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SUBJECT WATER IMMERSION AND ITS COMPUTER SIMULATION
AS ANALOGS OF WEIGHTLESSNESS

Water immersion experiments and computer simulations of water immersion are discussed in this report with regard to their utility as analogs of weightlessness. Emphasis is placed on describing and interpreting the renal endocrine, fluid, and circulatory changes that take place during immersion. Limitations of both experimental and theoretical approaches are discussed. Where possible, water immersion is compared to other experimental analogs of zero-g.

It is concluded that water immersion studies are valuable in understanding the short-term responses to weightlessness that result in the loss of body fluids and electrolytes. Furthermore, the Guyton model of circulatory, fluid, and electrolyte regulation is capable, not only of accurately simulating water immersion, but also of providing a means to study specific mechanisms and pathways involved in the immersion response. A number of hypotheses are evaluated with the model concerning the effects of dehydration, venous pressure disturbances, the control of ADH, and changes in interstitial volume. The discussion of mechanisms satisfies, in part, the task of this contract concerned with fluid-electrolyte regulation.

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WATER IMMERSION AND ITS COMPUTER SIMULATION

AS ANALOGS OF WEIGHTLESSNESS

Prepared by

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August 1982

WATER IMMERSION AND ITS COMPUTER SIMULATIONS

AS ANALOGS OF WEIGHTLESSNESS

ABSTRACT

Experimental studies and computer simulations of water immersion are summarized and discussed in this report with regard to their utility as analogs of weightlessness. Emphasis is placed on describing and interpreting the renal, endocrine, fluid, and circulatory changes that take place during immersion. A mathematical model, based on current concepts of fluid volume regulation, is shown to be well suited to simulate the dynamic responses to water immersion. Further, it is shown that such a model provides a means to study specific mechanisms and pathways involved in the immersion response. A number of hypotheses are evaluated with the model related to the effects of dehydration, venous pressure disturbances, the control of ADH, and changes in plasma-interstitial volume. By inference, it is suggested that most of the model's responses to water immersion are plausible predictions of the acute changes expected, but not yet measured, during space flight. One important prediction of the model is that previous attempts to measure a diuresis during space flight failed because astronauts may have been dehydrated and urine samples were pooled over 24-hour periods. It is suggested that future studies should include the requirements that subjects are well hydrated and that urine voids be collected during the first few hours of flight.

WATER IMMERSION AND ITS COMPUTER SIMULATION AS ANALOGS OF WEIGHTLESSNESS

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True weightlessness is achieved only in space flight, and thus, only in circumstances which make the detailed study of its effects difficult or impossible. This was true for the manned flights that preceded Skylab, because movement in the small space cabins was highly restricted; it was also true for the shirt-sleeve research workshop of Skylab where measurements were limited by operational constraints. Similar operational constraints prevent detailed measurements during routine Shuttle flights. Imperfect methods of simulation must, therefore, be used, in order to gather data and develop hypotheses; bed rest and water immersion have come to be accepted as reasonable approximations of the weightless state. This report is concerned with an analysis of water immersion in relation to its ability to simulate weightlessness.

An hypothesis guiding the present analysis is that the circulatory, renal, and fluid-electrolyte responses to weightlessness are initiated by a redistribution of the blood volume; this leads to an engorgement of the headward regions of the circulation and a partial emptying of the peripheral vessels in the legs. Immersion of the body in water has proved to be an excellent means of simulating and examining the details of this condition. In addition, water immersion has proved to be a useful tool for studying volume homeostasis and renal physiology in man (Epstein, 1978). It is primarily from these investigations that most of the theories regarding the very early effects of zero-g on fluid balance and blood volume control have been obtained. No comparable data have been collected during space flight, or, to a large extent, during supine bed rest.

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The redistribution of blood during water immersion is mediated primarily by a hydrostatic pressure gradient (pressure exerted on body surfaces increases by 22.4 mm Hg per foot of water depth) acting on the vascular columns of the body. This increase in transmural pressure forces blood and other body fluids from the lower extremities toward the cephalad region and central venous pool. In true weightlessness (i.e., during space flight), no such external forces exist. Rather, the normal elastic forces and muscle tone of the limb tissues propel fluids headward in the absence of the pooling effects of gravity. Nevertheless, the nature of the fluid redistribution and especially the regulatory responses which occur during water immersion have been presumed to be similar to those which take place during weightless space flight (Gauer, 1975).

In terms of fluid volume regulation, the two most significant responses to the blood redistribution resulting from water immersion are an acute diuresis and a reduction in the plasma volume. While the plasma volume loss is a nearly consistent finding in subjects returning from space missions, the expected diuresis has not yet been measured during any flights. Urine voids from the Skylab crew were pooled over a 24-hour period and showed decreased urine flow during the first several flight days. One of the challenges of the present analysis has been to examine the factors which may have led to this possible discrepancy between the expected and observed responses. Toward this end, the use of a computer model of the circulatory, fluid and electrolyte systems, has proved to be most valuable.

This study of water immersion will be discussed in terms of: a) a review of the overall physiological responses, including a conceptual framework with

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which to view the interrelationships between these responses, b) an analysis of computer simulations of water immersion with emphasis on certain factors that can alter the renal response, and c) a discussion of the limitations of immersion techniques as analogs to zero g.

