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TiR 2114-MED-4001

FROM	TO
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DATE	CONTRACT NO:	T.O. OR A.D. REF:	MIS OR OTHER NASA REF:
7/26/84	NAS9-17151		

SUBJECT Mathematical Modeling of Fluid-Electrolyte Alterations During Weightlessness

This report summarizes a number of separate systems analyses studies of fluid-electrolyte metabolism and renal-endocrine control as it pertains to adaptation to weightlessness. The report discusses the mathematical models that have been particularly useful. However, the focus of the report is on the physiological meaning of the computer studies. A discussion of the major ground-based analogs of weightlessness are included; for example, head-down tilt, water immersion, and bed rest, as well as a comparison of findings from those studies with space flight. Several important zero-g phenomena are described in detail, including acute fluid volume regulation, blood volume regulation, circulatory changes, longer-term fluid-electrolyte adaptations, hormonal regulation, and body composition changes. Hypotheses are offered to explain the major findings in each area and these are integrated into a larger hypothesis of space-flight adaptation.

This report provides a conceptual foundation for the contractual tasks concerning fluid-electrolyte metabolism, blood volume regulation, and cardiovascular regulation.

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Attachment

/db

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MATHEMATICAL MODELING OF FLUID-ELECTROLYTE ALTERATIONS DURING WEIGHTLESSNESS

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July 1984

ABSTRACT

A systems analysis approach has been developed to aid in the integration of many of the biomedical findings of space flight. The primary data analysis tool has been a group of mathematical models of physiological systems. The predictive capabilities of the models permit biomedical hypotheses to be assessed for their consequences on many physiological quantities. Using a data base system, these model responses can then be compared tc the behavior of corresponding space-flight responses. As a result of iterating between hypothesis generating and hypothesis testing, it is possible to obtain a refined hypothesis, improvements in the model, and increased insight into the dynamic behavior of the system as it adapts to weightlessness.

This report describes the results from using this approach in examining one particular discipline that has been intensively studied in weightlessness - the fluid-electrolyte metabolism and the renal-endocrine control of that system as it adapts to a new environment. The report defines the physiological system of interest and discusses the models that have been particularly useful (specifically, the Guyton model of circulatory, fluid, and electrolyte control and the Leonard model of erythropoiesis control in examining that system). However, the main emphasis of the report is not on the details of the model or the simulation studies. Rather, the primary conclusions of the computer studies are examined in terms of their physiological meaning and in the context of achieving a better understanding of physiological behavior in weightlessness.

A discussion of the major ground-based analogs of weightlessness are included; for example, head-down tilt, water immersion, and bed rest, as well as a comparison of findings from those studies with space flight. Several important zero-g phenomena are described in detail, including acute fluid volume regulation, blood volume regulation, circulatory changes, longer-term fluid-electrolyte adaptations, hormonal regulation, and body composition changes. Hypotheses are offered to explain the major findings in each area and these are integrated into a larger hypothesis of space-flight adaptation. These hypotheses are testable and have provided one of the basis for the next generation of space-flight studies in this discipline.

MATHEMATICAL MODELING OF FLUID-ELECTROLYTE ALTERATIONS DURING WEIGHTLESSNESS*

J. I. Leonard, Ph.D.

In recent years, a systems analysis approach has been developed to aid in the integration of many of the biomedical findings of space flight. The mathematical tools utilized in accomplishing this task include an automated data base, a biostatistical and data analysis system, and a wide variety of mathematical simulation models of physiological systems (1). The cornerstone of this simulation effort has been and continues to be the evaluation of physiological hypotheses using these tools and the prediction of the consequences of these hypotheses on many physiological quantities, some of which have not been amenable to direct measurement. This approach has led to improvements in the model, refinements of the hypotheses, a tentative integrated hypothesis for adaptation to weightlessness, and specific recommendations for new flight experiments (2).

The fluid and electrolyte systems of the body may be characterized by the volume of several fluid compartments (plasma, interstitial, and intracellular), the electrolyte concentrations (primarily sodium and potassium) in these compartments, and the major flowpaths for water and ions (dietary inputs, metabolic water, fecal loss, urine excretion, evaporative water) into and out of these compartments. These elements and their basic relationships are illustrated in Figure 1. In addition, a number of major physiological mechanisms exist which regulate these volumes, fluxes, and concentrations. Important examples of the mechanisms involved in regulating the extracellular compartment are illustrated in Figure 2. The three principal types of control elements shown in this figure are hemodynamic, neural, and hormonal. This report describes and characterizes the changes that occur in the renal-endocrine control of fluid-electrolyte metabolism (i.e., the systems illustrated in Figures 1 and 2) during adaptation to weightlessness).

* Based on a presentation at the Johnson Space Center Fluid-Electrolyte Workshop (Chaired by C. S. Leach), April, 1981.

FIGURE 1

MAJOR ROUTES OF FLUID-ELECTROLYTE METABOLISM

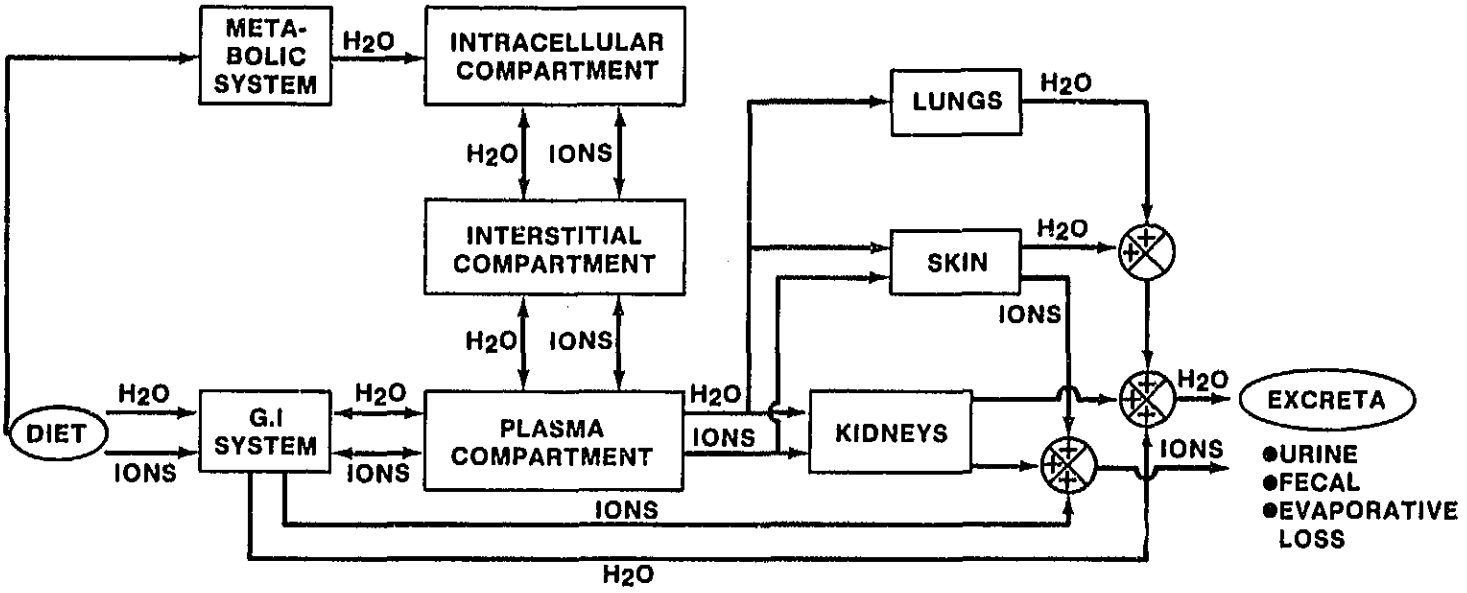
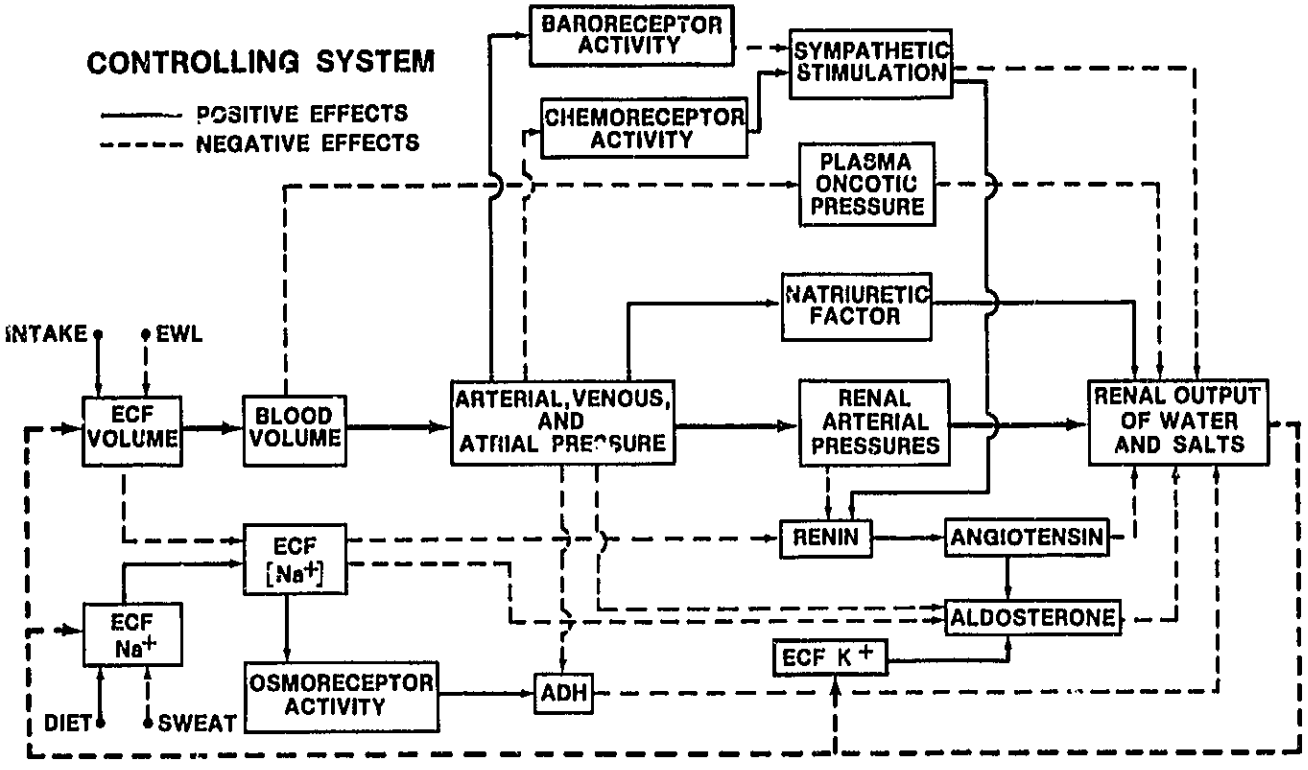


FIGURE 2

MODEL REGULATION OF EXTRACELLULAR AND CIRCULATORY DISTURBANCES



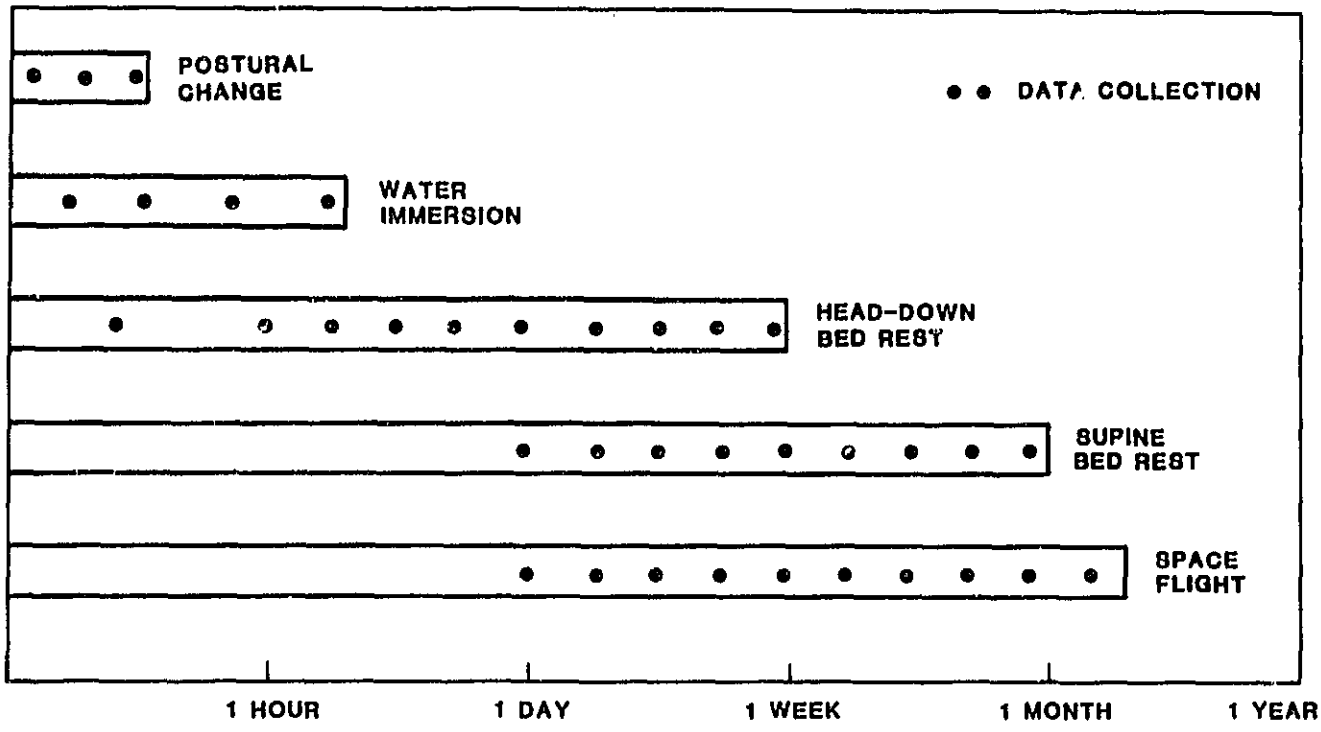
The task of developing a sound understanding of the space-flight responses of these systems was confounded by the lack of adequate data in some cases and by an incomplete physiological epistemology in other cases. Several novel approaches to the problems of data analysis and interpretation were developed as spinoffs from the main objective of these studies. For example, a new technique was devised to permit dynamic changes of body composition to be estimated from inflight cumulative metabolic balances without incurring the large errors that usually occur when this is done. This procedure provided useful information regarding the behavior of total body water, electrolytes, and proteins and showed how weightlessness may have altered the major metabolic routes of intake and excretion. Another innovative technique involved the use of a mathematical model of whole body fluid-electrolyte/renal-endocrine regulation. This model was used to simulate the weightless state and predict the behavior of the major body fluid compartments and quantities (such as hormonal levels and blood pressures) that often were not measured directly or frequently. Such modeling permitted a more complete utilization of the space-flight data base and enhanced the understanding of the processes of adaptation to weightlessness. Because certain useful information had not been collected in space flight, or was incomplete, it was necessary to draw upon the results of those ground-based studies which purport to simulate the zero-g state. Therefore, extensive analyses were performed using results from such "analog" stresses as water immersion, head-down tilt and bed rest to complement evidence obtained from space flight.

