magnitude and time course of some crucial quantity such as blood volume, but one can also assess the relative contribution of individual mechanisms which eventually are integrated and lead to the final results. Such an evaluation, of course, provides not only an interpretation of previously collected data, but also establishes a theoretical foundation for designing future verifying experiments.

In addition to its ability to realistically assimilate a large number of logical and connected relationships, the model proved valuable by its capability to test scientific hypotheses and thus help explain certain observations. Models may be used to test hypotheses in a variety of ways, including a simple adjustment of the value of a fixed parameter (i.e., adjusting the gain or set point of a control loop), clamping the value of a variable (i.e., opening a feedback loop), or, in some cases, introducing an entirely new control mechanism into the model. One of the more usual ways of testing hypotheses using models is related to the determination of certain model parameters by optimizing the model output relative to experimental data. Such parameter estimation techniques are extremely useful in certain situations, but these "curve-fitting" approaches were not normally appropriate, by themselves, for the analyses discussed in this report. The state of knowledge

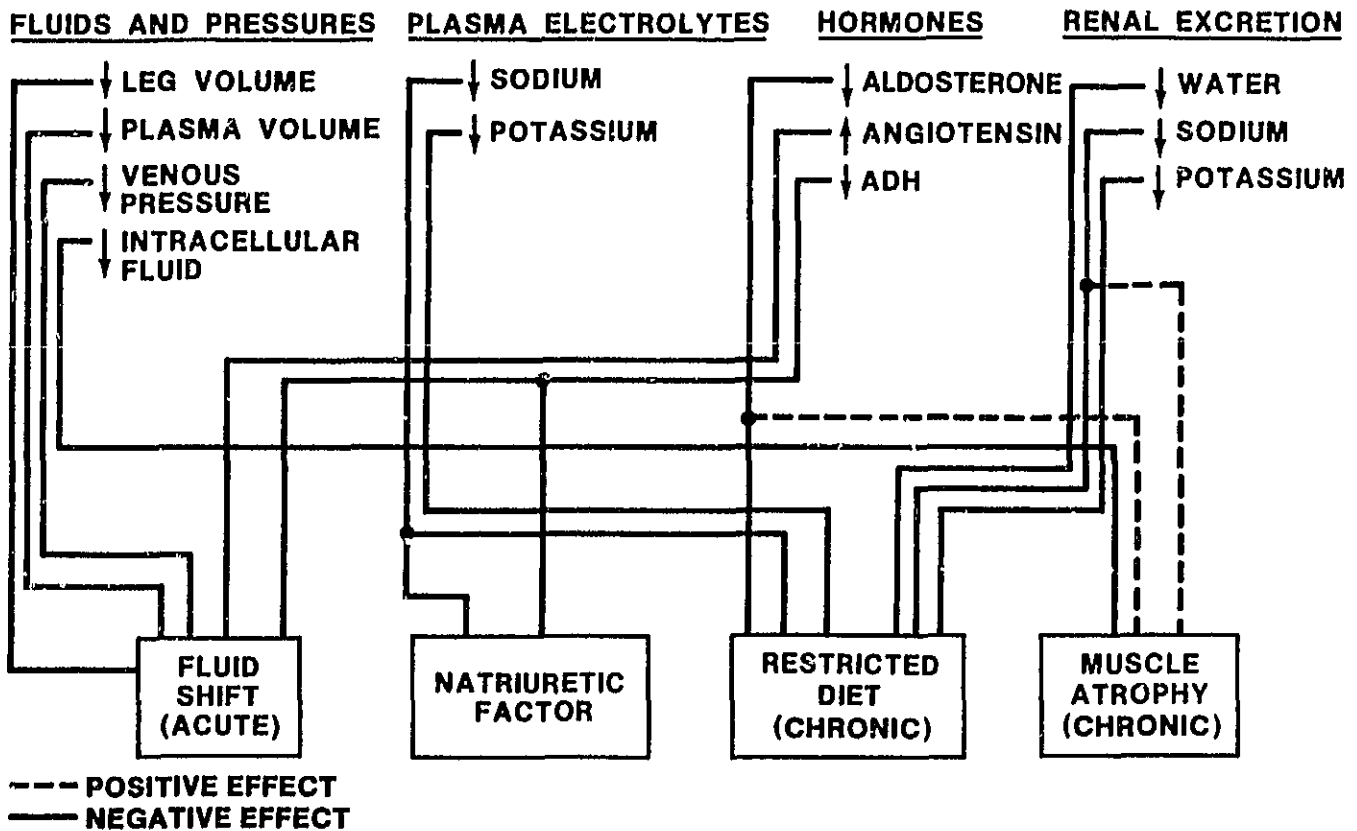
of space-flight physiology is such that it is often more useful to assess which pathways are involved in a particular system response than it is to determine the value of some fixed parameter related to producing that response. Thus, the hypothesis testing approach usually involved qualitatively evaluating a collection of model output responses for their plausibility (emphasizing the direction of response and the general dynamic behavior), rather than quantitatively "fitting" a single response to specific data. Figure 20 illustrates the model hypotheses that were invoked in the present study (bottom of figure) in order to reproduce the set of observations (top of figure) obtained during the 7-day head-down bed-rest study.

A useful result of this study is the demonstration that various types of maneuvers, which have been used as experimental analogs of weightlessness, can all be simulated by a common mathematical model. The analogs which have been discussed in this report include head-up and head-down tilt for both short-term and long-term durations. Previous reports have also addressed simulations of water immersion as a zero-g analog (Leonard, 1982), and the stress of space flight itself (Leonard et al., 1977; and Leonard et al., 1979). In all cases the same quantitative model was used which embodies elaborate but essential relationships describing circulatory, fluid, and electrolyte regulation. Thus, a conclusion of this study is that adaptation to weightlessness is a normal response of the feedback control circuits of the body to gravitational disturbances. Furthermore, as we have suggested some time ago (Fitzjerrell et al., 1975), the simulation of weightlessness by postural changes or water immersion truly seems to affect the same physiological mechanisms that are activated during space flight. This implies that most of the relevant homeostatic pathways that participate in the hypogravic stress response are known, at least to the point where they can explain presently documented measurements.