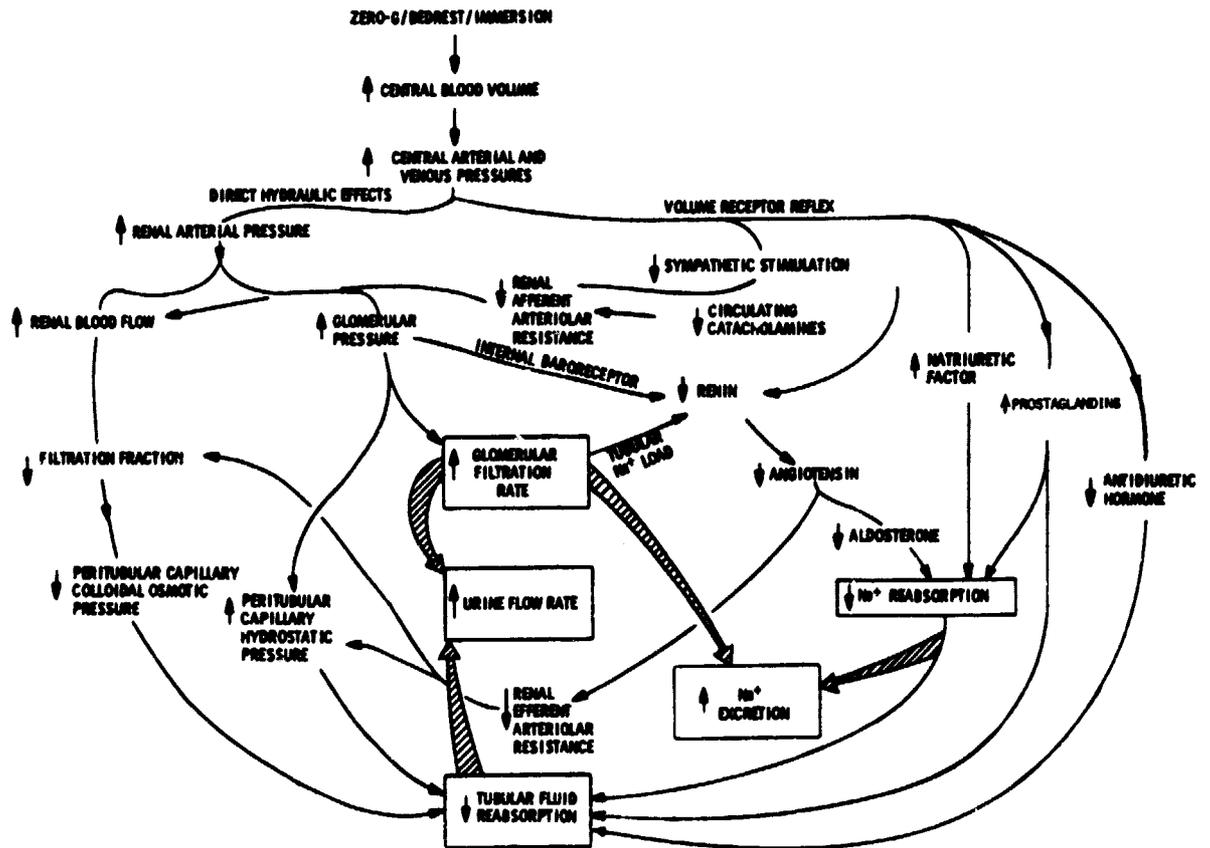## 1.0 PHYSIOLOGICAL RESPONSES TO WATER IMMERSION

Water immersion studies whose findings are directly applicable to the space-flight program have typically been directed toward studying only one of three broad physiological systems including circulatory control, fluid volume regulation, and renal-endocrine responses. The following description represents a composite picture of the immersion response as taken from a variety of sources and summarized in several recent reviews (Gauer, 1975; Epstein, 1976, 1978; Kollias et al., 1976). The major physiological pathways involved in producing the diuresis, natriuresis, and reduction in plasma volume associated with water immersion are illustrated in Figures 1, 2, and 3. Not all of the mechanisms shown have been conclusively demonstrated in the intact, normal, immersed human subject. However, experimental findings and computer simulation studies do support these hypotheses. Typical experimental results related to renal, endocrine and hemodynamic changes are shown in Table 1 and Figures 4, 5, 6, 7, and 9, and are discussed below.

Circulatory Response

The primary effect of water immersion can be characterized by the translocation of fluid from the leg (*) to the upper body, primarily the intrathoracic compartment. In addition to the intravascular movement of blood, there also appears to be a significant increment in plasma volume(*)
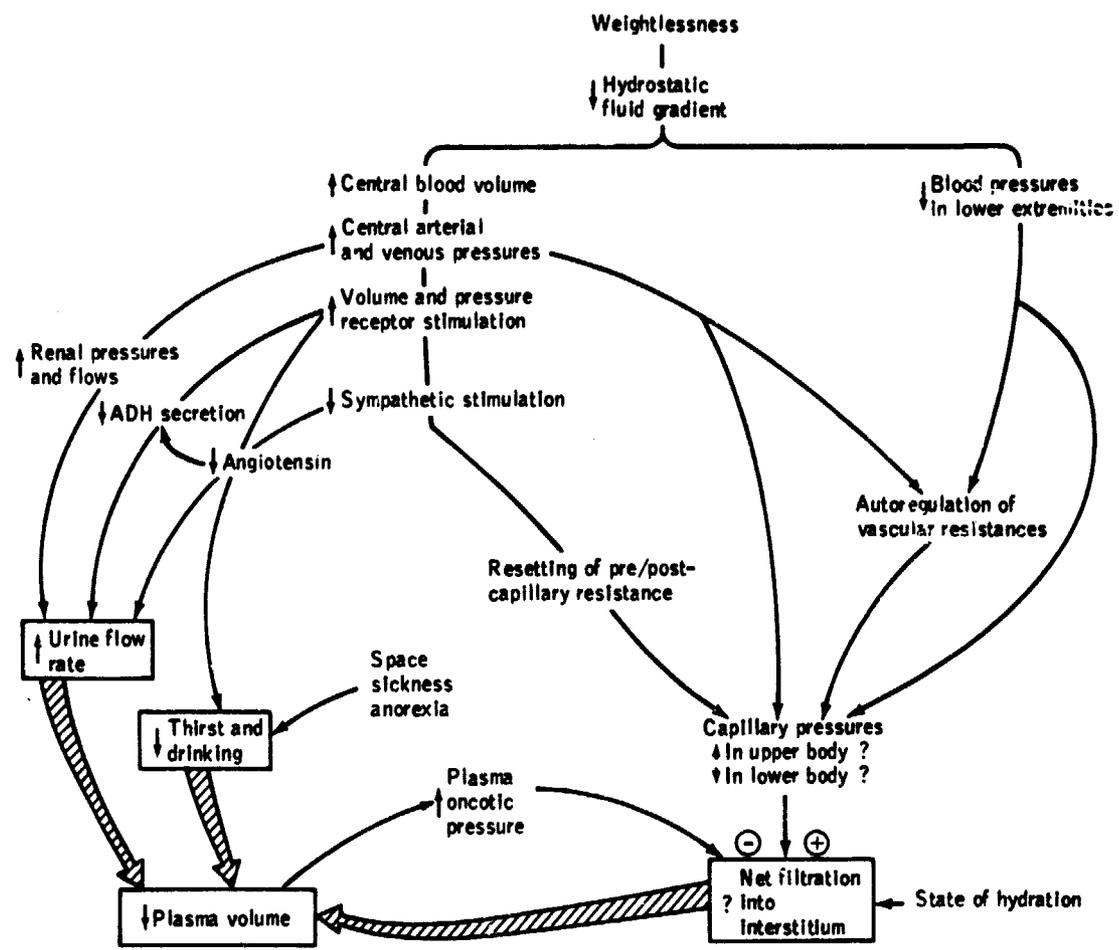
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* Immersion responses that are starred have been successfully simulated by the mathematical model of circulatory, fluid, and electrolyte regulation. These will be discussed in Section 2.0 of this report.

PATHWAYS AFFECTING RENAL EXCRETION

DURING ACUTE WATER IMMERSION

FIGURE 1

Weightlessness

↓ Hydrostatic fluid gradient

↓ Central blood volume

↑ Central arterial and venous pressures

Blood pressures ↓ in lower extremities

↑ Volume and pressure receptor stimulation

↑ Renal pressures and flows

↓ ADH secretion

↓ Sympathetic stimulation

↓ Angiotensin

Autoregulation of vascular resistances

Resetting of pre/post-capillary resistance

↑ Urine flow rate

Space sickness anorexia

↓ Thirst and drinking

Capillary pressures
↓ In upper body ?
↑ In lower body ?