APPROACH AND METHODS

For the purpose of the present analysis, the fluid-electrolyte responses to zero-g were divided into an acute phase (hours to days) and an adaptive phase (days to weeks). The acute phase is characterized primarily by a significant reduction in body fluids and electrolytes (mostly extracellular), while the adaptive phase is characterized by approaches to new homeostatic levels, especially for renal excretion, endocrine secretion, body fluid volumes and composition, and losses of intracellular material. Ground-based studies have been extremely useful in providing supplementary information, especially for the acute stress stage where flight data is sparse. These useful one-g analogs of weightlessness, listed in Figure 3, include postural changes, water immersion, head-down bed rest, and supine bed rest. All of

FIGURE 3

HYPOGRAVIC-STRESS STUDIES



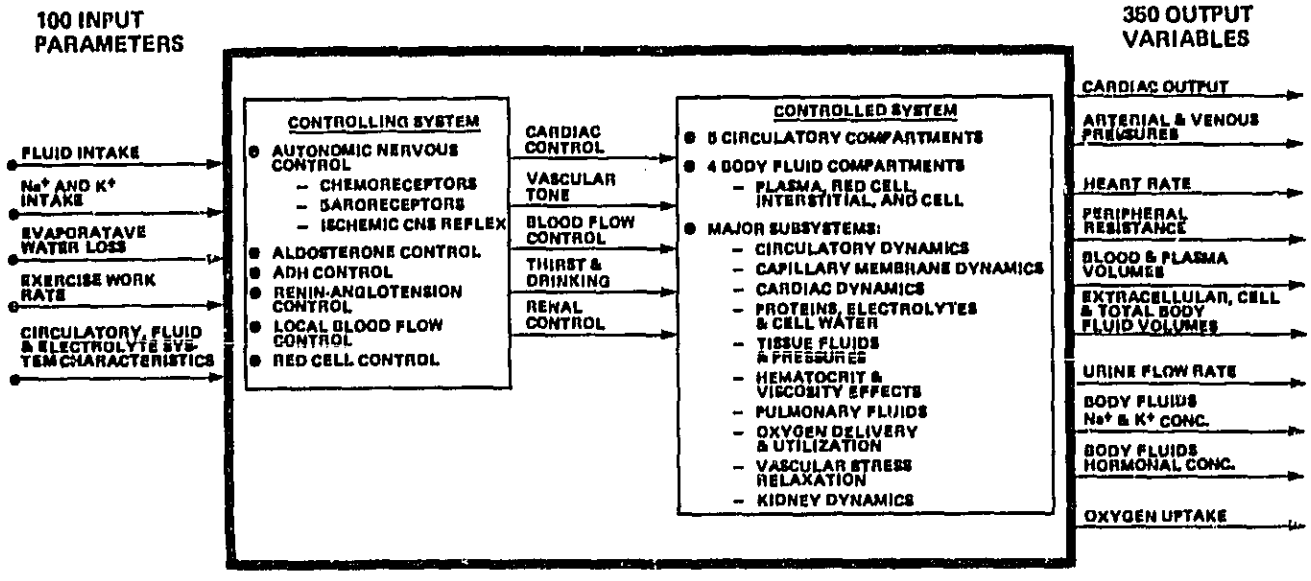
these stresses include a reduction in hydrostatic gradients and a rapid headward shift of fluid. This phenomenon, more than any other, is believed to be largely responsible for many of the most dramatic physiological events which occur at the onset of weightlessness. However, each of these stresses is different with regard to physical activity, external hydrostatic pressure, fluid/salt intake, sweat losses, the amount of fluid shifted headward, and musculoskeletal atrophy. The interaction of these factors is complex and unraveling their individual influences should lead to a better understanding of longer-term fluid-electrolyte responses to hypogravity.

It is clear that until microgravity research becomes more commonplace, the development of an understanding of the fluid-electrolyte responses during space flight will be intimately connected with the integration of the findings from one-g analog studies. As indicated in Figure 3, such integration is confounded by the fact that each class of study is typically of a different duration and the frequency of data collection varies widely from study to study. A suitable mathematical model provides one means to systematically examine each of these stresses as well as a framework for the study of their commonalities and differences. Such studies using models have led to a tentative description of the complete spectrum of temporal responses resulting from exposure to weightlessness and have provided a coherent explanation of many of the time-dependent observations (3).

A model which has proved invaluable in these studies (Figure 4) was developed some time ago by Arthur C. Guyton for the study of overall circulatory, fluid, and electrolyte regulation (4,5). This model contains subsystems which describe fluid and electrolyte exchanges between the major volume compartments, cardiovascular and renal dynamics, hormonal control, and blood volume regulation including separate control of plasma and red cell components. Both short-term and long-term adaptive control mechanisms are represented. Recent modifications include adding leg vascular and tissue compartments, gravity dependent circulatory elements, and a natriuretic factor. These additions provide the capability for simulating postural changes and fluid shifts between upper and lower body. Figure 2 depicts a number of the elements involved in the regulation of extracellular volume and composition that are represented in the Guyton model. It is clear that this biological control system is extremely complex. It encompasses a wide variety of passive and active elements, employs multiple sensors to obtain direct and

FIGURE 4

CIRCULATORY DYNAMICS, FLUID AND ELECTROLYTE BALANCE MODEL



ADDITIONS OR IMPROVEMENTS

- IMPROVED RED CELL SUBSYSTEM
- RECOMPARTMENTED TO PROVIDE LEG COMPARTMENTS
- IMPROVED RENIN/ANGIOTENSIN SUBSYSTEM
- IMPROVED STRESS RELAXATION
- IMPROVED BARORECEPTOR BLOCK
- RESPONSE TO GRAVITATIONAL GRADIENT

indirect estimates of changes in the controlled variables, and can be represented by several complicated, interacting neuroendocrine feedback loops (6). The interactions shown in Figure 2 will assist the reader in understanding some of the simulation results presented in this report.

A second and less complex model was developed by Leonard et al to examine the more limited area of erythropoiesis control (7). This model incorporates the most current understanding of the dynamics of red cell production and the associated feedback regulation based on the balance between tissue oxygen supply and demand. Simulation studies with this model have provided useful insights into the still perplexing problem of the loss of red cell mass during bed rest (8) and space flight (9,10), and have allowed conclusions to be inferred concerning human erythropoiesis from results of animal surrogate experiments (11). It is possible to use this model on a stand-alone basis, and it has also been incorporated into the Guyton model as a replacement for the original red cell algorithm which was found to be inadequate under certain conditions. The Guyton model and the Leonard model together form the theoretical basis to study the loss of plasma volume, red cell mass, and total blood volume in space flight. (In this report, any mention of "the model" will refer to the Guyton model, unless the erythropoiesis model is specifically noted.)

In practice, both models were used to simulate the dynamic physiological responses of humans exposed to a gravity-free environment. The accuracy of the computer response is verified by comparison with actual space flight or ground-based analog findings. The models' responses could be altered, if necessary, by formulating one or more hypotheses, and modifying the model in accord with this formulation. Computer simulation techniques could then be applied to test these hypotheses and assess their plausibilities. These techniques might include merely changing the value of a fixed parameter (i.e., adjusting the gain or set point of a control loop), or 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. The most plausible of these results may then become a starting point for the design of validation experiments in the laboratory and eventually lead to permanent improvements of the model. This interaction between model simulation and experimental studies is valuable and synergistic.

One of the important modeling challenges was to determine the techniques that would permit realistic simulation of headward fluid shifts. Three useful methods were devised. The most straightforward approach (from a mathematical viewpoint) was to force fluids from the unstressed to the stressed "compartments" of the peripheral circulatory blood volumes at the same time as forcing fluid from the leg interstitium to the leg vasculature. Although this initiating maneuver is somewhat artificial, it results in a realistic behavior of fluid redistribution and volume regulation. A second method, used to simulate water immersion, was the application of an external compressive force on leg interstitial and venous compartments. Finally, the most recent technique employed was designed to simulate head-down tilt experiments by altering the angle of tilt and thereby changing the direction and magnitude of the gravity vector as it affects blood pooling in the legs. Each of these stimuli, once initiated, permit the elastic forces of the tissues and vessels to redistribute fluids in a manner favoring upper body hypervolemia. Subsequently, feedback controllers respond by regulating blood flow, blood pressure, and blood volume toward more normal values. Autonomic, renal, and hormonal control elements contribute significantly in this response, as suggested in Figure 2. The primary observable differences between these three methods of initiating headward fluid shifts are the magnitudes and rates of change of fluid movement and the relative participation of intravascular versus extravascular fluids. Qualitatively, these methods produced quite similar results.

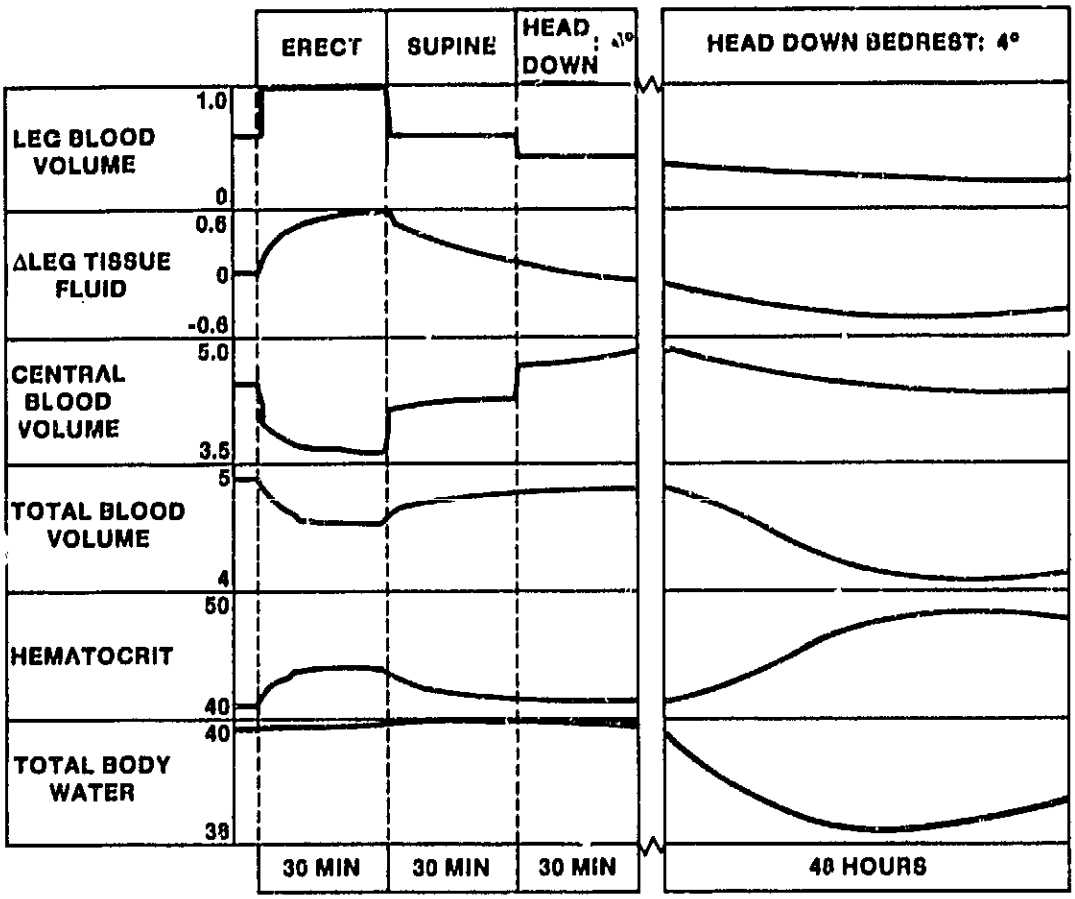
SUMMARY OF FINDINGS

Computer Simulation

The capability of the model to realistically simulate short and longer-term exposures to hypogravic stimuli is illustrated in the following summary. First, the fluid redistribution responses to short-term postural shifts (30 minutes in the erect, supine, and head-down positions followed by 48 hours of head-down tilt) are illustrated in Figure 5. The negative angle of tilt is similar to that used experimentally to simulate space flight. Two kinds of acute fluid shifts are exemplified in Figure 5: a) movement of blood between upper and lower body, and b) plasma exchange between intravascular and extravascular compartments. In addition, during more chronic conditions such

FIGURE 5

SIMULATED FLUID-SHIFTS DUE TO POSTURAL CHANGES



(VOLUMES IN LITERS)

as the 48-hour head-down tilt shown in Figure 5, there is an additional shift of fluid out of the body as represented by a decrease in total body water. The model is, therefore, capable of realistically demonstrating blood pooling in the legs and tissues during standing, central hypervolemia during head-down conditions, and the net loss of total blood volume during both short-term orthostasis and longer-term anti-orthostasis (12,13).

A typical water immersion simulation (5 hours), shown in Figure 6, demonstrates that a wide range of fluid volume, hemodynamic, renal and hormonal responses can be satisfactorily described by the model. The dynamic behavior of all the variables shown are in qualitative agreement with experimental findings by various investigators (14,15,16). Our present expectations of the acute physiological responses to weightless space flight (which have not yet been measured in any detail) is derived primarily from water immersion studies. The mathematical model has served to provide tentative descriptions of intra- and inter-compartmental fluid exchanges, local blood flows and pressures, and autonomic and endocrine stimulating factors, in lieu of a capability to measure these processes during one-g or zero-g studies (17).

The recent success of head-down tilt as a realistic experimental analog of zero-g behavior has prompted its computer simulation, with the results shown in Figure 7 (2,18). Comparison of model output and experimental data, as shown in Table 1 for 24-hour head-down tilt and in Table 2 for 7-day head-down tilt, indicates that these simulations are quantitatively as well as qualitatively accurate. As suggested in Figure 7 (and described in more detail below), there is a reversal in direction of many variables after the initial response to head-down tilt. Thus, head-down tilt, particularly the studies of Blomqvist and co-workers (19,20), has provided a bridge between the acute response to headward fluid shifts as exemplified by short-term water immersion results, and the delayed responses as represented by longer-term supine bed rest findings. This aspect of the experimental studies was predicted years ago by our original zero-g simulations (21), and suggests that it is a natural consequence of the negative feedback circuits which control pressure, volume, and ion concentrations.