Having said this, it is prudent to qualify the statements in the above paragraph in the following manner. First, because a model is only a partially accurate representation of the real system, any conclusion derived therefrom should be taken guardedly, and only as an unverified hypothesis. Second, the data with which model outputs are often compared are often limited in scope and were collected to measure physiological status on only a gross

FIGURE 20

## HYPOTHESIS FOR HEAD-DOWN BED REST OBSERVATIONS



level. Therefore, our knowledge of relevant mechanisms only extends to these self-imposed limits; it is undoubtedly true that as finer and more detailed measurements are made during space flight we will quickly find ourselves limited by our theoretical knowledge to explain all the observations. And thirdly, it must be acknowledged that the optimal simulation of each stress studied was not achieved without some additional functions included in the model. The fact that modifications were required should not necessarily be construed as evidence of model inadequacy but rather, their identification can also be considered a contribution to understanding the underlying basis of zero-g adaptation. Thus, realistic simulations of head-up tilt required additional assumptions reflecting leg muscle pumps, abdominal compression, and reduced venous capacitance. Head-down tilt simulations required modifications to the leg vasculature elements which prevented venous collapse in the face of negative body angles. Further modifications were necessary to appropriately simulate longer-term head-down tilt as shown in Figure 20; these included accounting for a natriuretic factor, a restricted dietary intake, and muscle atrophy in addition to the simple fluid shifts of acute studies. In all cases the modification was plausible and realistic, often being based on quantitative experimental evidence. Also, the change was entered into the model as a disturbance of some relationship or parameter which previously existed in the model. Thus, this consideration does not alter the conclusion stated above that only the behavior of known feedback systems are necessary to account for most of the findings accrued to date.

#### Dynamics of Head-Down Tilt

The study of short-term and long-term head-down tilt provided a useful picture of the dynamic nature of the zero-g adaptation processes. According to the model and experimental responses, during the first hour or so of head-down tilt, there are significant disturbances in the fluid-regulating systems which are exemplified by internal fluid shifts and elevated pressures and flows in the thoracic circulation. This is followed by a short period in which feedback mechanisms (both active and passive) act to correct these disturbances. Thus, with the exception of the fluid volume compartments which remain suppressed (particularly leg volume and blood volume), all other variables examined exhibit a transient biphasic behavior during the first 24

hours, with a return toward baseline. However, it has also become clear that the body appears to be seeking a new baseline, that is, the head-down position seems to alter the "normal" physiological state. This is demonstrated by the fact that the longer-term head-down tilt does not result in a state identical to the original pre-tilt state. In addition to the fluid volume disturbances noted above, there are offsets from normal for blood pressures, flow resistances, plasma electrolytes, hormones, renal excretion, and so on. Thus, it was shown that longer-term head-down tilt, up to 7 days, can result in one or more reversals in the direction of individual quantities and counter-intuitive patterns of overall response. These changes have become more understandable by accounting for the intricate relationships and dynamic characteristics of a model system. In particular, much of the data can be explained by a shift from short-term volume control to long-term metabolic control. Volume control refers, in general, to regulation of extracellular fluid volume by thirst and renal mechanisms, and, in particular, to the vascular control systems that respond to headward fluid shifts. And, metabolic control in this case is taken to mean those events which directly influence the metabolism of dietary substances and are affected by physical activity. In model simulations, the definition of metabolic control becomes even more specific and refers to the consequences of alterations in dietary intake, sweat rates, oxygen uptake, and intracellular loss of electrolytes resulting from muscle atrophy. A secondary effect includes the elevated hematocrit and resulting enhancement of oxygen supply. These phenomena are offered as explanations to account for some of the reported differences between acute and chronic zero-g analog studies as suggested in Figure 20.

It is useful to compare the various responses related to fluid-electrolyte regulation that occur during ground-based analogs such as water immersion and head-down tilt in relationship to those found during space flight. Some of these responses are presented in qualitative fashion in Table 5. Each stress provides a picture of hypogravity over a different slice of time. Thus, water immersion results are obtained normally over a 4 to 6 hour period, short-term head-down tilt for 24 hours, long-term head-down bed-rest for up to 7 days, and Skylab data represents a mean response during a 3-month interval. The lack of a common time frame of study, and inconsistent methodological procedures in each case makes true comparison difficult. Also,

TABLE 5

## COMPARISON BETWEEN SPACE FLIGHT AND GROUND-BASED ANALOGS

<u>QUANTITY</u>	<u>SKYLAB</u>	<u>HEAD-DOWN BED REST*</u>	<u>HEAD-DOWN TILT</u>	<u>WATER IMMERSION**</u>	<u>SUMMARY</u>
Dietary Intake					
Water	+	-	?	+	
Sodium	+	-	?	?	
Potassium	+	-	?	?	
Excretion					
Water	+	-	+	+	
Sodium	+	-	-	+	
Potassium	+	-	-	+	
Plasma Electrolytes					
Sodium					
Angiotensin	+	+	-	-	0
Aldosterone	+	-	-	-	0
ADH	-	-	-	-	0
Hemodynamics					
Arterial Pressure	0	+	-	+	
Venous Pressure	?	-	+then-	+	
Fluid Volumes					
Plasma	-	-	-	-	●
Body Water	-	-	-	-	●
Leg Volume	-	-	-	-	●
Hematocrit	+	+	+	+	●

\* Findings from 7th day

\*\* Findings from 1st 6 hours

Skylab findings based on composite after 5th day.

●,0 Agreement exists between the short-term stresses of head-down tilt and water immersion

● Agreement exists between all stresses, short-term and long-term

+ Increase

- Decrease

? Unknown

each stress differs from space flight in aspects other than the period of hypogravity. In water immersion, hydrostatic forces compress the tissue fluids from outside the body, and in head-down tilt there is little or no physical activity. Dietary intake, especially of fluids, electrolytes, and calories can also be considerably different in these different situations. As we noted several times in this report, it is possible to account for a number of physiological observations on the basis of dietary changes alone. But in all cases there is a severe reduction in hydrostatic forces and fluid pooling with a consequent tendency for fluid to shift headward. There is also a reduction in both gravitational deformation and a need for leg locomotion so that conditions are ripe for musculoskeletal atrophy.

It is of interest to note in Table 5 that there are only a small number of physiological quantities which change in the same direction for all types of hypogravic stress situations. These include decreases in fluid volumes such as plasma volume, body water, and leg volume. In addition, a decrease in ADH is a common finding (except on Skylab 2). Otherwise, different qualitative responses are observed for at least one of the four situations shown. The present simulation study suggests quite tentatively that the significant differences between stress responses that are shown in Table 5 can be ascribed in large part to the highly variable dynamic time course of adaptation to hypogravity which in turn reflects the interplay between acute and chronic controllers.