Plasma ↑ oncotic pressure

⊖ ⊕

Net filtration ? into interstitium

State of hydration

↓ Plasma volume

PATHWAYS DETERMINING PLASMA VOLUME LOSS

DURING WATER IMMERSION

FIGURE 2

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POSTULATED EARLY EFFECTS OF SPACE FLIGHT
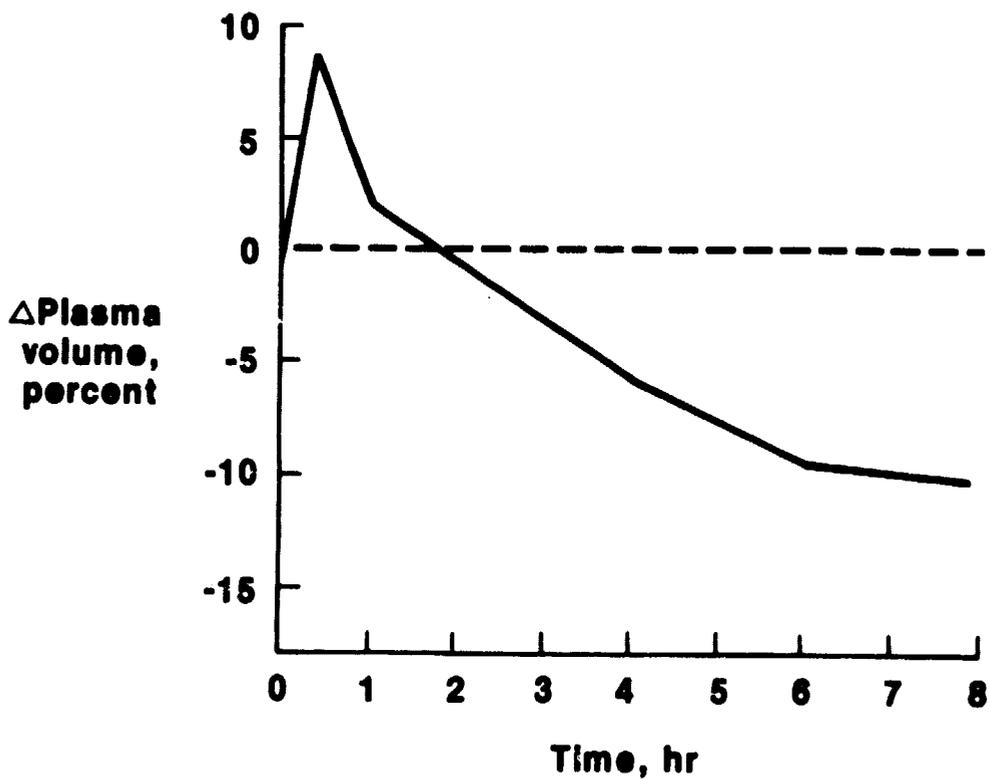## ON SODIUM EXCRETION PATHWAYS

FIGURE 3

TABLE 1

EXPERIMENTALLY DETERMINED WATER IMMERSION RESPONSES[*]
(MINIMUM OR MAXIMUM VALUES)

MEASUREMENT	CHANGE FROM CONTROL	TIME OF MEASUREMENT FROM START	REFERENCE[**]
Primary Effects:			
Central Blood Volume	+700 ml	10 min	A
Heart Volume	+180 ml	<1 hr	G
Central Venous Pressure	+12 to +18 mmHg	10 min - 3 hr	G,A
Intrathoracic Pressure	+5 mmHg	<1 hr	G,A
Transmural Pressure	+8 to +13 mmHg	<1 hr	G,A
Plasma Volume	+10%	<30 min	GL
Secondary Effects:			
Circulation			
Stroke Volume	+35%	10 min	A
Cardiac Output	+32% to +14%	10 min - 4 hr	A,E
Total Peripheral Resistance	-30%	10 min	A
Peripheral Venous Tone	-30%	3 hr	G
Arterial Pressure	+10 mmHg	10 min	A
Endocrines			
Anti-Diuretic Hormone	-50% to -88%	5 - 8 hr	E,GL
Renin	-75%	6 hr	E,GL
Aldosterone	-70%	5 hr	E
Renal			
Urine Volume Rate	+500%	1 - 3 hr	G,E
Sodium Excretion Rate	+50 to 125%	3 - 5 hr	G,E
Potassium Excretion Rate	+30%	2 hr	E
Volume			
Plasma Volume	-10 to -15%	5 - 8 hr	G,GL
Total Body Water	-1.5 liters/8 hrs	8 hr	G

[*]This table taken in part from
Gauer (1975).

[**] A = Arborelius & co-workers
E = Epstein & co-workers
G = Gauer & co-workers
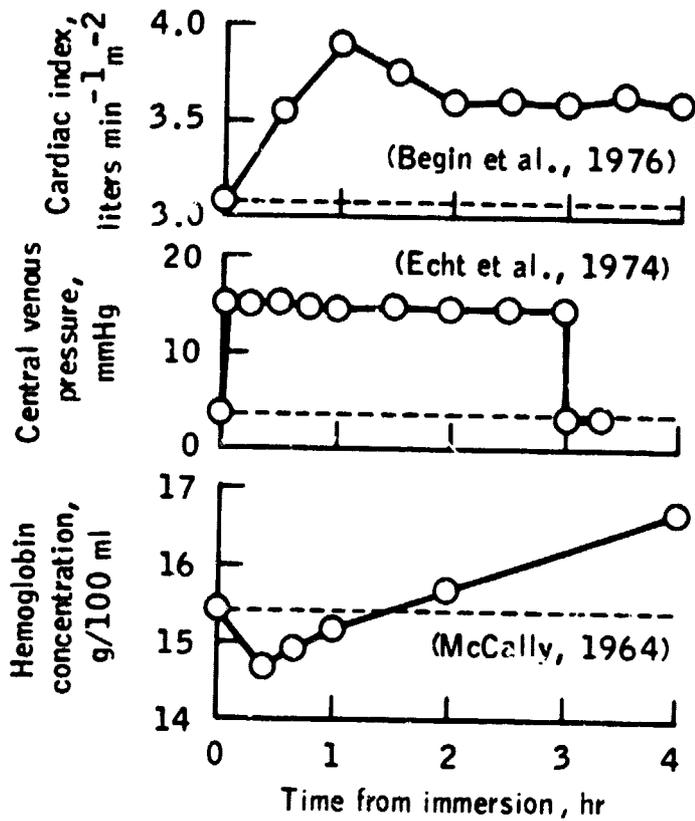GL = Greenleaf & co-workers