Finally, longer-term effects were studied by simulating two months of space flight using the simple forcing method to move fluids headward, and then using Skylab crew fluid and electrolyte dietary intake data as model driving

TABLE 1

COMPARISON OF SIMULATION AND EXPERIMENTAL RESPONSE

FOR 24-HOUR HEAD-DOWN (-5°) TILT STUDY

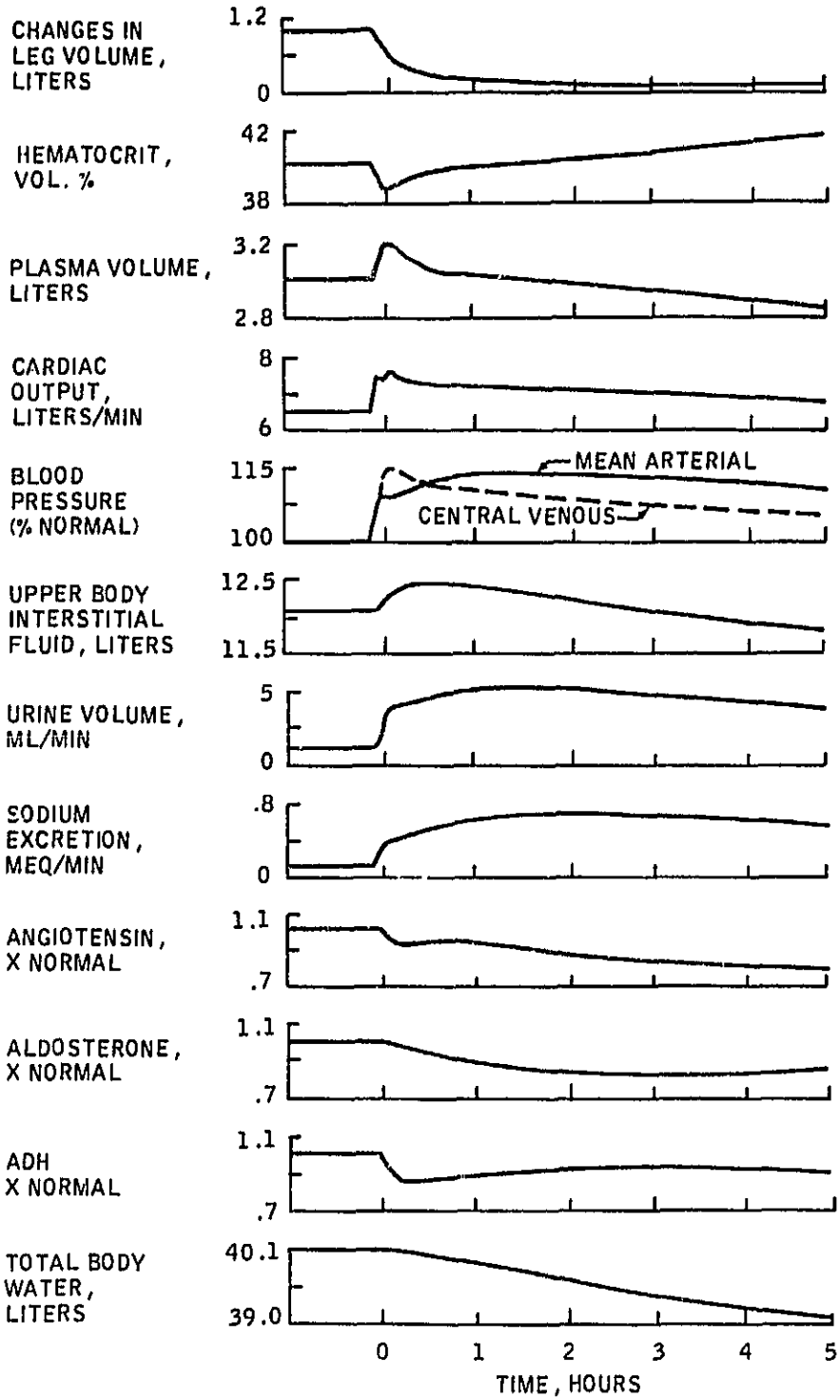
QUANTITY	VALUE @ 24-HOURS COMPARED TO CONTROL	
	HEAD-DOWN TILT	MODEL
FLUID SHIFTS		
TOTAL BODY WATER	- 1300 ml	- 1130 ml
LEG VOLUME	- 900 ml	- 710 ml
LEG BLOOD VOLUME	-	36 %
LEG INTERSTITIAL VOLUME	-	64 %
		100 %
TOTAL BLOOD VOLUME	- 425 ml	- 563 ml
URINE RATE, 8 HR/24 HR.	127 %	190 %
HEMODYNAMICS		
CARDIAC OUTPUT	- 7.8 %	- 11.1 %
STROKE VOLUME	- 8.5 %	- 9.8 %
HEART RATE	0 %	1.4 %
ARTERIAL PRESSURE, MMHG & %	3.7 mmHg/+4 %	2.6 mmHg/+3 %
CENTRAL VENOUS PRESSURE, CM H_2O & %	- 2.4 cmH_2O/-49%	0.5 cmH_2O/-9%
LEFT ATRIAL PRESSURE	-	0.7 cmH_2O/-50%
HORMONES		
ALDOSERONE	+ 35 %	+ 12 %
ANGIOTENSIN	+ 25 %	+ 17 %
ADH	+ 57 %	+ 3 %
NATRIURETIC FACTOR	-	+ 14 %

TABLE 2

COMPARISON OF SIMULATION AND EXPERIMENTAL RESPONSE

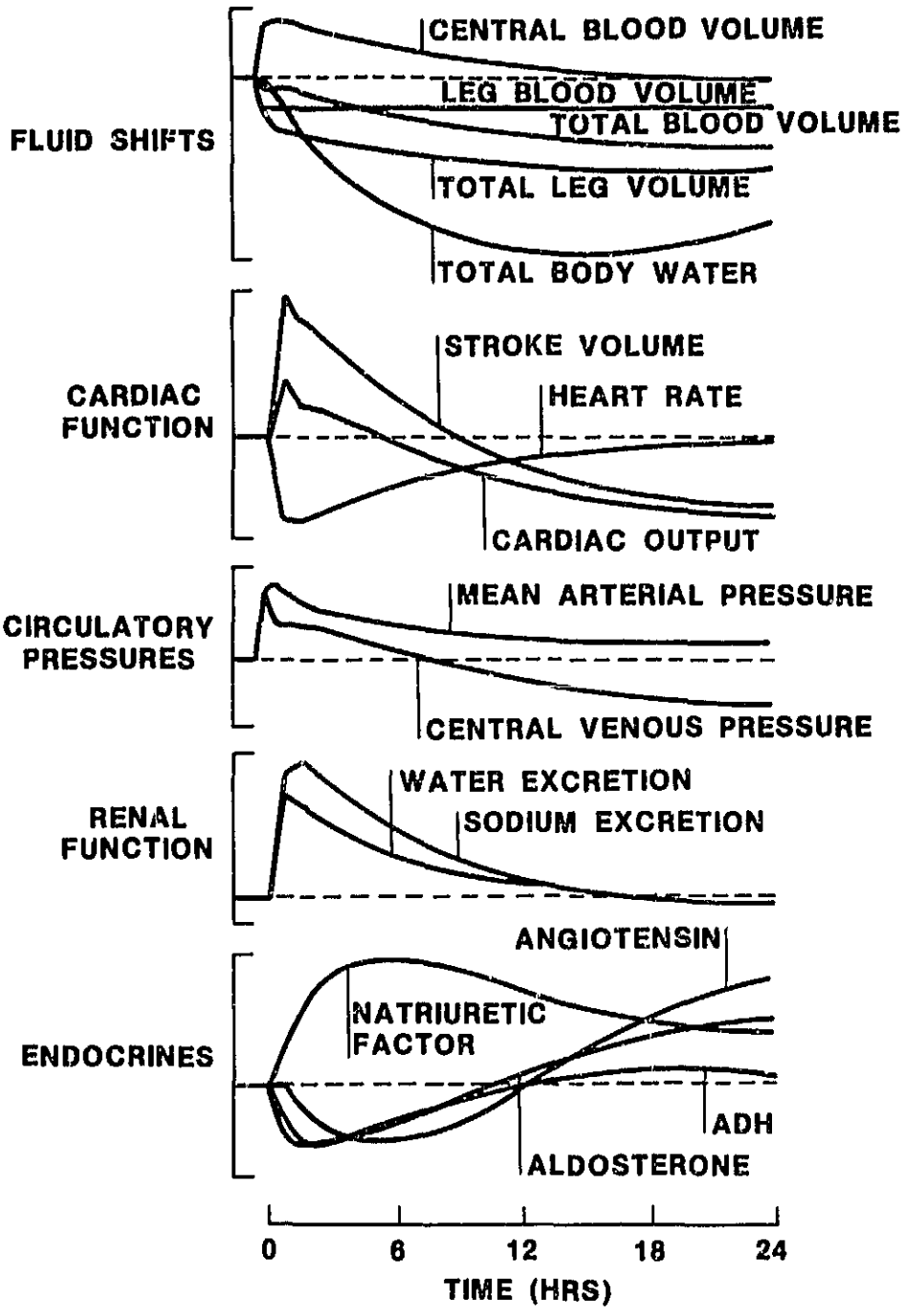
FOR 7-DAY HEAD-DOWN (-6°) BED-REST STUDY

QUANTITY	VALUE @ 7 DAYS COMPARED TO CONTROL	
	BED REST	MODEL
FLUID SHIFTS		
TOTAL BODY WATER	- 600 ML	- 430 ML
LEG VOLUME	- 460 ML	- 650 ML
PLASMA VOLUME	- 8 %	- 18 %
RED CELL MASS	- 9 %	- 5 %
HEMATOCRIT	+ 7 %	+ 9 %
HEMODYNAMICS		
CARDIAC OUTPUT	- 9.5 %	+ 10.7%
ARTERIAL PRESSURE	+ 9.5 %	0 %
VENOUS PRESSURE	- 2 % (EDV)	- 9 %
RENAL FUNCTION		
WATER EXCRETION	- 39 %	- 30 %
SODIUM EXCRETION	- 39 %	- 32 %
POTASSIUM EXCRETION	- 13 %	- 11 %
PLASMA ELECTROLYTES		
SODIUM	- 3 MEQ/1	- 4.8 MEQ/1
POTASSIUM	- 0.5 MEQ/1	- 0.4 MEQ/1
ENDOCRINES (PLASMA)		
ALDOSTERONE	- 28 %	- 24 %
ANGIOTENSIN	+116 %	+ 55 %
ADH	- 65 %	- 37 %



SIMULATION OF WATER IMMERSION

FIGURE 6



SIMULATION OF HEAD DOWN TILT (-6°)

FIGURE 7

functions. The results, shown in Figure 8, provide a theoretical foundation to explain many of the biochemical and fluid findings of the extensive Skylab studies. As will be discussed later in this report, the model simulation exercises suggest that weightlessness, per se, leads to reduction in body fluids and particularly blood volume, but that other indices of fluid-electrolyte status, such as hormone levels, renal excretion rates, or Figure 8 plasma/urinary biochemical concentrations, are influenced significantly by other, more mundane, factors such as dietary intake, sweat losses, and physical activity (22).

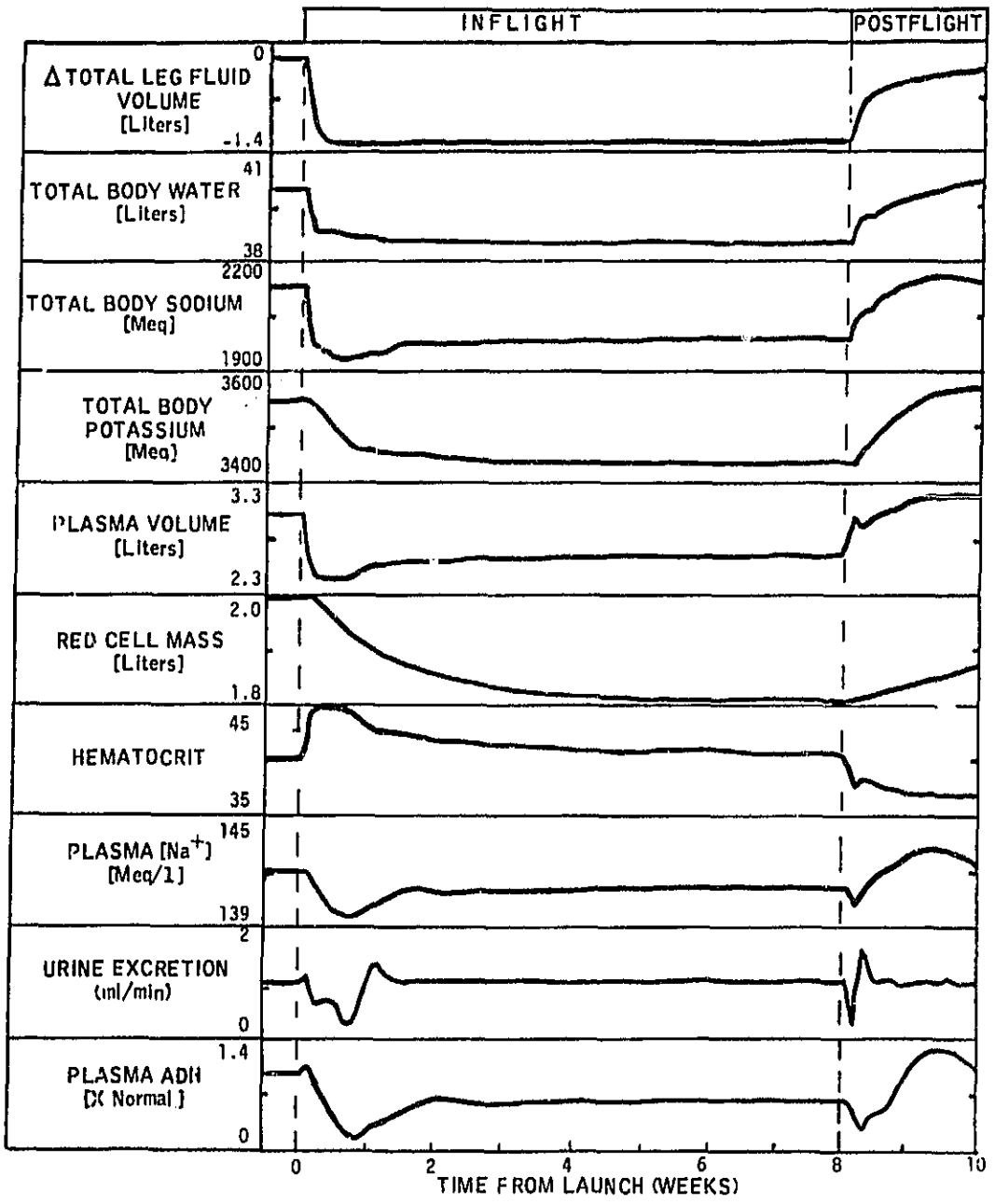
An accurate simulation of hypogravic maneuvers is indeed possible using mathematical models, as these results indicate. However, even more meaningful are the insights regarding system behavior which are revealed as a result of the model's predictive, integrative, and heuristic characteristics. Some of the major conclusions reached during the course of this modeling research are summarized below. In most cases, these conclusions are speculations based on a theoretical model and should be treated with appropriate caution. Nevertheless, they do represent hypotheses that are testable and, in fact, have provided the basis for the next generation of space-flight studies in this discipline (23,24).