The comparison of water immersion and short-term head-down tilt is of particular interest because they both provide clues about the dramatic changes that are suspected to occur at the onset of weightlessness but have not yet been measured during space flight. Clearly, there is a striking similarity in both stresses with regard to the initial central fluid shift, the hyperkinetic response of cardiac and vascular components, the diuresis, and the reduced plasma volume. Also, the transient suppression of the major renal-regulating hormones - ADH, angiotensin and aldosterone - is a common finding in both maneuvers. The events during water immersion appear to occur somewhat more rapidly and may be more severe in comparison to head-down tilt. In the case of head-down tilt one finds that the circulatory, renal and hormonal parameters return towards control if the study is carried out beyond the 5 to



6 hours usually associated with immersion studies. The modeling analysis suggests that if immersion experiments are continued for longer times (up to and beyond 24 hours) they might yield a similar response as the head-down tilt results. As of now, it is not clear why venous pressure remains significantly elevated for the first several hours of immersion in comparison to its milder rise and subsequent decline during head-down tilt. Arterial pressure also behaves differently (see Table 5). Direct measurements during the acute phase of space flight would help determine the more appropriate experimental analog.

Although head-down tilt was of primary interest in this study (because of its implication to zero-g adaptation), the head-up stress was also described in some detail. The data base for head-up tilt (short-term) is much more complete than for its head-down counterpart and this can be used to advantage in validating models. In the head-up position, the model was shown to have some inherent limitations that prevented adequate circulatory flows and pressures in the upper body. However, various modifications to the model, representing orthostatic defense mechanisms of the upright human, provided a more realistic response to orthostasis for a number of variables. We believe that these efforts should be continued in order to achieve a model referenced in the upright rather than supine position. The physiological changes which occur as a result of weightlessness are of interest primarily with respect to humans who are upright much of the time; the chronically maintained supine position, according to conventional wisdom, is not much different from the weightlessness adapted state.

#### Testable Predictions of the Model Simulations

By our criteria, the ultimate value of a model lies in the degree to which understanding of the system under study is enhanced. However, any worthwhile scientific endeavor will tend not only to answer questions, but to raise new questions and to suggest new hypotheses. Thus, testable hypotheses should be a natural by-product of a modeling study and the present study is no exception. Some of the more important hypotheses which have been formulated and addressed in this study are discussed below.

1. Central venous pressure and cardiac output will behave in space flight similarly to that reported in head-down tilt, that is, an acute rise in each quantity is followed by a fall below control which is maintained for the remainder of the mission. This prediction is counter to that which has been anticipated on the basis of water immersion results (Gauer, 1975), in which venous pressure does not return to normal. However, according to detailed model analysis reported herein, a fall in central venous pressure and cardiac output can be expected if hemoconcentration, angiotensin, and other factors cause peripheral resistance to rise chronically as it has been observed to do in bed rest.

2. Related to the above, the model predicts that central blood volume returns to normal as a result of feedback regulation affecting renal excretion, transcapillary exchange and thirst. A contrary opinion is that central hypervolemia persists throughout a period of weightlessness, thus posing a continual pressure challenge and potential danger to the cardio-pulmonary system (Gauer et al., 1978).

3. A diuresis is predicted during the very early phases of hypogravic stress. Dehydration of space sickness may attenuate the diuresis response but it will not be abolished. Space-flight studies to date have failed to reveal a diuresis although a loss of body water has been demonstrated (Leach and Rambaut, 1977). The present studies indicate that the possibilities of observing the diuresis during space flight is enhanced by ensuring that the crews are well hydrated before launch and thereafter by collecting urine voids frequently. Although increased renal excretion during water immersion is thought to be caused by alterations in hormone levels (Epstein, 1978), the model predicts that the diuresis will occur primarily as a result of hemodynamic disturbances (i.e., a pressure diuresis).

4. A decrease in drinking has been observed in space flight, bed rest, and during computer simulation (Leonard, 1982). This is likely to be due in part to a reaction to central hypervolemia rather than entirely a symptom of space sickness or due to a heavy workload. Decreased fluid intake will augment the loss of body fluid as well as attenuate the diuresis discussed above. A model prediction is that body fluid volume will decrease

in space flight by about one liter by some combination of decreased intake and enhanced renal excretion. This means that if normal fluid intake is ensured, then renal excretion will increase until the required loss of body fluids has occurred.

5. The model predicts the suppression of the three primary renal-regulating hormones - ADH, aldosterone, and angiotensin - during the acute stress phase in accord with results from acute head-down tilt and water immersion studies. However, in longer-term studies, the direction of these hormones are not easy to predict because they depend on metabolic factors such as exercise, diet, muscle atrophy, and sweat rates. Nevertheless, the model clearly indicates the role that each hormone plays and does not play in the zero-g adaptation process. For example, ADH may play a more important role in regulating plasma osmolarity than in fluid volumes. Also, aldosterone appears to be primarily concerned with the chronic control of potassium and not with sodium excretion, except in the short-term. Rather, a still to be identified natriuretic factor appears to be required for the regulation of sodium. Finally, the elevation of angiotensin may not be due to pressure disturbances but rather to a reduced volume of distribution and diminished sodium concentration. Most of these concepts, although reasonable, have yet to be adopted or seriously addressed by other investigators in spite of the fact that these hormones continue to be used as an index of fluid-electrolyte status during space flight.

6. Renal excretion of potassium is a net result of dietary intake, fecal excretion, and atrophy of lean body tissue. Thus, by measuring the main components of metabolic balance, it is possible to derive the loss of lean body mass. Model simulations have demonstrated during a 7-day bed-rest study that the loss of potassium from intracellular sources plays a significant role in explaining renal excretion and in understanding intracellular hydration.

7. Transcapillary filtration into the interstitium is known to provide relief to central volume overload but the model has demonstrated this effect is only transitory. The model suggests that an increase in transcapillary permeability to protein may occur which increases the effectiveness of the interstitium as a temporary reservoir.

8. The model has predicted some aspects of dynamic system behavior that should be experimentally verified in the head-down tilt maneuver. These include the initial spikes in arterial pressure and cardiac output, the rebound effect of total body water, and the complex waveform of the hormone responses.

All of these items are legitimate research issues amenable for experimental verification and concern areas of hypogravic physiology that have been addressed by others in varying levels of detail. In many cases the model has provided a scientific rationale for an alternative or contrary hypothesis.