PERCENT CHANGES OF PLASMA VOLUME DURING WATER IMMERSION

(A COMPOSITE OF TEN STUDIES: DERIVED FROM GREENLEAF ET AL., 1980)
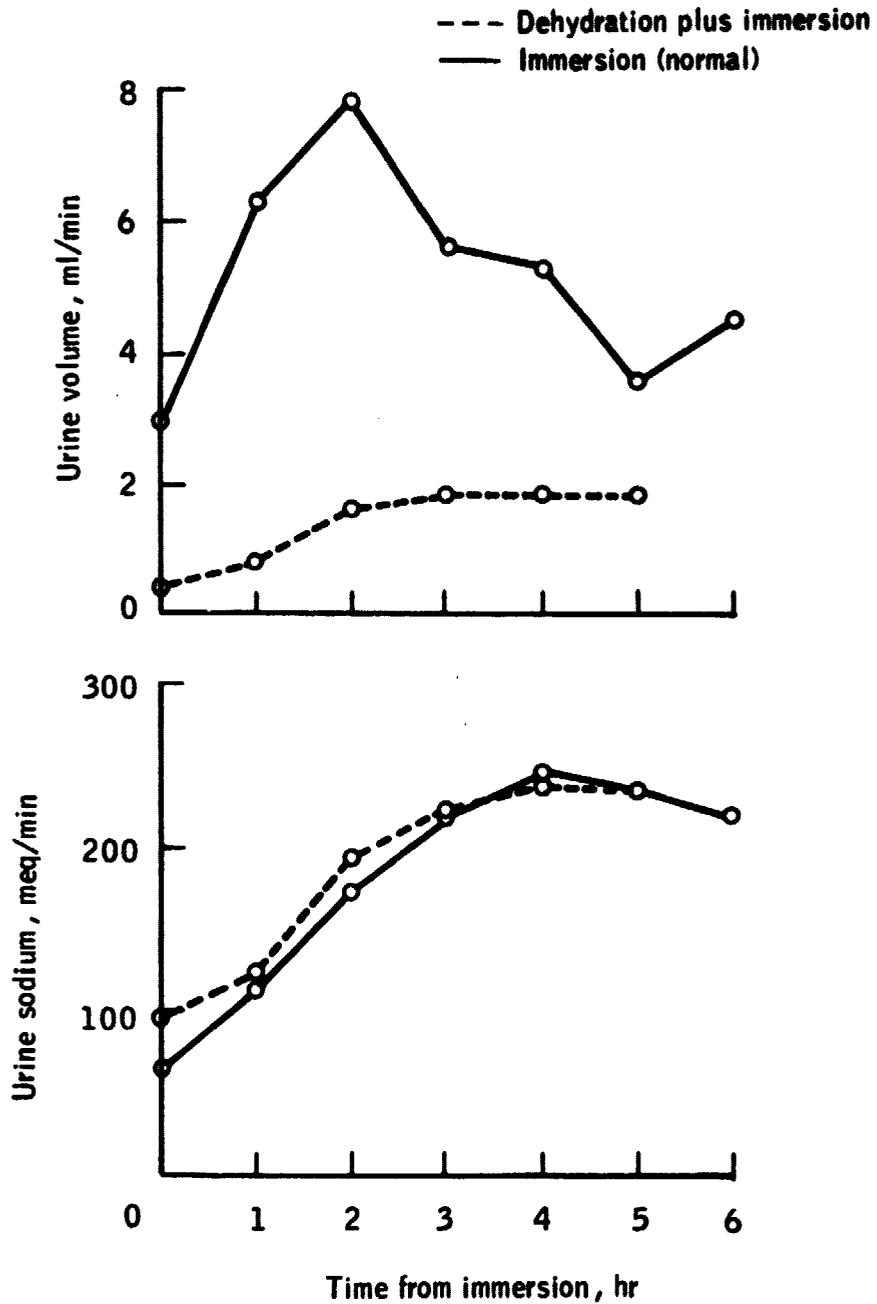
FIGURE 4

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HEMODYNAMIC CHANGES DURING WATER IMMERSION

FIGURE 5

(Fig. 4) demonstrated also by a transient decrease in hematocrit (*; see hemoglobin concentration, Fig. 5). The augmented plasma volume most likely results from interstitial leg fluid being forced, by external water pressure, into the leg capillaries. Increases in central blood volume, heart volume, and blood pressures (Fig. 5 and 9) in the central veins and pulmonary vessels have all been observed accompanying these fluid shifts (Arborelius et al., 1972).

Secondary cardiac effects, including increases in stroke volume(*), cardiac output (*), and decreases in heart rate (*), can be expected from this autotransfusion into the upper body. Autonomic reflexes are probably responsible for the observed decreases in total resistance (*) and venous tone of the peripheral circulation (Echt et al., 1974). These responses have been observed to reach their full magnitude within the first 10-15 minutes of immersion (Fig. 9).

Renal Response

Within the first hour, there is a dramatic rise in urine excretion of extracellular fluid (*) and salts (*) (the latter consisting primarily of sodium), which may continue for several hours before subsiding toward normal (Fig. 6). The urine formed is relatively dilute, demonstrating a free-water rather than an osmotic diuresis. In many studies, the peak urine flow occurs within the first few hours, while the natriuresis may reach a maximum somewhat later. This suggests independent mechanisms mediating renal water and sodium handling (Epstein, 1978). Potassium excretion is more variable than that of either water or sodium. The ratio of sodium to potassium in the urine increases, and this has been related to the opposite effects of aldosterone on the renal control of these two electrolytes.

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DIURESIS AND NATRIURESIS OF WATER IMMERSION

IN NORMAL AND DEHYDRATED SUBJECTS

(DRAWN FROM EPSTEIN ET AL., 1972 & 1975)