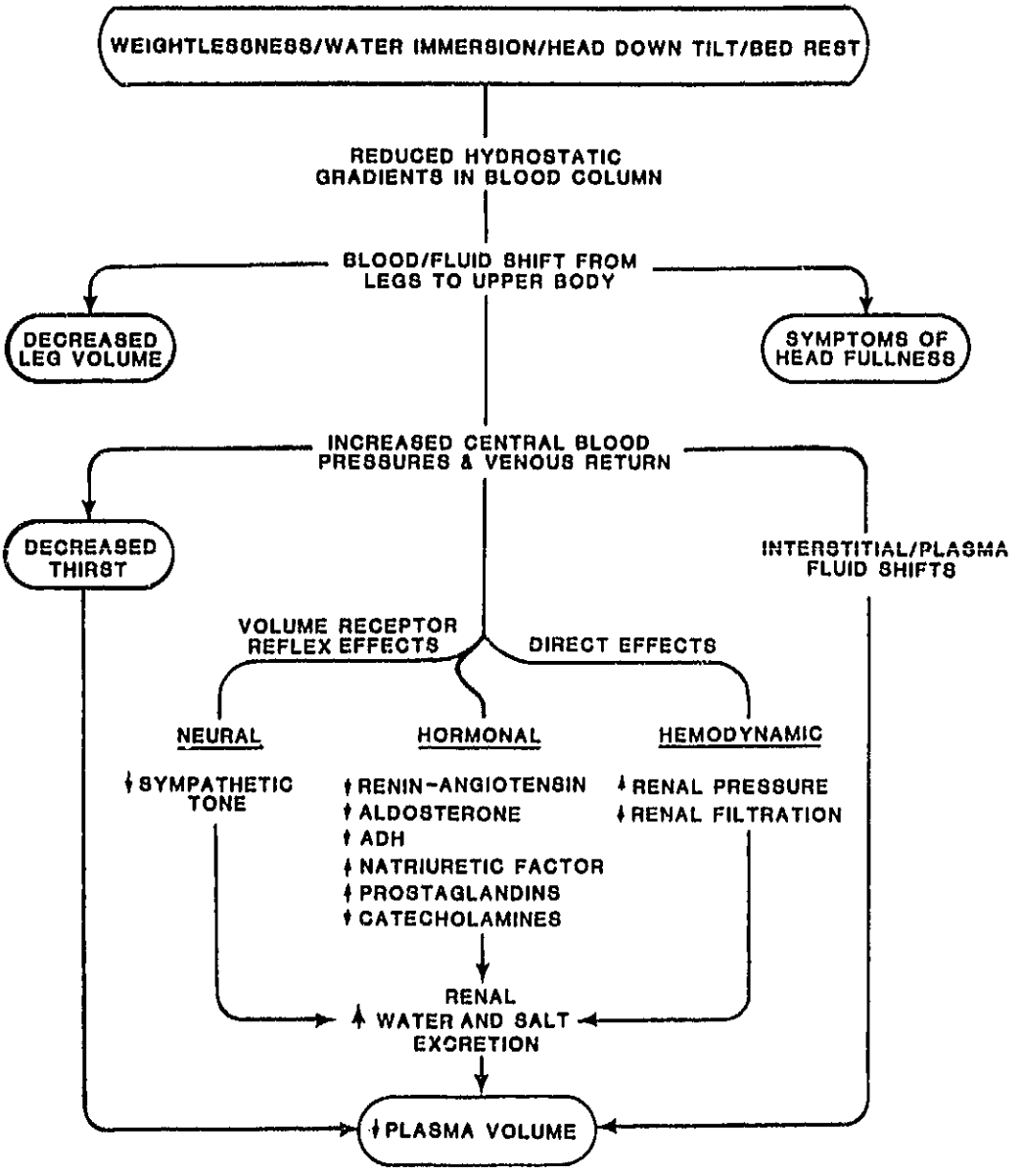
Acute Fluid Volume Regulation

There is unequivocal evidence that hypogravic stresses result in significant fluid redistribution within the body (16,20,25,26). The removal or reduction of the hydrostatic pressure in the blood column, coupled with the normal tissue elastic forces and muscle tone of the lower body, result in shifts of blood and tissue fluid from the lower body to the intrathoracic circulation. The consequences of this event are widespread and long lasting, as suggested by Figure 9, and lead to a loss of plasma volume. According to the current understanding which has been derived from model simulations (e.g., Figures 5-8) and ground-based analog studies, 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 9. They include capillary filtration into the tissues, renal excretion, and a thirst mechanism. Of these, the renal mechanisms are the most complex and can be further separated into three other groups, mediated by neural, hormonal, and

FIGURE 8

SIMULATION OF COMPOSITE SKYLAB MISSION





FLUID – SHIFT HYPOTHESIS

FIGURE 9

hemodynamic factors. Although the pathways connecting these factors are not indicated, they are known to be highly interrelated and tightly coupled.

Theoretically, it is possible for a reduction in plasma volume to occur by any one of the three major routes shown in Figure 9. In practice, it appears that each pathway's contribution depends on its unique characteristics and the circumstances of the experimental study. For example, on Skylab most of the fluid losses can be accounted for by deficit drinking, while during water immersion and head-down tilt studies, fluid losses are related to a renal diuresis. One of the important findings from the simulation studies is that a diuresis should occur during the first few hours of space flight, but that it can be obscured by the pooling of urine into 24-hour aliquots (as was done on Skylab), especially if the subjects are dehydrated (17). (Astronauts, in the past, have frequently limited their fluid intake prior to launch.) Model simulations have also been used to assess the role of transcapillary fluid shifts and have demonstrated that this pathway is self-limiting as a means of relieving central hypervolemia. This self-limiting phenomenon occurs because plasma colloidal concentration increases as fluid moves into the interstitium, which opposes further filtration. Simulation studies demonstrated that even if capillary permeability to proteins dramatically increases (as seems plausible in hypervolemia), the amount of plasma fluid capable of being accepted in the interstitium is quite limited. This means that in the well-hydrated subject, the kidneys can be considered to be the principal avenue of fluid regulation during weightlessness.

One of the more instructive computer simulations of acute hypogravic stress was shown in Figure 7. Within the first several hours the model predicts a marked decrease in leg volume associated with changes in fluid volumes, hemodynamics, and renal-endocrine function, all of which are in essential agreement with the hypothesis diagram of Figure 9. Following this early phase, nearly all variables examined (except for fluid volume changes) exhibit a transient biphasic behavior, with a return to (or an overshoot beyond) control by the end of 24 hours. This simulation indicates that the hypothesis diagram of Figure 9 (typical of those found in the literature) represents only a static picture of the earliest responses, while a more realistic dynamic analysis indicates that secondary changes occur which are completely opposite to those initial changes. If one wishes to reconstruct

the events during the first day of weightlessness (as will be attempted on Shuttle/Spacelab missions), it is obviously crucial to make measurements early in time and frequently thereafter.

Blood Volume Regulation: Causes and Consequences

A typical finding in astronauts returning from space flight is a reduction in total circulating blood volume of about 10 percent. Although not measured directly during flight, this blood volume reduction is believed to be due to an acute plasma volume loss, followed by a more gradual loss of red cell mass. As suggested in the previous section, the etiology of the plasma loss is believed to be due to a response to headward fluid shifts (i.e., central hypervolemia). Gauer (27) has suggested that the tendency of fluids to redistribute toward the central circulation during weightlessness, can lead to potentially dangerous cardiopulmonary fluid congestion. This concept is supported somewhat by the observations that head and neck veins, facial tissues, and sinus cavities are full and distended throughout prolonged space missions (26). However, these sites of congestion are all anterior to the thoracic region which has not yet been studied directly during flight. Furthermore, Russian cosmonauts have not reported problems of upper body circulatory congestion after more than six months in space. Model simulations predict that central blood volumes return to near normal following the plasma volume correction, thus disagreeing with the concept of congestion (see Figure 7). More direct evidence is obviously warranted.

The moderate loss of plasma volume in space flight has widespread consequences. First, the failure of plasma volume to return to normal during prolonged flight (even with a normal fluid intake) suggests the active involvement of blood volume controllers and perhaps a change in set-point. Thus, although an expected diuresis has not yet been observed early in a flight, volume receptors and renal excretion pathways may be continually responding to the tendency for fluids to pool headward and thereby are acting to maintain a reduced blood volume. Second, the hemoconcentration that develops as plasma volume is reduced would be expected to enhance oxygen delivery to the tissues and possibly initiate several feedback reactions including: an autoregulatory increase in circulatory resistance, a reduction in cardiac output, and a suppression of erythropoietin and erythropoiesis. Third, this latter hypothesis of erythro-suppression may be responsible for

the measured reduction in red cell mass (8,10), although this is far from being settled (11). It is of interest, and perhaps important to note, that although the reductions in plasma volume and red cell mass noted in each Skylab crew varied widely, the total blood volume loss was nearly the same after each flight regardless of flight duration. For example, if plasma losses were relatively large, then the same individual would incur a relatively smaller loss of red cell mass. This observation suggests that it is blood volume which is tightly regulated rather than either plasma volume or red cell mass. Fourth, a reduction in plasma volume would lead to increases in all hormone concentrations, unless hormone secretion was reduced. However, whether the elevated hormone levels observed in space flight are caused by a reduction in the volume of distribution is a question yet to be resolved. Fifth, the loss of blood volume is believed to be responsible for some of the impaired circulatory responses noted in astronauts returning from space. This issue is addressed below.

Circulatory Changes

There is a tight coupling between fluid-electrolyte and circulatory regulation that must be examined in order to understand the space flight findings in either area. For example, in the simulation studies, the elevations in blood pressure which are expected immediately upon entering weightlessness were found to give rise to a diuresis and blood volume reduction (Figures 5 to 9). Thus, acute loss of blood volume, in turn, contributed to longer-term degradation of the circulatory responses to orthostasis and postflight exercise (28). The two most important findings concerning circulatory adaptation to space flight have been the loss of blood volume and the phenomenon called cardiovascular deconditioning. While the deconditioning process can be largely explained by a decreased blood volume, the belief is widely held (and verified by our modeling studies) that the total extent of deconditioning is due to multiple factors, none of which (other than blood volume loss) have been positively identified (19,29).

An additional finding from water immersion and bed rest studies is that during hypogravity, blood pressure and blood flow levels behave in a biphasic manner (see Figure 7). This has important implications in understanding fluid regulation, but it has not yet been studied in space flight. Apparently, the elevated venous and arterial pressures and increased cardiac output during the

acute stress phase of hypogravity is followed, after a number of hours or days, by a decline, reaching levels which are sometimes below normal. This hyperkinetic-hypokinetic phenomenon undoubtedly has an influence on those fluid regulating pathways which depend on volume-receptor activity. Whereas, the initial hyperkinetic state is a consequence of headward fluid shifts, the long-term hypokinetic state has not yet been explained. Investigations using the simulation model suggest that several previously proposed hypotheses, including decreased blood volume, lowered metabolic rate, altered autonomic function, and increased venous compliance, do not necessarily account for these hypokinetic responses. Instead, the modeling studies indicated that venous pressures and cardiac output could be suppressed during space flight due to increased systemic resistance secondary to the vasoconstrictor action of angiotensin and tissue hyperoxia brought on by hemoconcentration. Increases in peripheral resistance have been observed in ground-based analog studies (19,30). The currently proposed experiments for Spacelab on humans and rats will be able to test this relationship between peripheral resistance and central venous pressure (24).

Longer-Term Fluid-Electrolyte Adaptations

During prolonged space flight (i.e., Skylab) after the major acute fluid disturbances have stabilized, a number of alterations in fluid-electrolyte status have been observed. Some of the more significant alterations have been summarized in the top part of Figure 10. They include reductions in body water and other major fluid compartments such as plasma and intracellular volume, losses of sodium and potassium and alterations of the electrolyte composition in body fluids, and changes in renal excretion and hormone levels (31,32).

Most of these disturbances occur gradually, are of a more subtle nature than the acute changes, and are more difficult to characterize and understand. Though there is a generalized theory to account for the acute fluid disturbances, none exists to account for the long-term adaptive effects. Nevertheless, it has been possible to use metabolic balance and computer simulation techniques to assess the most plausible pathways by which these changes took place (22,33,34,35). The resulting hypotheses and the observations they account for are shown schematically in Figure 10 and in more detail in Table 3.