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## APPENDIX A

### DESCRIPTION OF THE MODEL OF CIRCULATORY, FLUID, AND ELECTROLYTE REGULATION (GUYTON'S MODEL)

The most comprehensive mathematical model of fluid and electrolyte control available to date, is that developed by Guyton and co-workers (1972). The systems analysis of overall circulatory regulation as developed by Guyton involves a large number of physiological subsystems. The current model, illustrated in Figure A-1, is based on cumulative knowledge of the circulation and on experimental data.

A description of this model should include a list of the following capabilities:

1. Predicts volume and electrolyte composition of the major fluid compartments, including plasma, interstitial, and intracellular fluid compartments,
2. Contains capillary and membrane interfaces between these compartments and the capability to simulate exchange of fluids and electrolytes under the influence of hydrostatic, oncotic, osmotic, and active transport forces,
3. Contains representation of the two major body cations, sodium (extracellular ion) and potassium (intracellular ion),
4. Can predict realistic urine excretion of salts and water especially under such conditions as fluid/salt loading and restricted fluid intake,
5. Contains neural, hormonal, and hemodynamic feedback control pathways regulating the volume and composition of the extracellular fluid compartment,
6. Contains a circulatory system that simulates blood pressures, flows, and volumes in arteries and veins during acute and long-term disturbances such as hemorrhage and infusions,
7. Contains an autonomic system that responds to changes in blood pressure, plasma osmolarity, and tissue oxygenation, by adjusting blood flow and pressures, hormonal secretion (ADH, angiotensin, and aldosterone), and body water, the latter by thirst and renal mechanisms.
8. Contains a representation of adaptation effects in the heart, vessels, and pressure receptors for controlling long-term blood pressure disturbances.

The relevant physiological systems have been divided into a number of major subsystems, each describing some important physiological aspects of circulatory, fluid, and electrolyte control (Figure A-1). The circuit of blood flow in the present model is divided into seven volume compartments: upper and lower body arterial volumes, upper and lower body venous volumes, and three heart and lung compartments (Figure A-2). Three parallel flow paths are assumed through the kidneys, leg muscle, and non-renal, non-muscle tissues.

The circulation is not closed but "leaks" through the capillaries, "excretes" through the kidneys, and "drinks" directly into the blood. Fluid intake is controlled by plasma osmolarity and tissue oxygen tension. Fluid excretion is based on glomerular filtration and the action of ADH. The blood, composed of plasma (with dissolved proteins and electrolytes) and red blood cells, serves as a filterable fluid. Other fluid-volume compartments include the interstitial compartment (composed of a gel volume and free fluid volume), the intracellular volume, and pulmonary fluid volume (Figure A-2). The model takes into account the rate of capillary filtration as determined by transcapillary Starling forces, the rate of lymph flow, the net rate of protein production, and the rate of transcellular fluid exchange as a function of osmotic imbalance between cellular and extracellular fluids. Of the two electrolytes considered in the model, sodium is distributed evenly in the extracellular fluid, and potassium is stored primarily in the intracellular fluid. This distribution is maintained by active transport. Dietary intake of both these electrolytes is considered as well as renal excretion.

The model uses basic cardiac function curves modified by the effects of autonomic stimulation, arterial pressure afterload, and cardiac hypertrophy or degeneration of the pumping ability of the heart. The unstressed volumes of each capacitive region are controlled by the level of autonomic stimulation, the level of angiotensin in the blood and the pressure in the veins (through stress relaxation). The flow resistances are controlled by a combination of local effects, autonomic and hormonal effects. The oxygen transport features of the circulation are present and hematocrit and red cell control are considered. The autonomic system included is basically regulated by mean blood pressure and tissue oxygen tension and includes the effects of the baroreceptors, chemoreceptors, and ischemia of the central nervous system.

The model's complexity precludes an easily understood detailed pictorial representation of its entire system. However, an example of the relationships embodied in the model for controlling aspects of extracellular and circulatory disturbances is illustrated in Figure A-3. The response of the model to head-down tilt, described in this report, are based largely on the elements shown in this diagram, including hemodynamic, hormonal, and autonomic control of renal excretion and, by feedback compensation, blood volume and pressure.

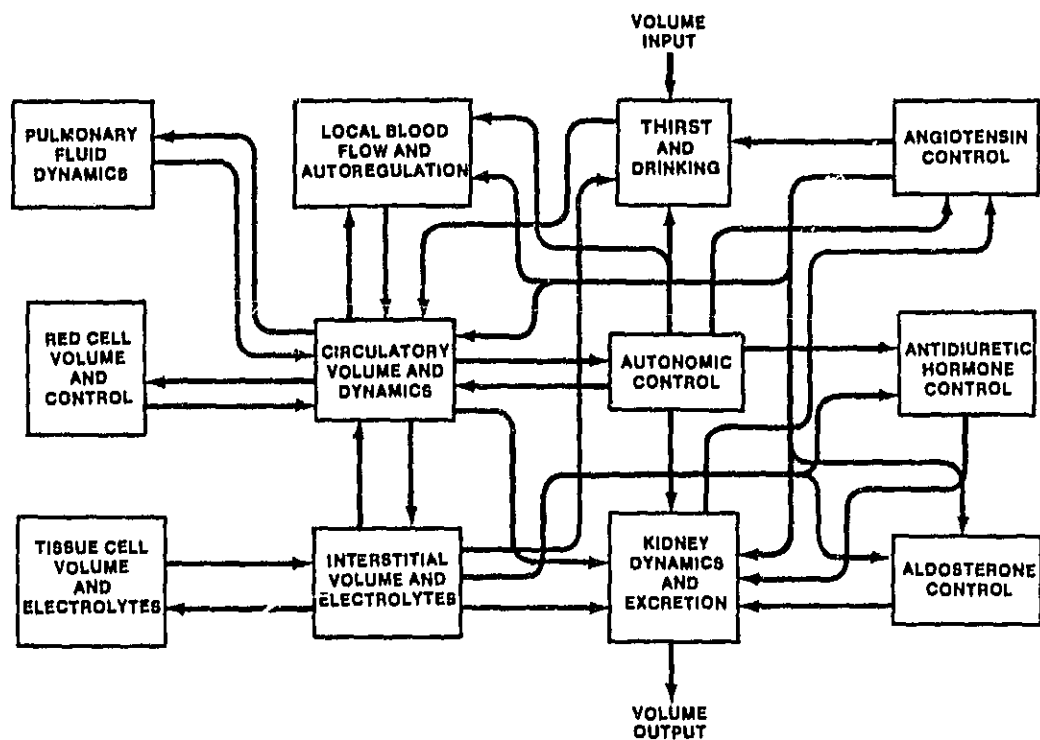
The Guyton model clearly illustrates the importance of considering the interaction between various subsystems in predicting fluid volumes and electrolyte levels. This interaction is especially important if it is to be used in the study of intermediate to long-term phenomena. One of the most important features of this model is that it is large enough to mimic the stability of the real system despite the fact that each subsystem is modeled in a gross sense with many minute details omitted. This characteristic of stability also permits using the model for long-term experiments.