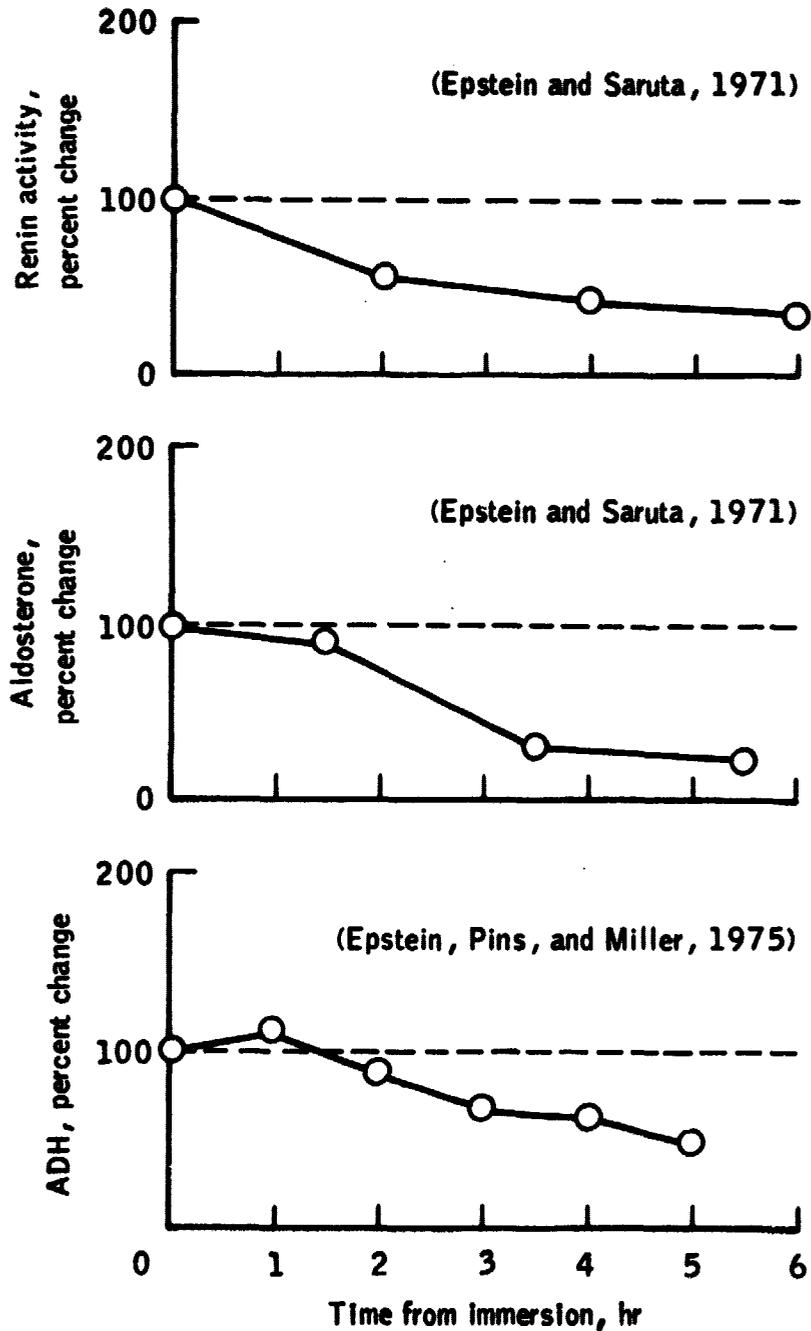FIGURE 6

Renal Mechanisms: Neural, Endocrine, Hemodynamic

There are numerous mechanisms available which can potentially contribute to the diuresis and natriuresis of water immersion. These include hemodynamic factors associated with the increase in central blood pressure, autonomic factors resulting from stimulation of the cardiopulmonary mechanoreceptors, and biochemical factors stemming from the release of the endocrines which regulate renal excretion (see Figs. 1 and 3). Although there is no clear agreement on which mechanisms predominate, all of these pathways appear to be responding to a central volume overload and lead to reflex compensation by reducing the volume of circulating blood (Figure 2).

The following neural-endocrine factors have been observed or proposed as possible mechanisms, all of which are a direct result of increased central blood volume and stimulation of cardiopulmonary receptors (see Figs. 1 and 3): a) suppressed ADH (*), b) increased prostaglandins (which normally inhibit the action of ADH), c) diminished sympathetic activity (*), d) suppression of the renin-angiotensin-aldosterone triad (*), and e) release of a humoral natriuretic factor (*) which has not yet been identified. In a recent review of the renal effects of immersion, Epstein (1978) suggested that the immersion diuresis is controlled by the first three factors (in the order of importance as shown), while natriuresis is under the regulation of ranked items (d), (b), (c), and (e). Some of the important hormonal changes that have been observed are illustrated in Figure 7.

In addition, hemodynamic effects arising from upper body blood expansion exist which are known to elicit increased renal fluid excretion. These include increased renal plasma flow (i.e., a pressure diuresis (*),

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ENDOCRINE CHANGES DURING WATER IMMERSION

FIGURE 7

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intrarenal flow redistribution, and altered renal peritubular forces (Leonard et al., 1977, and Vander, 1980). Evidence for a contribution of renal hemodynamic influences, however, is not strong (Epstein, 1978).

Fluid Volume Response

The net result of these events, in terms of body fluid volume, is a reduction in extracellular fluids (*). Approximately 20-25 percent of the total fluid loss from the body is derived from plasma (*). This proportion is expected inasmuch as the normal ratio of plasma/interstitial fluid is approximately 1:4. The increase in plasma volume at the onset of immersion, mentioned earlier, is therefore followed by a gradual decline of plasma volume below control as various volume-regulator mechanisms reverse the engorgement of the intrathoracic compartment.

The plasma volume reduction following 1-2 hours of water immersion (Fig. 4) may be a result of two independent effects: a) a diuresis of primarily extracellular fluid, and b) movement of fluid from the intravascular compartment into the interstitium of the upper body due to normal transcapillary filtration (*). The latter of these effects has been difficult to quantitate because it is not presently possible to distinguish between the decreased interstitial volume loss in the lower limbs and any increased interstitial volume in the upper body (see Fig. 2). Also, as will be discussed in the next section, the increase in blood pressure which favors transcapillary filtration is opposed by an increase in colloidal osmotic pressure which develops as plasma is lost from the circulation.

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Effect of Water and Salt Restriction

The above characterization of the immersion response is based on studies of well hydrated and otherwise normal subjects. It is known that the state of dehydration is an important determinant of the renal response, the fluid distribution, and the ultimate loss of body water during immersion (Gauer, 1975). The _relative_ increase in urine excretion of water (immersion response vs. pre-immersion response) is not significantly different between normal and dehydrated subjects who have been subjected to overnight fasting (Behn et al., 1969). However, compared to the immersion response in well hydrated subjects, the _absolute_ quantity of urine flow is blunted and the peak diuresis is delayed in dehydration, although the natriuresis response is unaffected (Epstein, 1978; see Fig.6). An attenuation in the natriuresis response does occur, however, if dietary sodium is reduced. In addition, compared to a well hydrated state, a dehydrated state appears to favor a much smaller contribution from the interstitial volume and a larger contribution from the plasma volume toward the total fluid loss. Plasma volume reduction, in dehydration, may be achieved not only by renal excretion, but also by outward filtration into a previously dehydrated interstitium (Behn et al., 1969).

Orthostatic Tolerance

Tolerance for orthostasis (as determined by lower body negative pressure and tilt table studies), and for exercise to a lesser extent, frequently has been found to diminish after water immersion tests (Kollias et al., 1976). This phenomenon is of importance to the health and safety of crews who have experienced problems with orthostasis upon return from space flight. Most investigators agree that the reduction in blood volume resulting from immersion is at least partially responsible for orthostatic intolerance, which