FIGURE 10

HYPOTHESES WHICH ACCOUNT FOR SPACE-FLIGHT OBSERVATIONS OF THE FLUID-ELECTROLYTE SYSTEM

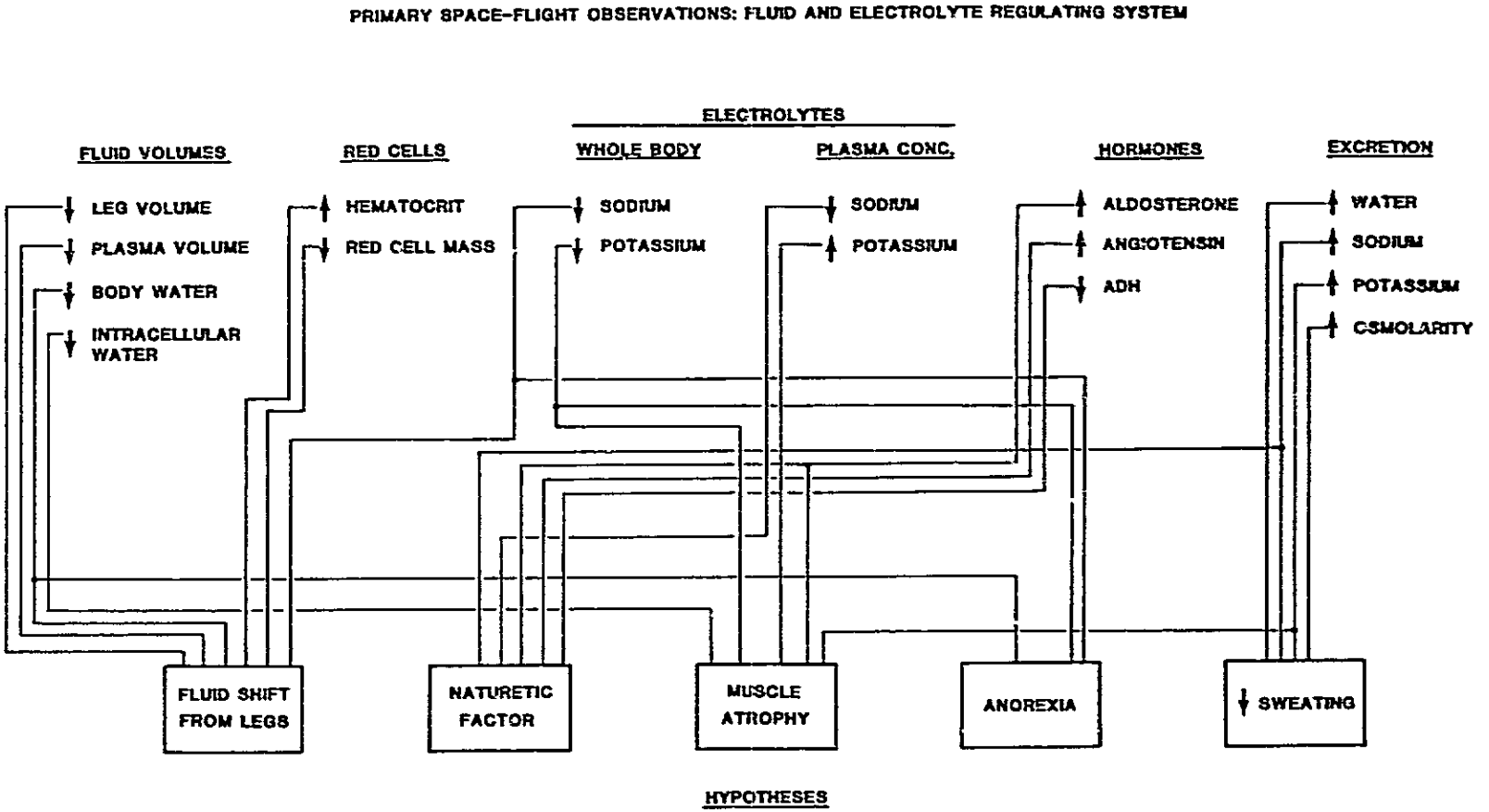


TABLE 3

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

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

(CONTINUED)

TABLE 3 (CONTINUED)

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

(CONTINUED)

TABLE 3 (CONTINUED)

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

TABLE 3 (CONTINUED)

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

According to the scheme in Figure 10, the "headward-fluid-shifts-from-the-legs" hypothesis accounts for a number of critical changes involved with loss of fluid, sodium, and red cells. However, this hypothesis does not explain many of the other observations illustrated in Figure 10. Some of these can be attributed to other potential causes: small disturbances in diet, evaporative and skin losses, intracellular mineral losses (muscle atrophy), and regulation by a natriuretic factor that controls sodium excretion and metabolism. The loss of evaporative water and associated electrolytes appears to be reduced in space flight and bed rest (35). Therefore, the findings of excess renal excretion of water and sodium does not necessarily imply that there is continued body loss of these substances. Rather, the model predicts that increased excretion could be offset by a decreased sweat component. Potassium loss occurs more gradually than water and sodium; it is undoubtedly secondary to atrophy of lean body mass. Cellular potassium loss may have widespread consequences, accounting for the findings of enhanced aldosterone levels, increased potassium urinary excretion, elevated plasma potassium, decreased intracellular fluid, and decreased body potassium (22,36).

Hormone levels are influenced significantly by electrolyte concentrations (primarily sodium and potassium) which in turn are disturbed by changes in the basic metabolic pathways (i.e., dietary intake, renal excretion, fecal excretion, sweat loss, and cellular loss). However, although potassium loss from the tissues helps explain the mild hyperkalemic condition (elevated plasma potassium) found in the Skylab crew, the regulatory pathways which frequently lead to hyponatremia (reduced plasma sodium) during hypogravic maneuvers is not entirely clear. Reduced dietary sodium and reduced aldosterone, which could lead to hyponatremia, were not present in the Skylab crew. The correction of hyponatremia in space flight could theoretically be accomplished by excretion of extracellular fluid volumes, but these are already significantly depleted. Resolution of this phenomenon is complicated by the considerable overlap and interactions between the systems which regulate extracellular volume and those which regulate extracellular osmolarity. Whatever the etiology of hyponatremia and hyperkalemia may be, these conditions appear to explain, in part, the long-term trends in hormone levels during the three-month Skylab missions (22,32). A similar analysis was performed for a one-week head-down bed rest study. Similarities between the

one-week and three-month hypogravic studies were striking and gave rise to a generalized explanation of the behavior of the renal-regulating hormones (32,36). This hypothesis will be described next.

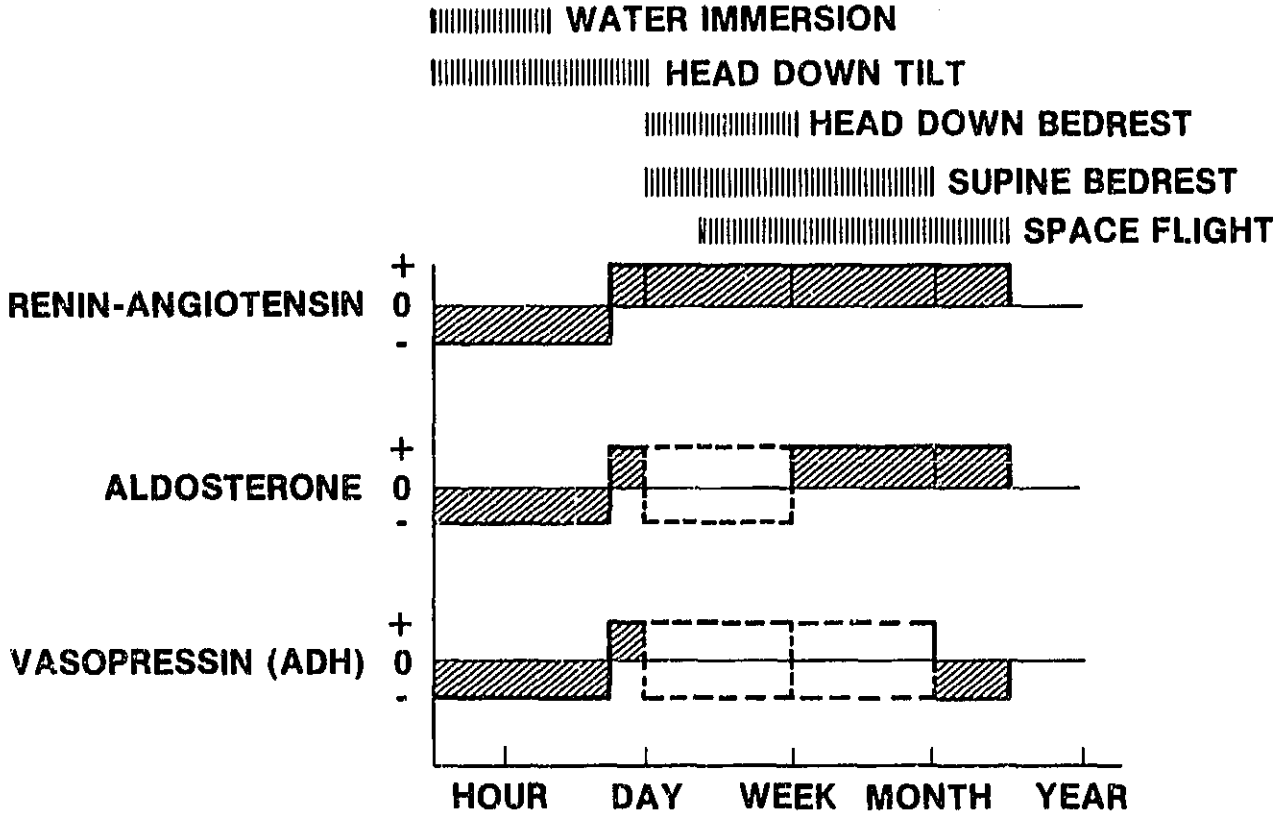
Hormonal Regulation

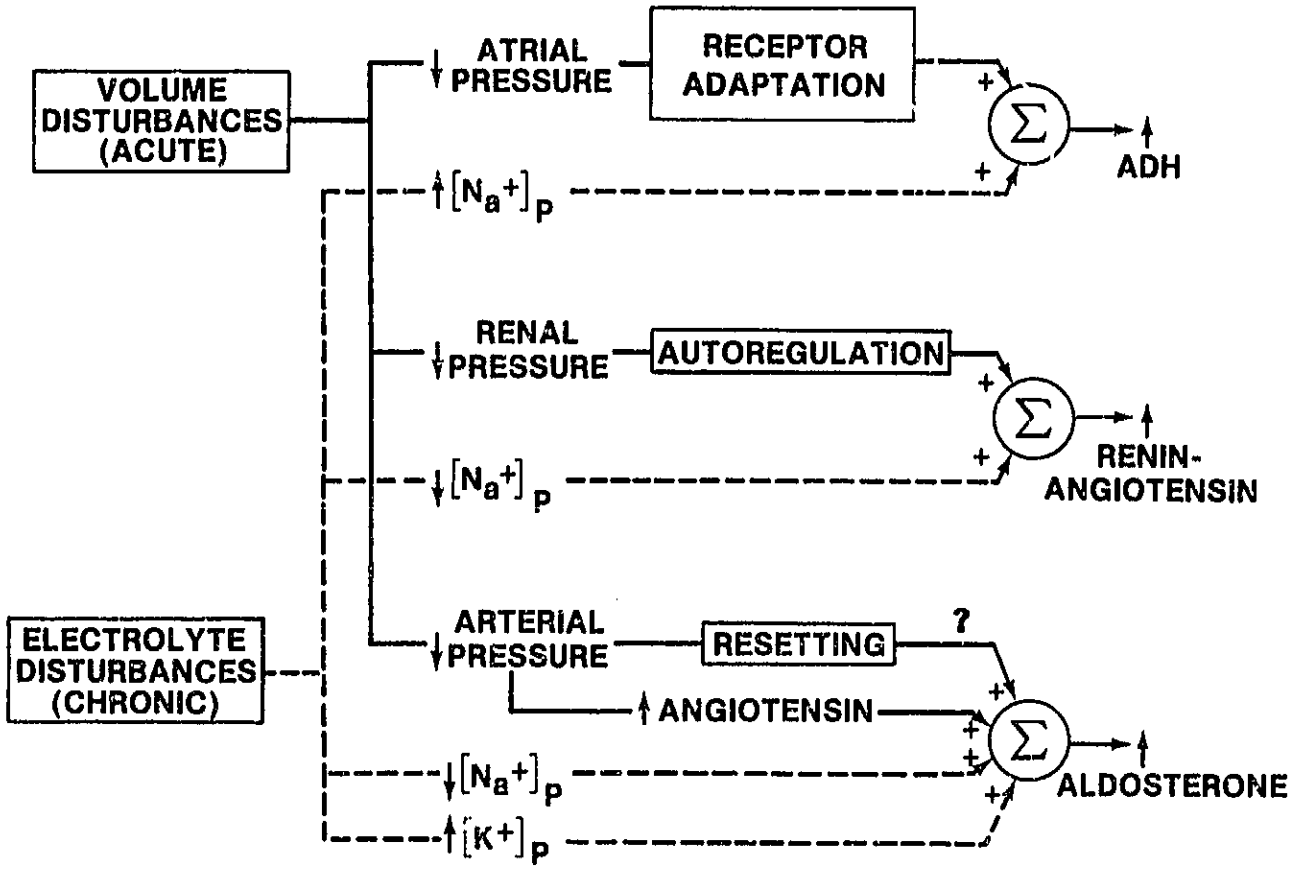
A group of renal-regulating hormones, consisting of anti-diuretic hormone, aldosterone, and angiotensin, have been the focus of many space-flight related studies. A knowledge of these hormone disturbances can provide insight into the status of the fluid-electrolyte and renal systems. However, the findings from space flight have been difficult to interpret or to reconcile with endocrine data obtained from one-g analogs of weightlessness. Figure 11 organizes the endocrine data from a number of hypogravic studies, whether performed in one-g or zero-g, into a qualitative, composite description. A goal of the present study was to reconcile the differences between the acute and chronic responses as well as the differences among the separate studies. A schematic description of the factors which influence the three hormones, as they are represented in the present Guyton model, reveal some important facets of hormone regulation. As shown in Figure 12, each hormone is responsive to two general types of controlling stimuli: volume disturbances (as reflected by atrial, renal, or arterial pressures) and electrolyte disturbances (plasma sodium or potassium concentrations). The volume stimuli may provide control only during acute disturbances, because of the existence of several types of adaptive mechanisms indicated in Figure 12, or because the volume disturbances are often easily corrected by volume-regulating mechanisms. However, the influences of the electrolyte disturbances are not known to adapt as a function of time.

During hypogravic stress, therefore, acute headward fluid shifts lead to an initial suppression of hormone levels (see Figure 9) which aids the renal-correction of the volume disturbance. However, the long-term response is variable and depends upon metabolic factors (such as diet, sweat loss, physical activity and muscle atrophy) that can alter the plasma electrolytes. Thus, the hyponatremia and hyperkalemia of space flight help explain the elevations of angiotensin and aldosterone, and suppression of ADH. With the exception of aldosterone, similar hormone changes were observed in a recent one-week head-down tilt bed-rest study. According to the simulations of this latter study, shown in Figure 13, the long-term changes in aldosterone,

FIGURE 11

HORMONAL CHANGES DURING HYPOGRAVIC STUDIES





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

FIGURE 12

angiotensin, and ADH are accounted for entirely by dietary restriction of fluids and electrolytes. These dietary alterations resulted in hyponatremia and hypokalemia, phenomena which led to the predicted hormonal response, whether or not head-down tilt was included in the simulation protocol.