The model was never originally contemplated to be required to simulate the weightlessness of space flight and its ground-based experimental analogs such as water immersion and head-down bed rest. Some of the required features which have been added to the model to handle this capability include lower body fluid compartments, collapsible leg veins, orthostatic mechanisms, and gravity-dependent effects on fluid columns.

The Guyton model represents an attempt to understand the interactions between acute and long-term adaptive control of the body fluids and the circulation. Because there is a notable scarcity of information regarding these complex processes in healthy subjects, long-term bed rest and space flight have been of particular importance in validating and modifying the original model of Guyton. This model is clearly relevant to space flight because some of the most notable physiological changes that occur can be traced to disturbances in fluid-electrolyte regulation. By accounting for long-term adaptive effects in the circulatory and autonomic systems, the model has been useful in predicting responses to stresses lasting up to several weeks or months.

References:

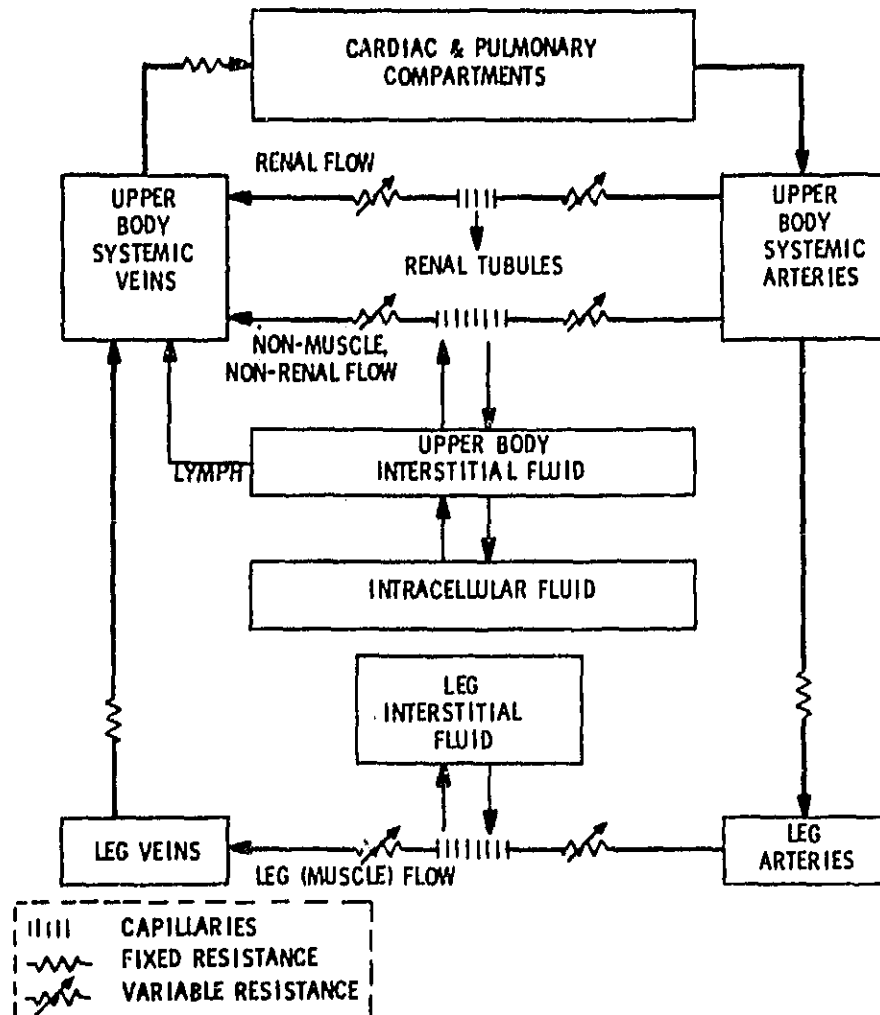
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SUBSYSTEMS OF GUYTON'S CIRCULATORY, FLUID, AND ELECTROLYTE MODEL