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is characterized by an increase in heart rate, a decrease in pulse pressure, and a tendency toward syncope. However, decreased sympathetic activity (as noted by reduced catecholamines) and reduced venous tone have also been recorded during immersion and have been implicated as contributing to greater venous leg pooling upon post-immersion standing.
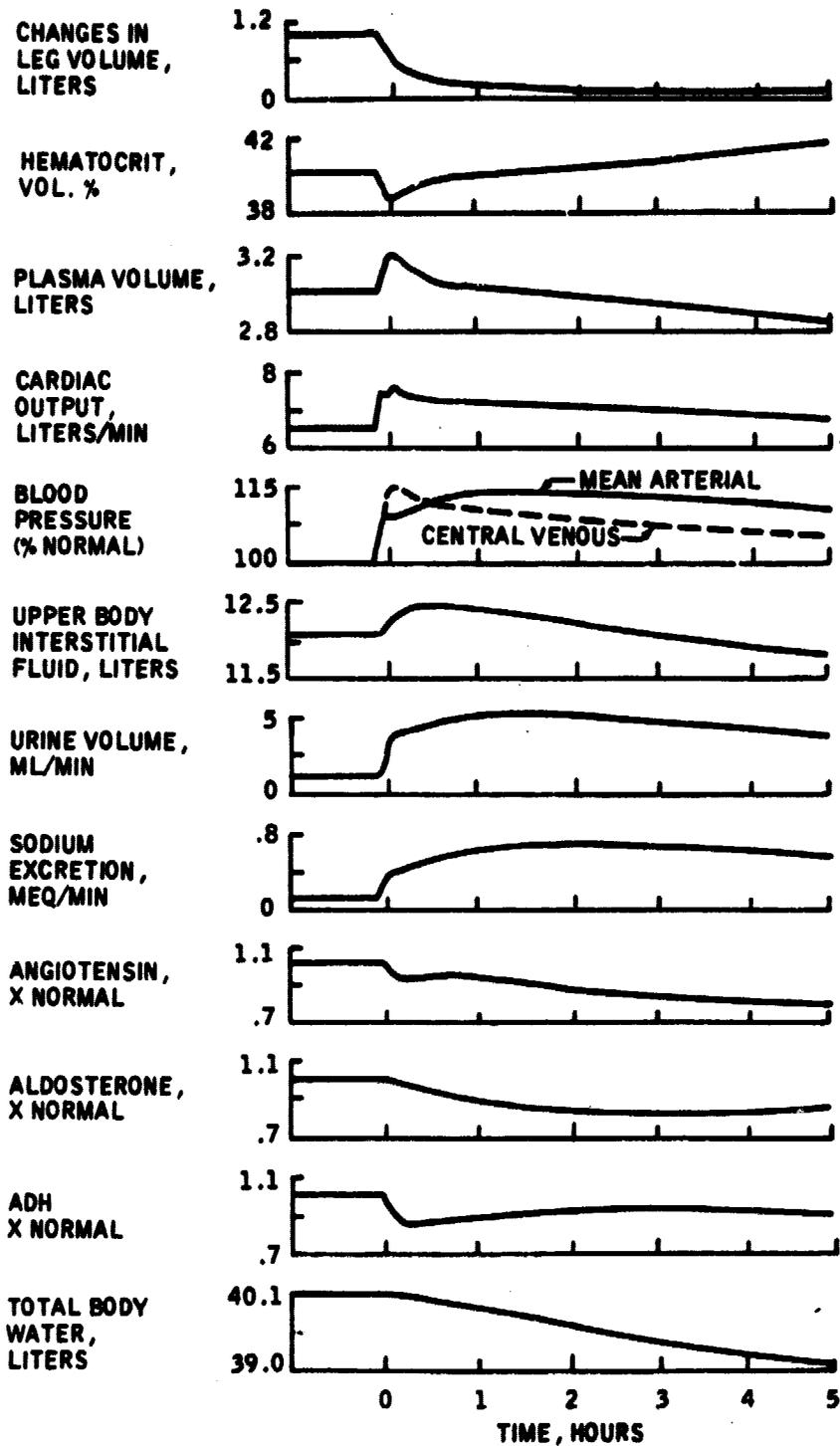
2.0 COMPUTER MODEL SIMULATIONS

The modified model of Guyton (see Appendix) was employed to study the theoretical response of the circulatory, renal, endocrine, and fluid volume regulating systems under conditions of a simulated water immersion experiment. The simulated dynamic responses to six hours immersion are shown in Figure 8 for selected quantities which have a known behavior. Agreement between the observed and simulated responses are quite reasonable as suggested by comparable data in Figures 4, 5, 6, and 7.

Simulations of immersion were performed by forcing fluids from the intravascular (500 ml) and interstitial (500 ml) leg compartments. The subsequent fluid redistribution in the upper body of the model was examined. No data exist to confirm whether these assumed headward fluid volume shifts during immersion are quantitatively realistic, but leg volume decrements totaling at least one liter have been recorded during orthostatic maneuvers from the erect to supine positions. This fluid shift consists off an acute 600 ml intravascular blood shift and a slower (30 min) 500 ml extravascular filtrate shift (Piemme, 1968; Henry, 1955). Furthermore, it has been shown that central blood volume increases by 700 ml immediately following immersion (Arborelius et al., 1972). The realistic behavior of the simulation response (with certain exceptions that are discussed below) attests to the basic validity of the model and the manner in which the controlling mechanisms are represented.

The fidelity of the model's hemodynamic response to a short-term (10 minute) immersion is indicated in Figure 9. A superior response was obtained by removing the short-term autoregulatory function of the model. This
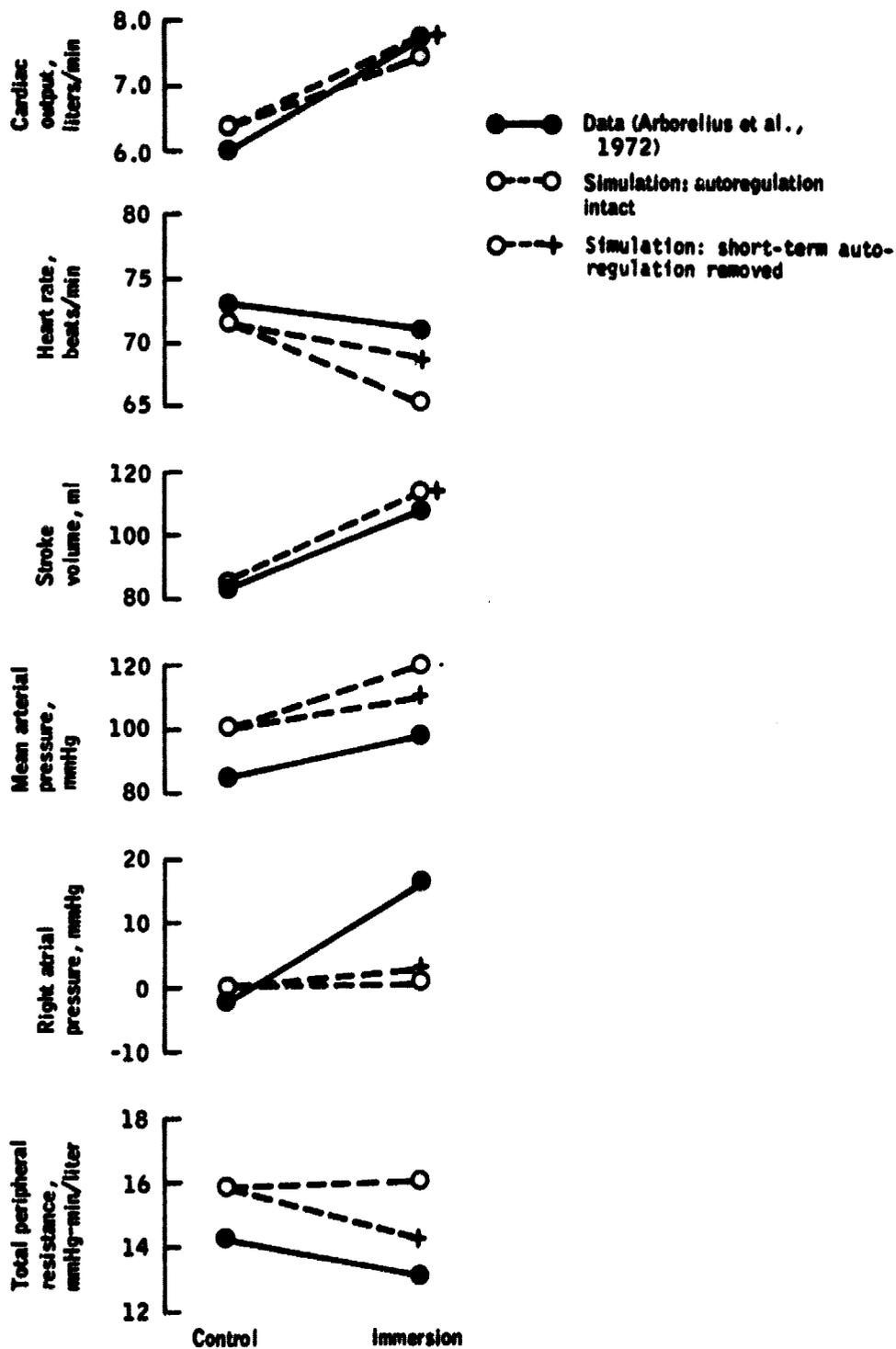
COMPUTER SIMULATION OF WATER IMMERSION