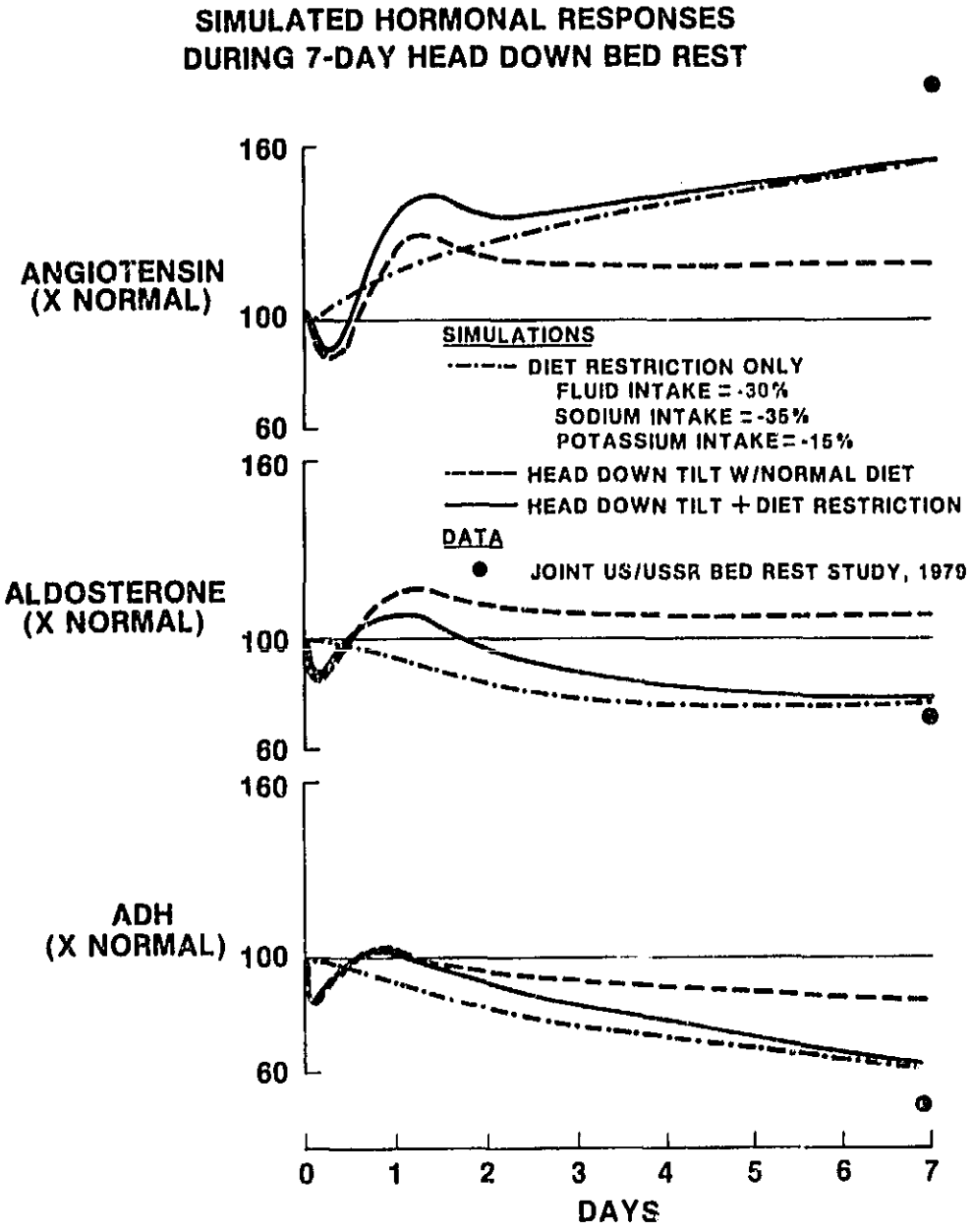
Each of the head-down tilt simulations of Figure 13 exhibits a multiphasic response which reflects the effects of competing and time-varying stimuli. As indicated in Figure 12 and discussed above, the acute hormone suppression is a result of early pressure and volume disturbances. However, due to normalization of pressure stimuli, and due to the gradual development of plasma-electrolyte alterations, control of endocrine secretion shifts from pressure to electrolyte control. Dynamic variations of endocrine levels can, therefore, be considered a normal response to hypogravity, dietary influences, or both, and thus may account for discrepancies often reported between different studies, subjects, and test conditions. These analyses are fully described in several reports and papers (17,18,33,36).

Body Composition Changes

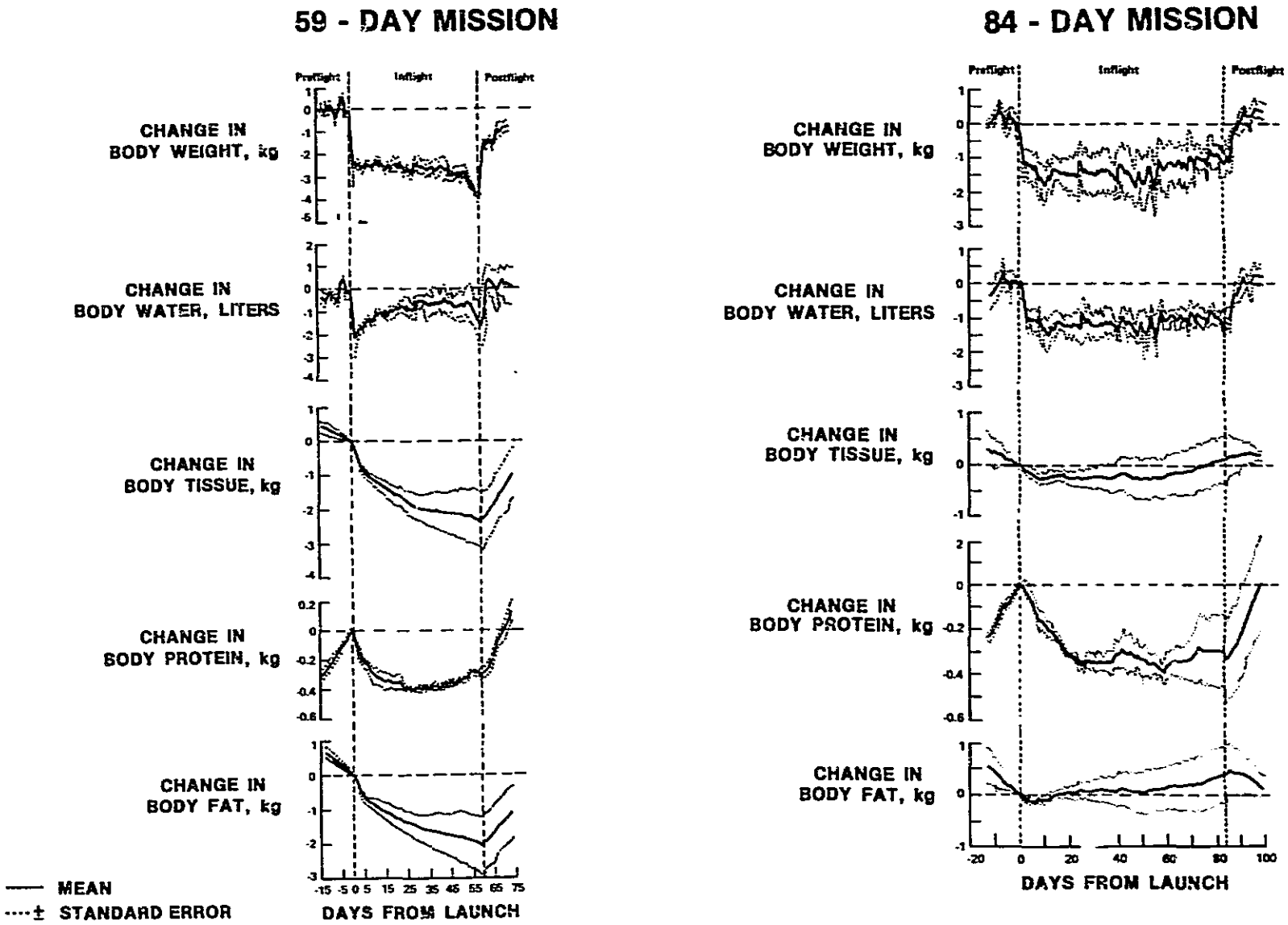
Although body mass has been measured directly during space flight, the particular components of the body that led to significant weight loss in astronauts returning from space have only recently been indirectly inferred from Skylab data (37). New techniques for analyzing conventional metabolic balance data made it possible to derive time-varying changes of body composition in subjects exposed to weightlessness (38). In Figure 14 the changes in body composition of the Skylab crews on the 59-day and 84-day flights are shown as changes measured from the morning of launch. In these figures, body mass changes are assumed to consist of either water or solid (dry) tissue; solid tissue can be further divided into either body protein or body fat.

Comparison of the 59-day and 84-day flights (Figure 14) leads to some interesting conclusions regarding space-flight adaptation. On both flights there is an acute decrease in body mass which can be attributable to a loss of body water. This is considered an obligatory water loss and has been described above in relation to the response to headward fluid shifts. The larger loss of mass and water in the crew of the 59-day mission was apparently a result of relatively severe space sickness and restricted dietary intake. Over the next few weeks of the 59-day mission, a portion of this depleted

FIGURE 13


SIMULATED HORMONAL RESPONSES
DURING 7-DAY HEAD DOWN BED REST
ANGIOTENSIN
(X NORMAL)
ALDOSTERONE
(X NORMAL)
ADH
(X NORMAL)
160
100
60
SIMULATIONS
DIET RESTRICTION ONLY
FLUID INTAKE = -30%
SODIUM INTAKE = -35%
POTASSIUM INTAKE = -15%
HEAD DOWN TILT W/NORMAL DIET
HEAD DOWN TILT + DIET RESTRICTION
DATA
JOINT US/USSR BED REST STUDY, 1979
0
1
2
3
4
5
6
7
DAYS

CHANGES IN BODY COMPOSITION DURING SPACEFLIGHT



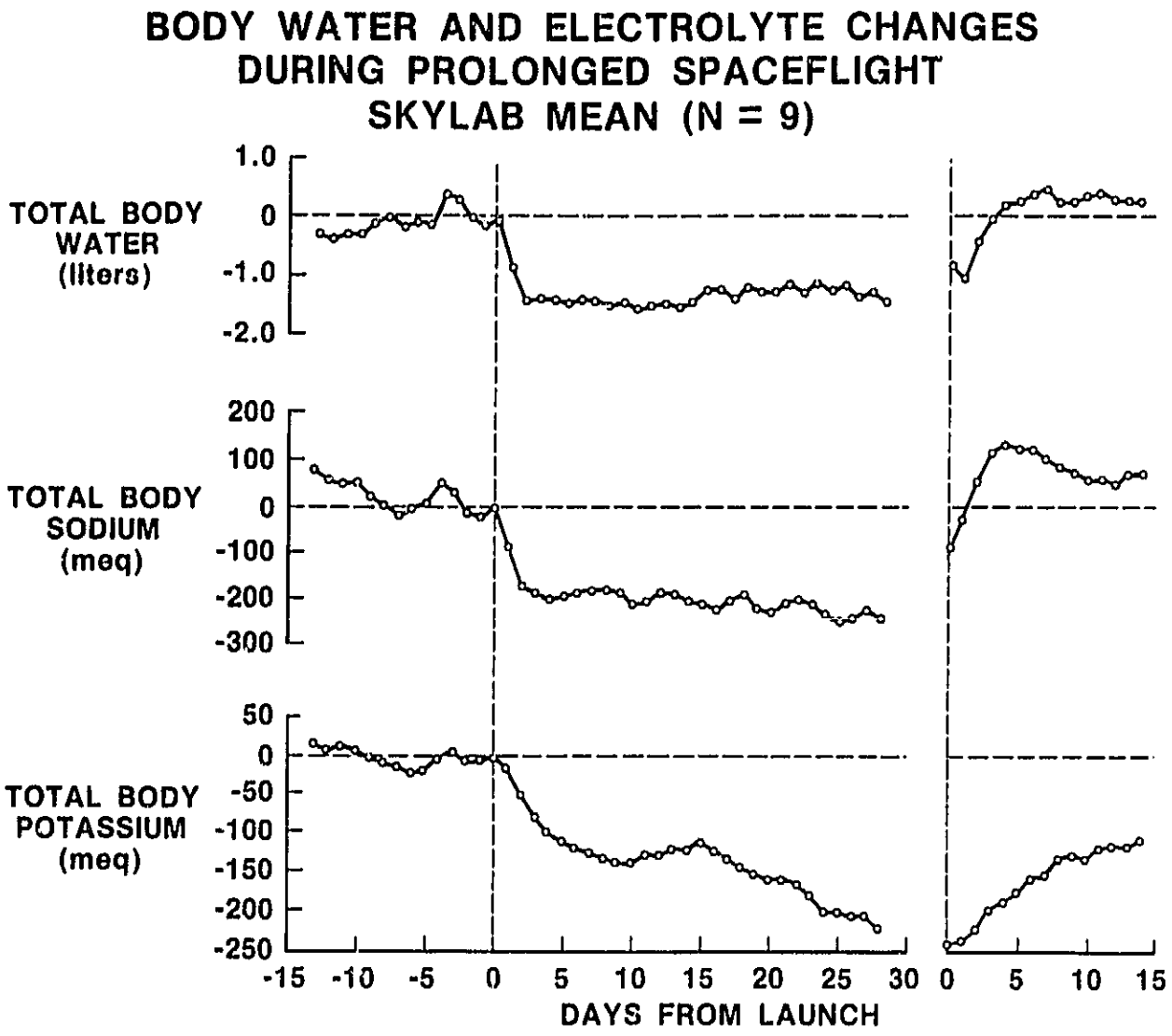
fluid was replenished. However, body mass continued to decline gradually as a result of losses of body fat and protein. In comparison, body mass and water levels essentially stabilized after several days of flight on the 84-day mission. Losses of fat were much less significant on that mission, presumably because caloric intake was more adequate. On both missions, however, body protein appeared to diminish over a three-week period before it stabilized. This may possibly reflect a decrease in postural muscle mass (due to disuse) and be independent of the caloric content of the diet and the amount of exercise, both of which were somewhat greater on the longer of the two flights. Contrary to former expectations, energy requirements to maintain body weight in a working space-flight environment do not appear to be less than required on the ground.

Body water loss is derived from either intracellular or extracellular fluid. Clues to the behavior of these compartments can be obtained from the behavior of body water, sodium, and potassium (Figure 15). The loss of sodium, the major extracellular ion, from the body is much more rapid than the loss of potassium, the primary intracellular ion. Also, inflight water and sodium depletion parallel each other, as do potassium and nitrogen losses. (Nitrogen losses are shown as protein changes in Figure 14.) Taken as a whole, this data supports the notion that the initial loss of body weight in space flight is primarily a result of extracellular fluid loss, and that the more gradual loss of body mass reflects intracellular degradation.

Integrated Hypothesis of Space Flight Adaptation

The fluid-electrolyte observations and hypotheses discussed above are only one aspect of the human responses to weightlessness. Space-flight research has been multi-disciplined in approach and investigators in each area have revealed a wide variety of changes. While these changes have previously proven reversible on return to Earth, many of them are physiologically significant and not entirely understood. Opportunities for conducting research in space have been limited by infrequent flights and the high cost of gathering data. Only a small number of subjects have been studied and the types of measurements made on man have been limited. These limitations have precluded the systematic study necessary to elucidate the underlying mechanisms of the disturbances which have been only grossly described. Interpretation of the space-flight observations has, therefore, been largely a

FIGURE 15


BODY WATER AND ELECTROLYTE CHANGES
DURING PROLONGED SPACEFLIGHT
SKYLAB MEAN (N = 9)
TOTAL BODY WATER (liters)
1.0
0
-1.0
-2.0
TOTAL BODY SODIUM (meq)
200
100
0
-100
-200
-300
TOTAL BODY POTASSIUM (meq)
50
0
-50
-100
-150
-200
-250
-15 -10 -5 0 5 10 15 20 25 30 0 5 10 15
DAYS FROM LAUNCH

speculative effort, aided to a significant extent by ground-based analogs of weightlessness, mathematical simulation, and other more fundamental studies.