FIGURE A-1

## CONTROLLED SYSTEM

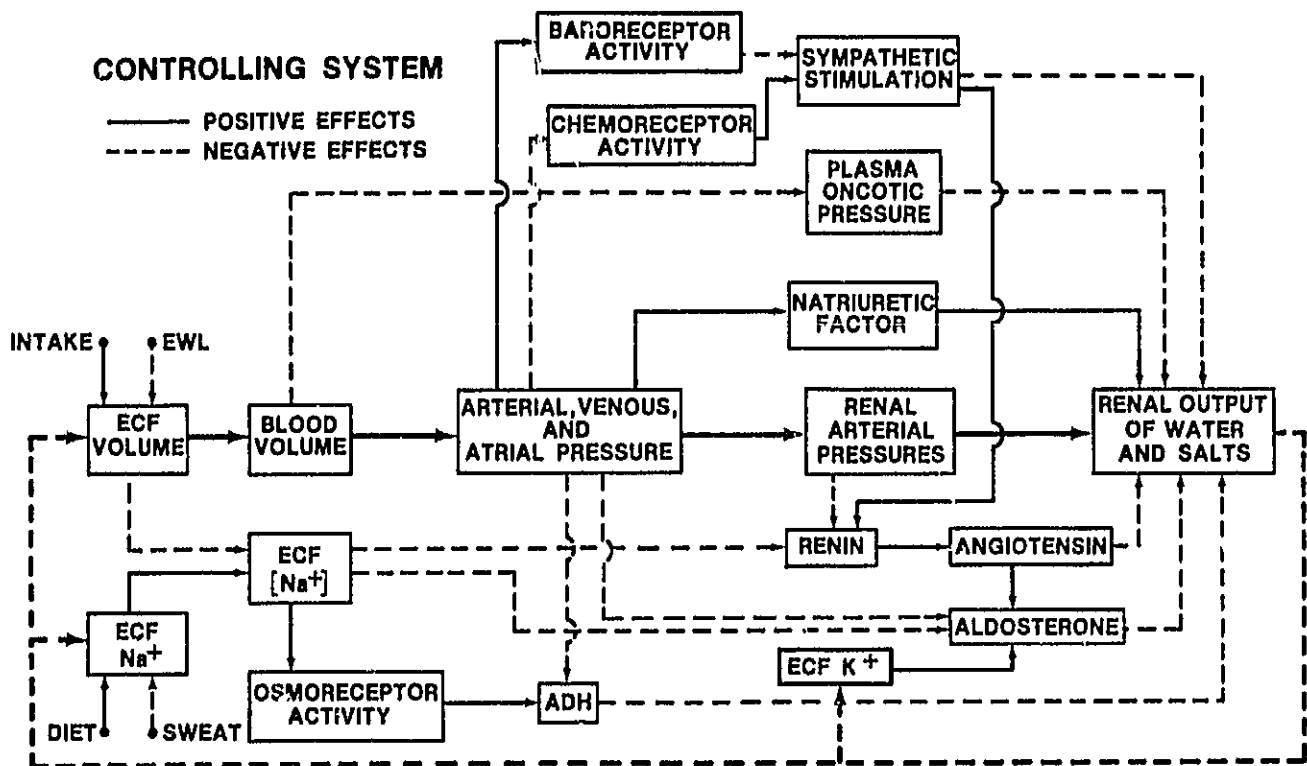


**CIRCULATORY AND FLUID COMPARTMENTS IN MODIFIED GRAVITY  
DEPENDENT MODEL OF CIRCULATORY, FLUID AND  
ELECTROLYTE REGULATION**

FIGURE A-2

FIGURE A-3

# MODEL REGULATION OF EXTRACELLULAR AND CIRCULATORY DISTURBANCES



## APPENDIX B

### SIMULATION OF A COMPOSITE SKYLAB MISSION

The Guyton model, modified to account for gravity-dependent stresses, was employed to perform a systems analysis of the biomedical data obtained from the Skylab missions (Leonard, et al, 1977). This analysis was based on the assumption that the weightlessness response is not pathological in nature. Rather, it can be explained in terms of normal, although complex, feedback regulatory processes many of which are represented in the mathematical model of Guyton. The simulations illustrated in this appendix represent a small segment of the overall study but demonstrate the general capabilities of the model as well as provide a partial description of the weightlessness response.

One important concept resulting from the simulation study was that it is extremely advantageous to divide the space-flight response into a short-term and a long-term segment. First, it is now known that the most dramatic disturbances in the fluid systems of the body occur during the first days following launch and reentry. The subsequent period seems to be characterized by an approach to new equilibrium levels. Secondly, the first five days of the Skylab flight were characterized by other unusual disturbances such as space sickness and high temperature excursions (on SL-2). It seems reasonable to dissociate these effects from the longer term period of flight (lasting up to three months). Third, it appears that the feedback regulatory mechanisms that are known to explain the acute effects of space flight may not be capable of accounting for the longer term effects. In fact, little is actually known of the long-term adaptive mechanisms which occur in weightlessness and it is possible that models such as those used here can play an important role in suggesting testable hypotheses.

The simulation results shown in Figures B-1 and B-2 were obtained from the Guyton model, by imposing the following conditions. First, the dietary intake (consisting of water, sodium and potassium) that was recorded for the Skylab astronauts was employed to drive the model intake. The same was true for the daily evaporative water rates that was computed by indirect means (Leonard, 1977). Secondly, a natriuretic factor was added to the model. This was necessary to simulate a realistic urinary sodium excretion. Third, potassium was allowed to leak from the cellular compartment at a rate which approximated the astronaut's loss of body potassium. This was important, because potassium has some far-ranging effects on fluid balance, hormone levels and renal function. Finally, in order to simulate the cephalad shift of fluid that occurs in weightlessness, fluid from the model's leg compartments was forced into the central circulation and subsequently became redistributed by natural processes (tissue elasticity, renal excretion, etc).

Figure B-1 illustrates the decrease in leg volume imposed on the model and the associated changes which occur in a number of hemodynamic parameters. For example, central blood volume initially increases, then decreases slightly but eventually returns to normal. The same is true of cardiac output, central venous pressure, and renal blood flow. (Note: immediately following the weightlessness response there are dramatic transients which are not adequately



shown on these figures because of poor resolution of the data display). This reflects an initial expansion of central fluid volume due to headward shifts, a subsequent compensation in the opposite direction, and a final adaptation. The causes for all these changes are not known. However, as the main text of this report discusses, model behavior points to the changes of peripheral resistance as a possible independent stimulus for other flow and pressure responses. Notice that, although head down tilt simulations suggest cardiac output and venous pressure are below normal for periods of less than a week and greater than a few hours, these longer term Skylab simulations suggest the return to normal of both hemodynamic indices. (These results are also noteworthy because they predicted a decline of blood flow and venous pressures following weightlessness in spite of the then current belief (based on water immersion studies) that these variables should be elevated, and years before the experimental confirmation was obtained from head-down tilt studies or measurements from space.

In Figure B-2 other fluid, electrolyte and hormonal responses are shown. Body water and body sodium both decrease rather rapidly and remain suppressed throughout the eight week period, reflecting losses of extracellular fluid. Potassium loss reflect decrease in intracellular content (i.e., muscle atrophy). Blood volume decreases due to a rapid loss of plasma volume and a longer term decrease in red cell mass. In the model, red cell mass decreases due to hyper-oxygenation of the tissues resulting from hemoconcentration. Hemoconcentration occurs early in flight following loss of plasma volume. Some other predictions of plasma electrolytes, urine excretion and hormones are also shown in Figure B-2. Analysis of model behavior shows a tight coupling between these variables, especially for long-term adaptive changes.

In general, it appears that the model's simulation of head-down bed rest is similar to the first week of space flight, thus validating the general belief that anti-orthostasis is a reasonable simulation of space flight. However, these simulations also suggest longer term adaptive behavior which requires months of exposure to weightlessness before the effects are fully measurable.