FIGURE 8

EXPERIMENTAL AND SIMULATED HEMODYNAMIC RESPONSES
TO 10-MINUTES WATER IMMERSION

FIGURE 9

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function was originally intended to permit arteriolar resistance elements to respond to short-term local pressure-flow disturbances. The increase in right atrial pressure observed in the human subject is not reproduced in the simulation. An improvement in the right atrial response, in particular, and in the immersion simulation, in general, may be accomplished by introducing a transthoracic pressure gradient in the region of the heart, which in immersion to the neck has been estimated as 20 cm H_2O (Regin et al., 1976). Aside from this discrepancy, the simulation of this very short-term response must be considered reasonable, especially since the circulatory, fluid, and electrolyte model was designed primarily to describe long-term events.
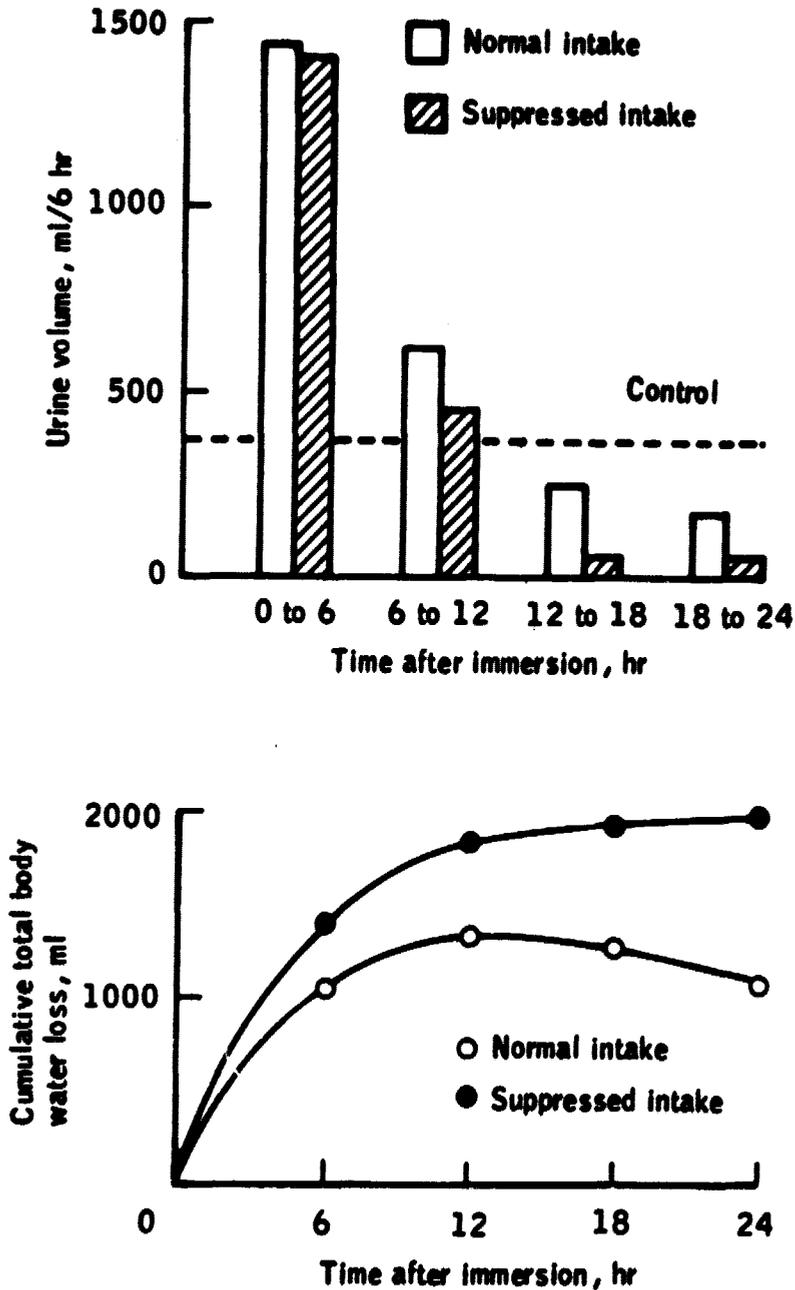
Although it is always desirable to obtain simulations which are in agreement with experimental data, the real value of a mathematical model lies in its ability to provide insight into the dynamic behavior of the system when there are multiple, redundant, and interrelated control pathways. A validated model can provide a theoretical framework by which to test hypotheses, analyze the mechanisms which contribute toward a given response, and identify areas which are ripe for experimental study. All of these benefits were realized to some extent in the present study, as the following discussion will demonstrate. In particular, four aspects of water immersion were given special attention. These include the effects of dehydration, the dynamic behavior of venous pressure, the dual control of ADH, and the importance of plasma-interstitial fluid shifts. They will be discussed below in this order.