Our current understanding of space-flight physiology, which has resulted from this effort, is outlined in Figure 16. This attempt to formulate a unified view of the adaptive processes should be treated with appropriate caution, since some of the interconnections shown have not been confirmed by direct experimental evidence. Nevertheless, several broad ideas emerge, as follows. First, there appear to be a number of physiological systems which exhibit gross disturbances in weightlessness, including the cardiovascular, fluid-electrolyte, erythropoietic, musculoskeletal, and metabolic systems. Second, these disturbances appear to be attributable to several major effects of weightlessness, including the redistribution and loss of body fluids due to an absence of hydrostatic forces, a degeneration of load-bearing musculoskeletal tissues due to an absence of deformation forces, and a long-term alteration of the metabolic state as reflected by diet, oxygen consumption, and energy storage. Third, the most significant and consistent consequences of these fundamental changes include a change in body composition (loss of body weight, body fluids, and electrolytes), blood volume loss and alteration of blood biochemistry, cardiovascular deconditioning (decreased orthostatic tolerance, degraded exercise performance upon return to one-g), atrophy of musculoskeletal tissue (loss of calcium, potassium, and nitrogen), and short-term vestibular disturbances (space sickness). Fourth, the time course to achieve a new state appropriate for zero-g is different for each major physiological system, as indicated by the width of the interconnecting lines in Figure 16 and by the time course for adaptation sketched in Figure 17. And fifth, there is a high degree of potential interaction between the major subsystems, indicating that a true understanding of these repsonses requires a rigorous interdisciplinary approach.

Adaptation to weightlessness can be said to occur when the body adjusts to the primary influences of weightlessness and when the changes noted above reach a new steady-state level. Figure 17 is an attempt to show the time course for achieving a new state appropriate for zero-g which is different for each major physiological system. The most rapid effects are observed in the vestibular system and the systems which respond to fluid volume regulation, notably the fluid-electrolyte and cardiovascular systems. At the other extreme are the body structures which respond to more slowly acting forces and

FIGURE 16

INTEGRATED HYPOTHESIS OF PHYSIOLOGICAL ADAPTATION TO PROLONGED SPACE FLIGHT

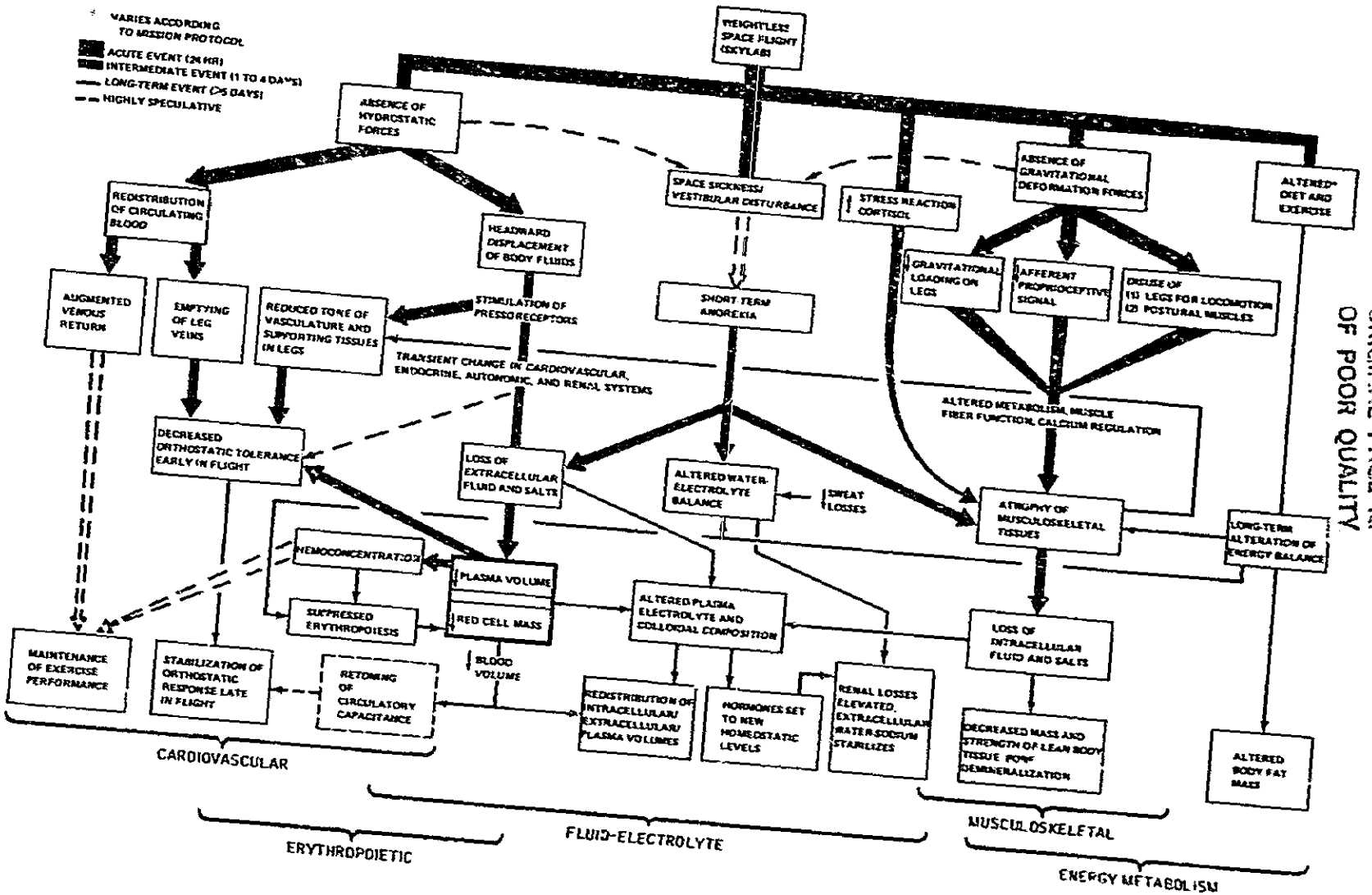
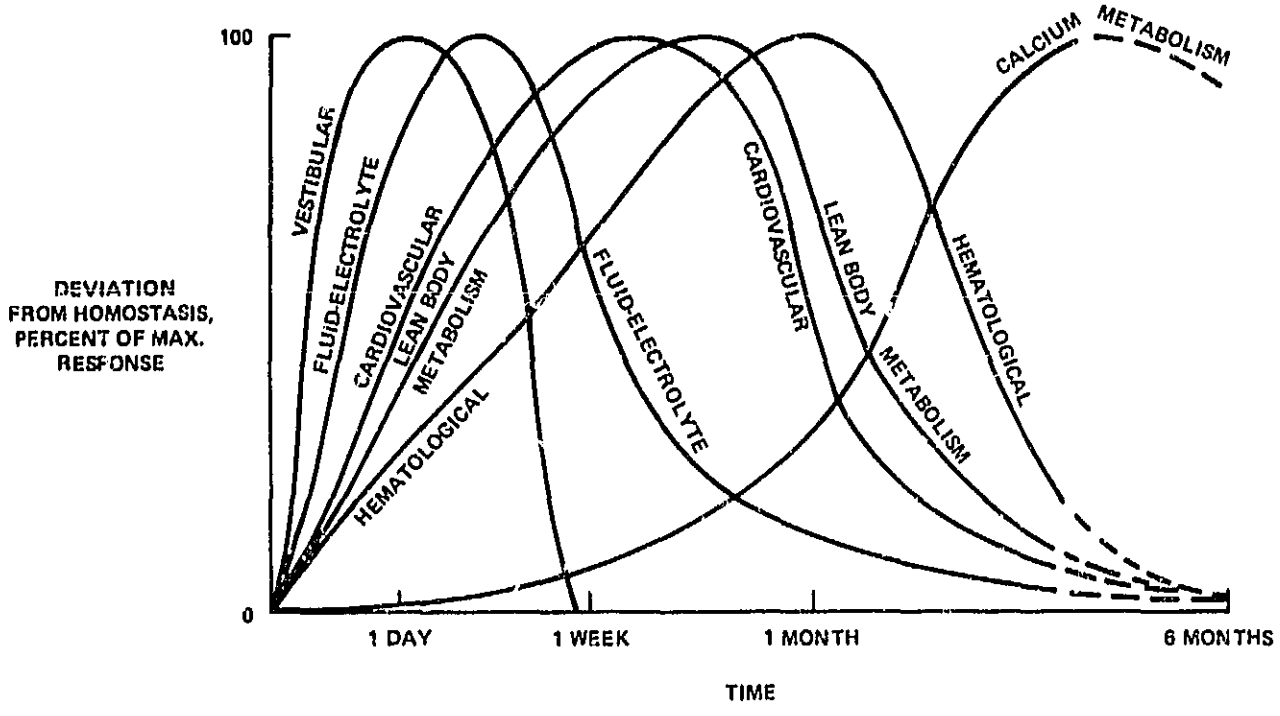


FIGURE 17

APPROACH TOWARD HOMEOSTASIS OF PHYSIOLOGICAL SYSTEMS DURING SPACE FLIGHT



which manifest their zero-g response by gross losses in red cell mass and bone calcium. However, even a slowly responding process such as bone demineralization is under the control of the more rapidly acting hormonal regulators. Muscle tissue appears to degrade at an intermediate rate, as exemplified by nitrogen and potassium losses. The loss of blood volume is believed to occur as a result of rapid decrements in plasma volume and more gradual changes in red cell mass, thus implicating the renal-endocrine and erythropoietic systems. In addition, the long-term adaptation of the circulatory system and its ability to respond to stress may depend, in part, on the manner in which the vascular elements accommodate to the reduced blood volume. The time course of adaptation for any of these systems is, undoubtedly, a function of the nature of the disturbance as well as the effective time constant of the correcting homeostatic system.

Future Work

Inasmuch as this research effort was concerned not only with the interpretation and integration of data in physiological terms, but also with specific mathematical models and simulation techniques, it is natural to consider the future directions of both of these areas. With regard to the tools of modeling, it is clear that the modified Guyton model has served well in studying complex, whole-body phenomena concerned with circulatory and fluid regulation. However, it is also apparent that the model is limited; it does not contain sufficient detail to allow the simulation of certain specific physiological behavior. Since the publication of the Guyton model in 1972, there have been advances in several areas which should be considered for incorporation into the model. The current renal subsystem, for example, lacks some of the known intricacies regarding peritubular capillary effects, third factor effects, and factors influencing intrarenal blood flow. Acid-base balance is not represented in the current model. A suitable acid-base subsystem model could assist in designing and interpreting future Shuttle experiments that will measure variables related to this system for the first time in space. Similarly, modification of the Guyton model's hormone regulating pathways should reflect current knowledge in this area, especially with regard to multiple and competitive influences, and identification of the different mechanisms which dominate short-term versus long-term control. Finally, a more realistic approach to mathematically simulating hypogravity

may involve changing the reference position of the model from the supine to the orthostatic position. Given these improvements, the model would become a better tool for analyzing space flight fluid-electrolyte/renal-endocrine physiology.

From an experimental viewpoint, it is possible to predict more rapid advances in data collection and hypothesis testing than has been witnessed in the past. No longer are observations limited only to pre- and postflight measurements, or to non-invasive measurements, or to studies on only a few crewmembers. The most pressing need in the fluid-electrolyte discipline is the information related to acute changes. Virtually no data has been collected during the first few hours of weightlessness, when many of the renal mechanisms for relieving fluid volume disturbances are believed to be activated. The Shuttle Orbiter (STS)/Spacelab is designed primarily for stays in space of less than 10 days, and therefore, is ideally suited for studying short-term phenomena. Important aspects of an acute study would be to confirm the expected headward volume shifts, disturbances of renal-regulating hormones, blood pressure disturbances, diuresis, enhanced renal clearances, and plasma volume reduction. Other experiments are required to study the influence of diet and circadian cycles on fluid-electrolyte status in general and the events which lead to plasma volume reduction in particular. The role of hormonal regulators of renal functions during the chronic or adaptive phase of flight is not yet clearly defined. A meaningful assessment of renal function would result from performing renal stress tests in humans (fluid loading, salt loading, dehydration) and from studying glomerular and tubular dynamics by renal micropuncture techniques in animals.

In response to these research needs, two comprehensive experiments, one on humans and one on primates, have been tentatively selected to examine renal-endocrine behavior during the first dedicated life sciences Space Shuttle/Spacelab mission (24,39). These two experiments are designed to examine the mechanisms responsible for adjustments in fluid and electrolyte homeostasis during both the acute (first day) and adaptive phases of the mission. Several other complementary experiments are scheduled which will study the mechanisms of erythrocyte loss and circulatory adaptation in the rat. The conceptual model which accounts for the rapid loss of extracellular fluid will be evaluated for the first time during space flight, concurrently in humans and primates. Circulatory mechanisms will be assessed by changes in blood

pressures, particularly venous pressure; heart rate and catecholamine levels will indicate sympathetic activity; the dynamic behavior of important renal regulating hormones will be observed by multiple blood samples; and renal function will be determined directly by clearance studies and collections of each urine void. In this way, the relative influence of the major pathways available for correcting rapid volume disturbances in zero-g can be evaluated. Similar measurements will be performed at other times later in the mission to assess the rate of adaptation during the seven-day space exposure. By this means, some of the puzzling aspects of endocrine adaptation may be resolved. In addition, body fluid volume studies in humans will be conducted to test the hypothesis that these compartments tend to equilibrate within several days of flight. The requirement for collecting frequent urine voids affords the unique opportunity to observe circadian rhythms in the urinary constituents in both humans and primates and to investigate circadian modulation of the renal response to cephalad fluid shifts. Supporting ground-based studies for these experiments include head-down tilt for human subjects and lower body positive pressure for primates. The inflight data will be used to confirm these one-g models for their applicability to study fluid shifts during weightlessness.

Conclusion

In summary, these metabolic-balance simulation studies indicate that a significant portion of the known responses to weightlessness can be explained in terms of normal, although complex, feedback-regulatory processes. Mathematical simulation has been shown to complement and extend routine statistical analysis of data by predicting (not extrapolating) beyond the observed results and describing behavior of parameters not easily measured. The human systems examined here are complex in terms of the numbers of relationships connecting various elements. Therefore, models which purport to address these problems must also be complex because they must include many competing and redundant pathways and contain the major components of the renal, circulatory, hormonal, neural, and fluid-electrolyte subsystems. The approach discussed in this report has been valuable in evaluating hypotheses and important mechanisms, identifying elements requiring further experimental description, providing a basis for analysis of selected data, and assisting in the development of a general hypothesis for gravity unloading.

This work was supported by the following NASA contracts:
NAS9-12932, NAS9-14523, NAS9-15487, NAS9-16328, NAS9-15850, and NAS9-17151.