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FIGURE B-1

**SIMULATION OF COMPOSITE SKYLAB MISSION  
HEMODYNAMIC RESPONSE**

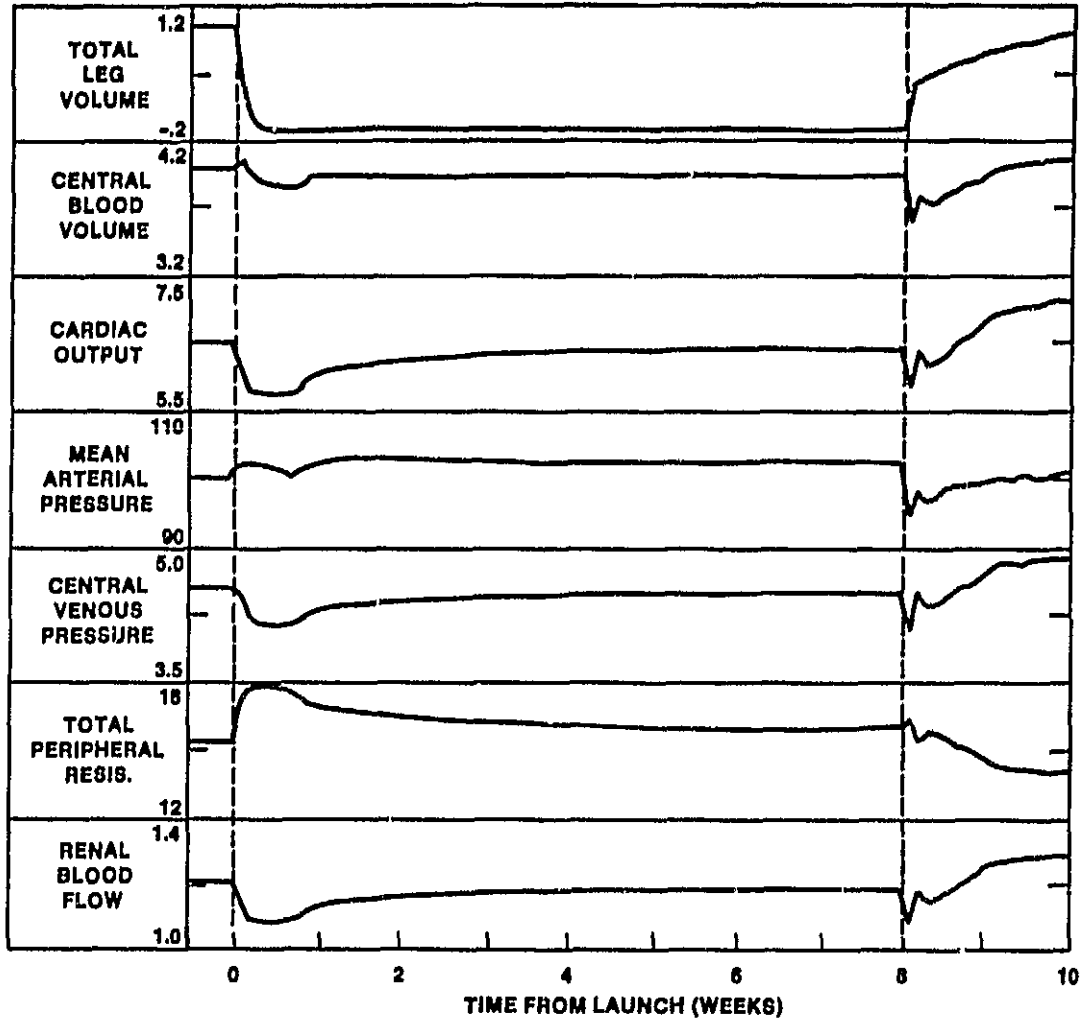
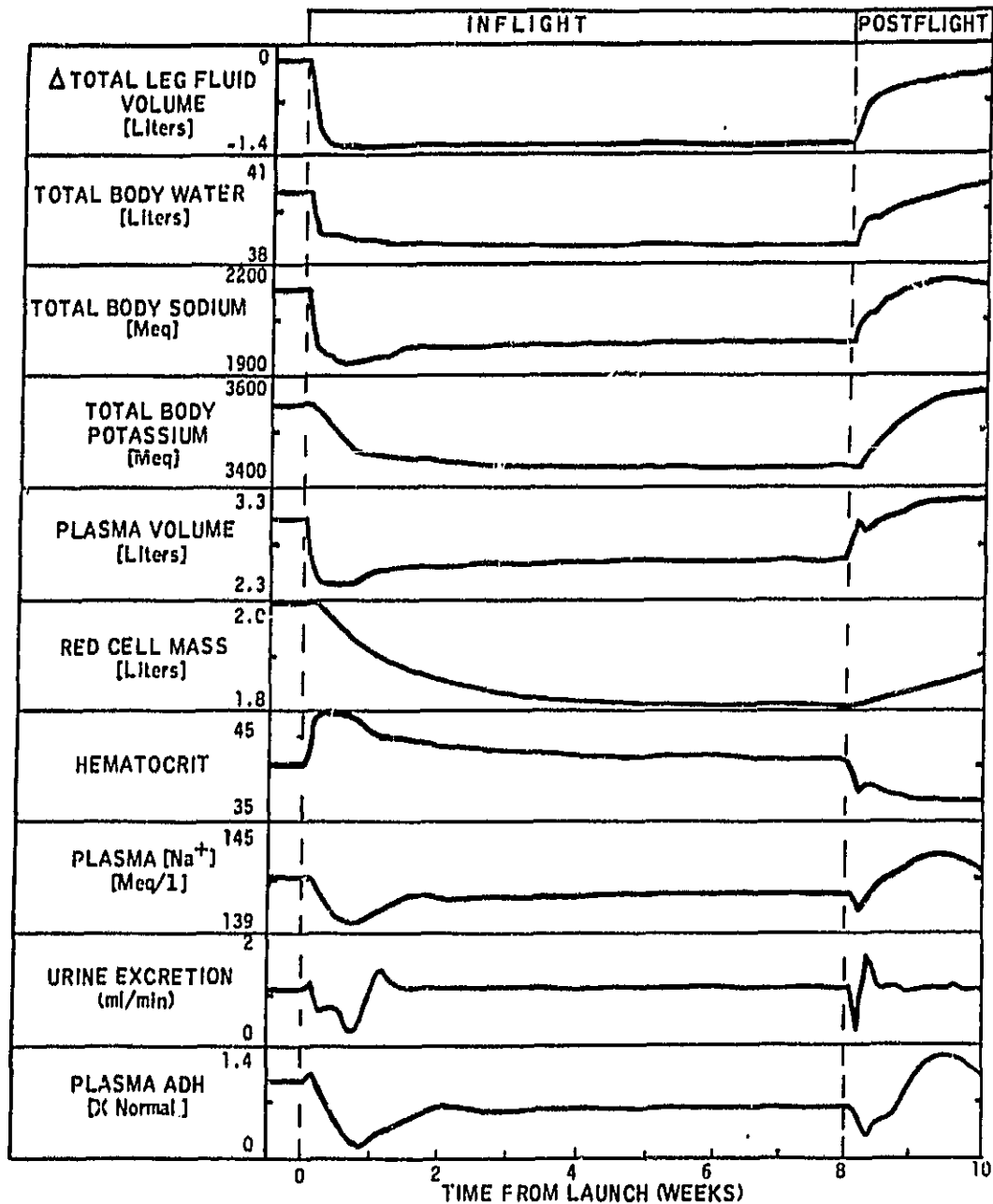