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APPENDIX

INTEGRATED METABOLIC BALANCE ANALYSIS

This appendix describes the analytical techniques which were employed to determine major changes in body composition including alterations of fluid volumes, electrolytes, and metabolism in the Skylab crewmembers. The fluid and electrolyte system of interest has been presented previously in Figures 1 and 2. Some of the quantities or fluxes shown in those illustrations were measured directly either during the flight on a daily basis (as in the case of plasma concentrations), or at the beginning and end of flight (as in the case of body fluid compartments). The specific space-flight measurements used in this analysis are summarized in Figure A-1. It was a major objective of the post-Skylab period to assemble this diverse and voluminous collection of data, develop the appropriate analytical techniques, and ultimately derive a quantitative explanation of body weight loss in soace flight showing dynamic behavior of body water, body protein, and body fat.

The integrated metabolic balance approach that developed is illustrated schematically in Figure A-2. This approach was based on fundamental equations of conservation for mass, water, and energy, and enabled a comprehensive characterization of body changes which occur during extended space flight. Some quantities listed in Figure A-2 were not measured directly, or were measured very infrequently. These included body water, body sodium, body nitrogen, body fat, evaporative losses, and metabolic water. Application of standard metabolic analysis combined with several new techniques permitted these quantities to be derived in sufficient resolution so as to provide their time-varying behavior as well. One of these new techniques was based on combining metabolic balance and total body determinations of a specified quantity in such a manner as to allow cumulative balances to be computed without accumulating the large statistical errors that normally occur when this is done. A second innovative technique that was employed was the use of a mathematical model of whole-body fluid-electrolyte regulation. Computer simulation of this model for a weightlessness state, driven by the recorded

crew dietary intake of water and salt, resulted in plausible estimates of daily changes in such quantities as the major fluid compartments, evaporative losses, electrolyte concentrations, and the hormones that regulate renal excretion. Typical simulations of the Skylab mission have been shown in Figure 8. Some of these parameters were not amenable to experimental measurement, and, therefore, these model predictions complemented the collection of data. Also, the mathematical model provide a means to understand the feedback control mechanisms which regulate the volumes and fluxes illustrated in Figure 1. By this dual approach (data analysis and model simulation), it was possible to interpret the Skylab metabolic balance findings in terms of an holistic theory of body fluid-electrolyte regulation as it is affected by weightlessness.

One primary issue of interest in a body composition study in a space environment is "why do astronauts lose weight in space"? This question can be answered in terms of changes in body composition and energy balance. Figure A-3 illustrates the mass and energy balance factors which enter into the equation describing body mass changes. The changes in body mass can be discussed from several vantage points as shown in this figure. From an energy balance vewpoint, the loss of body tissue, particularly body fat, implies an imbalance between caloric intake (diet) and caloric output (basal metabolism + exercise). From a mass balance viewpoint, body mass can change in accord with alterations in three major substances: muscle (dry), fat, and water. The changes in body water, in turn, can be said to be caused by changes in one or more components of the water balance: intake, metabolic water, urine, fecal water, and evaporation. Also, it is possible to trace the loss of body water to the major fluid compartments of the body, as shown in Figure A-3. All of these viewpoints are discussed in the various reports which integrate the energy balance, mass balance, water balance, and body fluid volume data of the Skylab astronauts. A selected bibliography related to the integrated metabolic balance analysis effort follows this appendix.

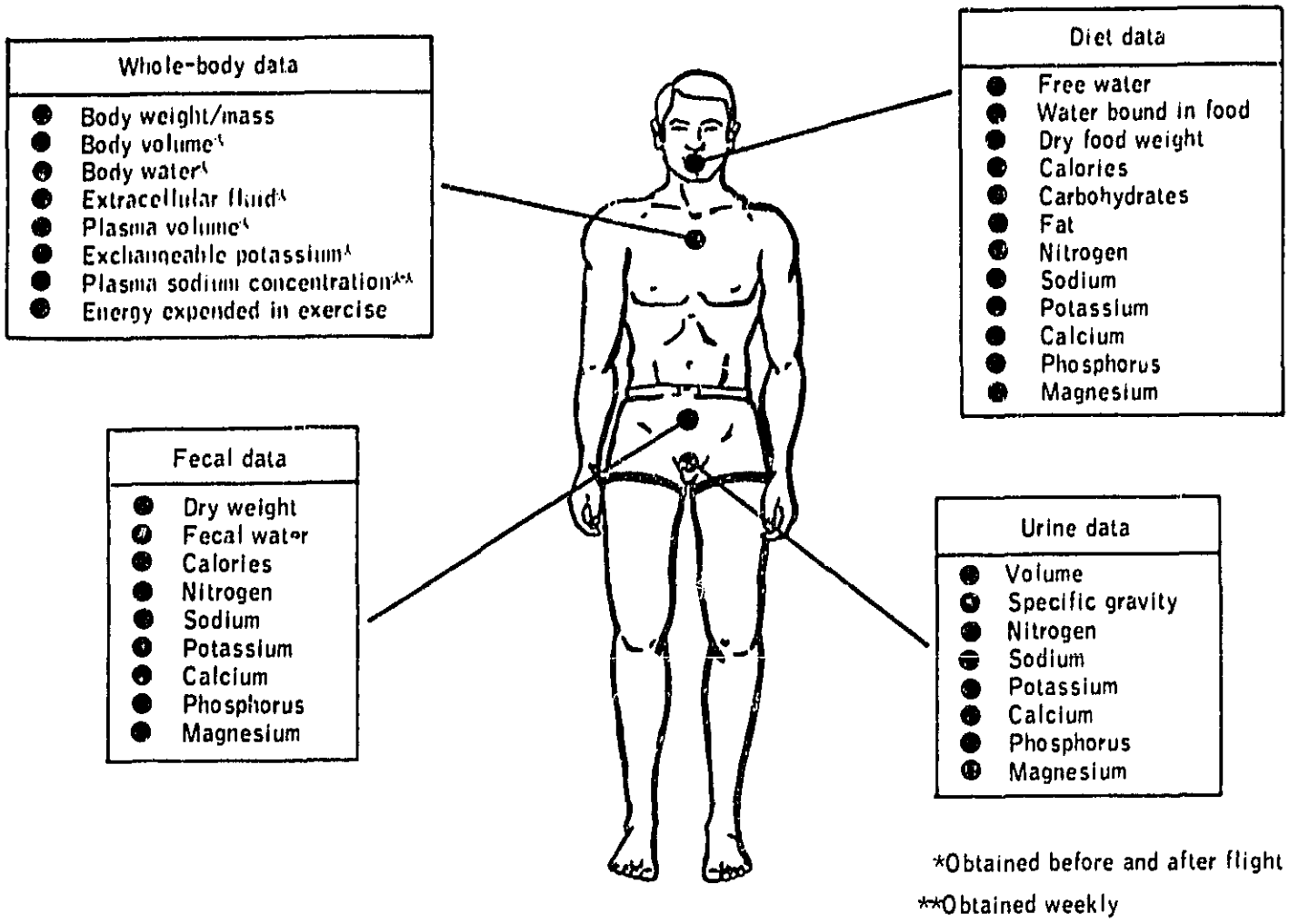
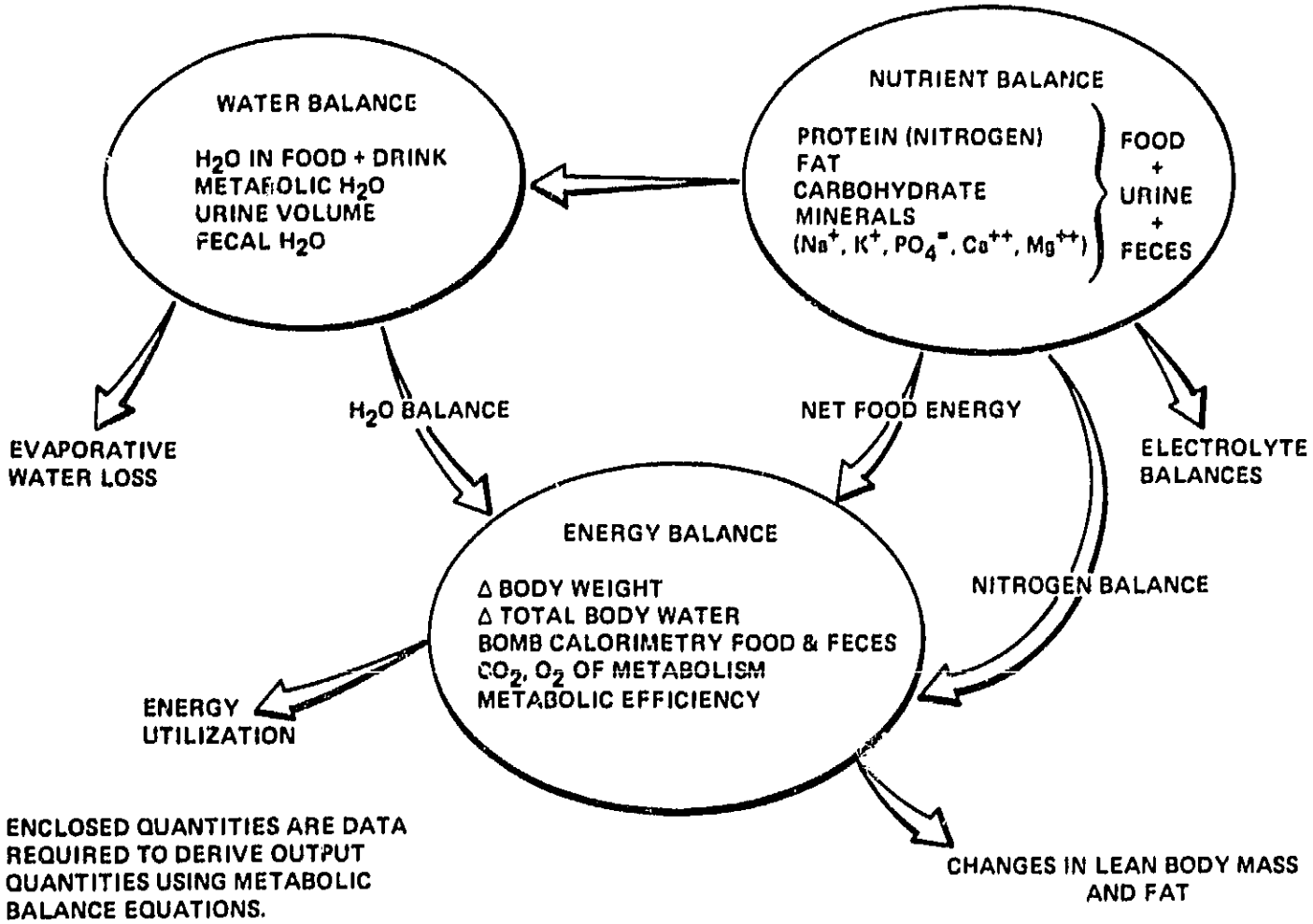


FIGURE A-1

METABOLIC BALANCE DATA COLLECTED ON SKYLAB CREW



INTEGRATED METABOLIC BALANCE ANALYSIS

FIGURE A-2

BODY COMPOSITION AND ENERGY BALANCE FACTORS RELATED TO BODY MASS CHANGES

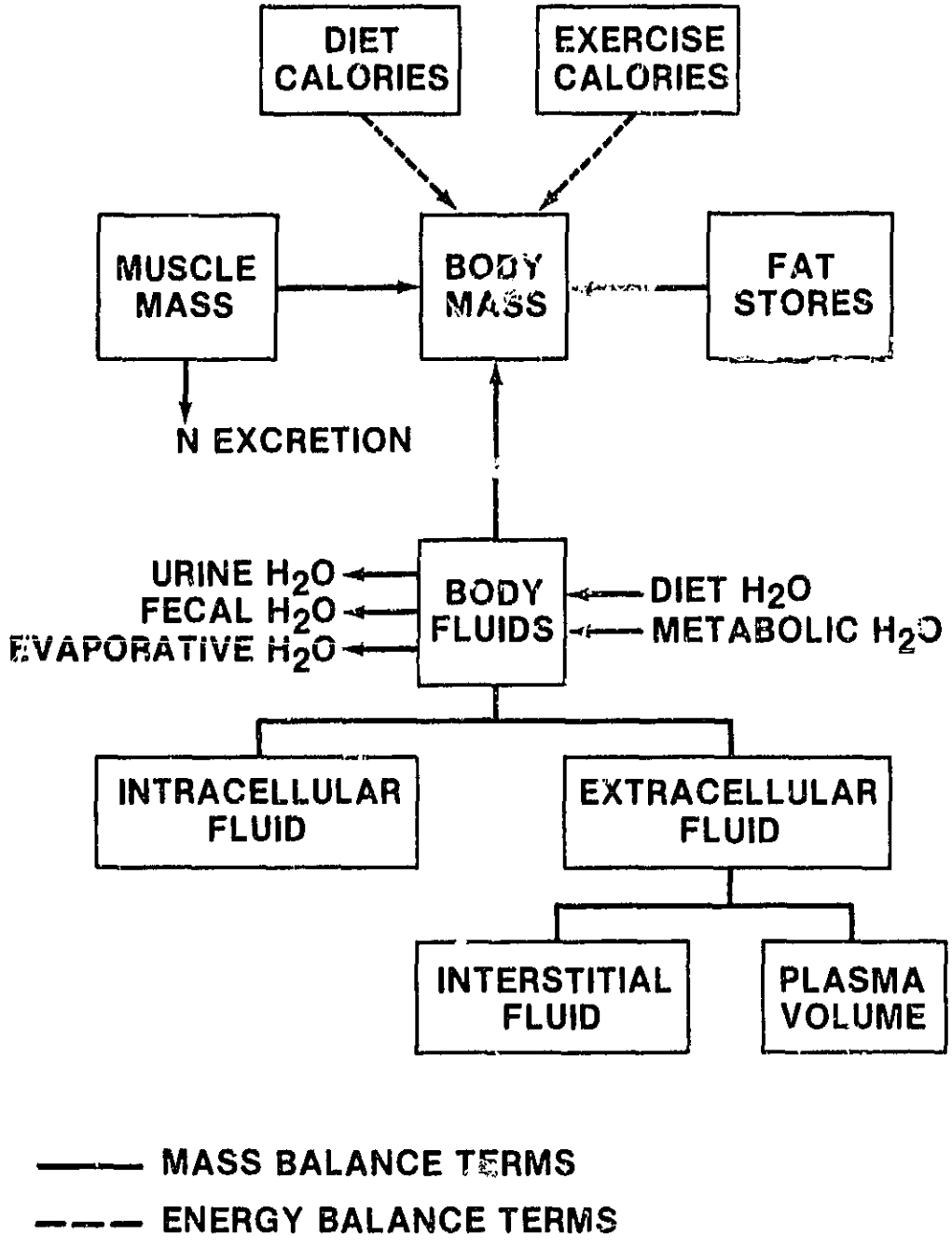


FIGURE A-3

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