FIGURE B-2

# **SIMULATION OF COMPOSITE SKYLAB MISSION:** **FLUID-ELECTROLYTE RESPONSES**



## APPENDIX C

### SIMULATION OF WATER AND SODIUM RESTRICTION

The simulation of bed rest, reported in this study, included an analysis of the effects of the dietary restriction that was imposed on the experimental subjects during their immobilized phase. As a means of determining whether the Guyton model's simulation of fluid and salt restriction was valid for the bed rested case, a separate validation study was conducted, and is reported here. In this study, no attempt was made to induce headward fluid shifts, but rather the pure simulation response to either a salt restriction or water restriction was examined. A summary of the results, for a selected set of important variables, is shown in Figure C-1, while Figures C-2 and C-3 provide the detailed simulation responses obtained. In all but one case (the ADH response for sodium restriction) the model responses agreed qualitatively with empirical evidence.

Sodium or water restriction was obtained by reducing the dietary intake of the substance to zero. In the case of dietary sodium restriction (Figure C-2), plasma sodium concentration falls rather slowly over a weeks period because of an equally severe decrease of renal sodium excretion. However, there is an accompanying decrease in extracellular fluid as the renal regulatory mechanisms attempt to eliminate fluid and maintain plasma sodium composition. On the other hand, a reduction of fluid intake (Figure C-3) dramatically raises plasma sodium which has the effect of inducing an osmotic reduction of intracellular fluid. In both cases total body water and sodium excretion decreases. But in one case, the penalty for sodium restriction is loss of extracellular fluid, while it is a loss of intracellular fluid in the case of water restriction. These characteristics of water and salt restriction were clearly simulated by the Guyton model and thus confirm its ability to predict the effects of dietary changes.

FIGURE C-1

SIMULATION RESULTS OF  
WATER AND SODIUM RESTRICTION

<u>VARIABLE</u>	<u>DIETARY WATER RESTRICTION</u>	<u>DIETARY SODIUM RESTRICTION</u>
Plasma Sodium Concentration	↑↑ *	↓ *
Renal Sodium Excretion	↓ *	↓↓ *
Extracellular Fluid Volume	- *	↓ *
Intracellular Fluid Volume	↓ *	- ?
Total Body Water	↓↓ *	↓ *
ADH	↑↑ *	↓ X

Notes

\* Direction of simulated variable agrees with empirical data (Ref. 1)

? Intracellular fluid is observed to increase slightly in human subjects (Ref. 1), but in simulation it decreases slightly.

X ADH is known to increase in this situation, not to decrease (Ref. 1).

Ref.(1): Roddie, I.C. and W.F.M. Wallace, The Physiology of Disease, Year Book Medical Publishers, Chicago, 1975.

FIGURE C-2

## SIMULATION OF DIETARY SODIUM RESTRICTION

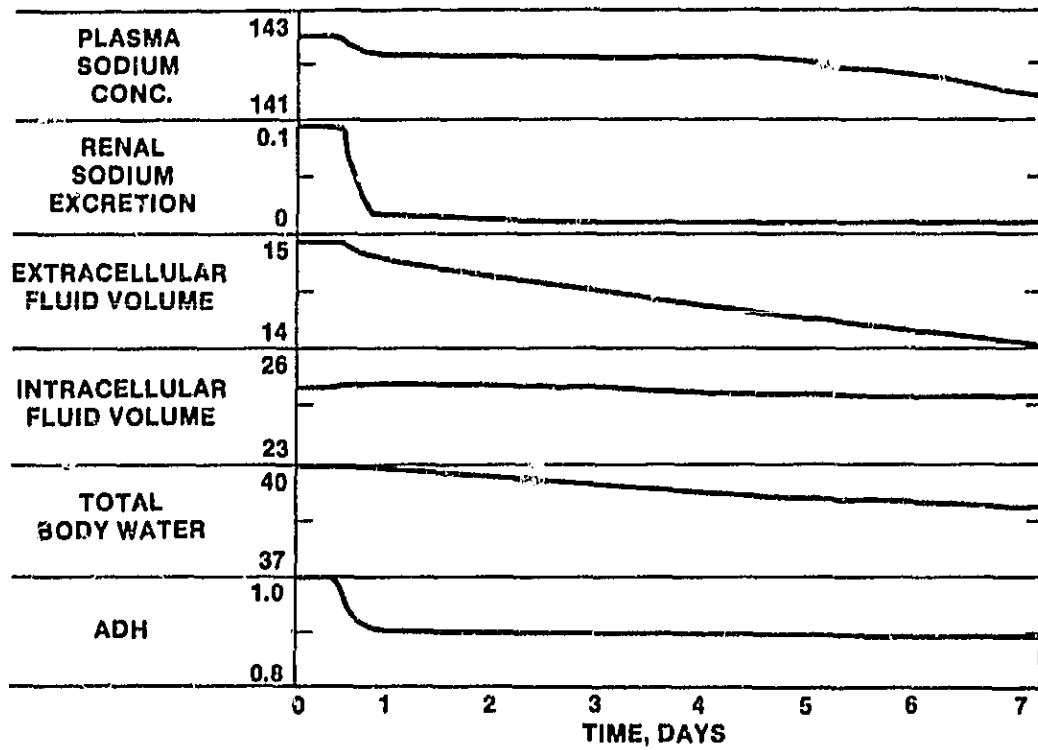


FIGURE C-3

## SIMULATION OF DIETARY WATER RESTRICTION