Effects of Dehydration

Inasmuch as dehydration due to water restriction has been found to attenuate the immersion diuresis (Fig. 6), it is natural to consider whether

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this phenomena could explain the absence of a measured diuresis during the first day of space flight. The effects of dehydration during the immersion maneuver were, therefore, studied by computer simulation. Some of the results of these analyses are shown in Figure 10 and Table 2. Intake of fluid was assumed to be either normal or zero for the 24 hours preceding, and 24 hours during, immersion. During the first six-hour period of immersion, the urine volume response was predicted to be similar for normal and reduced intake (Fig. 10). However, increasingly significant differences between these two cases were observed for each succeeding six-hour period. As a result, the cumulative losses of body water (taken as the balance between renal excretion and drinking) were nearly twice as great for the dehydrated case as the normally hydrated case at the end of 24 hours. Admittedly, the use of zero fluid intake for simulating dehydration is extreme. However, it should be noted that fluid intake for some of the Skylab crewmembers was reduced as low as 60 percent below normal on the first inflight day (Leonard, 1977).

These studies generally confirmed the experimental results established by Gauer and co-workers (Behn et al., 1969; Gauer, 1975) with regard to the effects of dehydration on renal excretion and plasma volume regulation during water immersion (see Table 2). Specifically, a) during dehydration the absolute increase in water and sodium excretion is smaller (compared to normal immersion controls) and the percent urine increase is larger (compared to pre-immersion controls); b) immersion is characterized by a larger decrease in free water clearance in the dehydrated subjects compared to the hydrated subjects; c) the absolute decrease in plasma volume is more severe in hydrated subjects; and d) the contribution of plasma volume to excess urine volume excreted during immersion is greater for the dehydrated subjects than for the hydrated subjects.   22
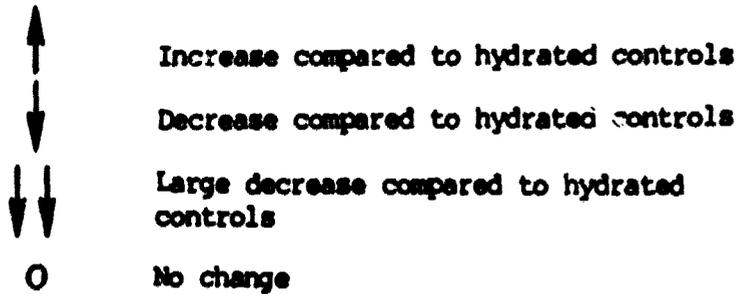
**EFFECT OF DEHYDRATION VIA SUPPRESSED INTAKE
ON SIMULATED WATER IMMERSION RESPONSE**

FIGURE 10

TABLE 2

EFFECT OF DEHYDRATION ON PRE-IMMERSION AND IMMERSION RESPONSE

	EXPERIMENT[*]		SIMULATION[**]	
	Pre-	Immersion	Pre-	Immersion
Urine Volume, V	↓	↓	↓	↓
Δ% V from pre-immersion		↑		↑
Urine Sodium, $U_{Na}V$	↓	↓	↓	O
Δ% $U_{Na}V$ from pre-immersion		↑		↑
Osmolar Clearance, C_{osm}	↓	O	↓	↓
Free Water Clearance, C_{H_2O}	↓	↓↓	↓	↓↓
ΔPlasma Volume, $\Delta PV_{immersion}$		↓↓		↓
$(\Delta PV/V)_{immersion}$		↑↑		↑

↑   Increase compared to hydrated controls

↓   Decrease compared to hydrated controls

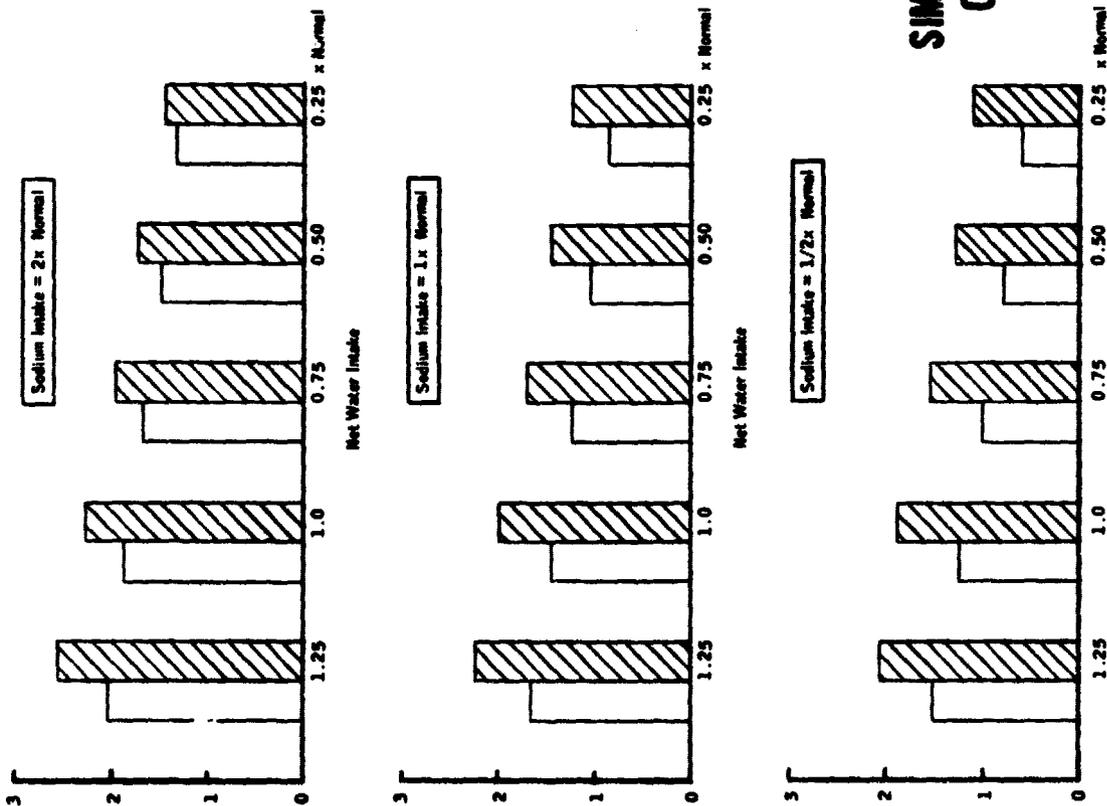↓↓   Large decrease compared to hydrated controls

O   No change

* Behn, Gauer, Kirsh & Eckert (1969)

**Guyton's Model of Circulatory, Fluid & Electrolyte Regulation

Disturbances in water intake are often accompanied by changes in salt intake. It was, therefore, of interest to examine the effects of simultaneous water and salt disturbances using computer simulation. A simulation study was designed to alter the dietary intake of both water and sodium and measure the urinary flow response over a 48-hour period. This time span included a 24-hour pre-immersion control period and a subsequent 24-hour immersion period. The results of this study are illustrated in Figure 11. On the left side are three series of bar graphs showing absolute urine volume. From top to bottom, these series represent twice, normal, and half-normal sodium intake, respectively. Within each series, water intake was allowed to vary between 0.25 of normal and 1.25 of normal. The blank bars represent the absolute urine volume excreted during the control period. The adjacent hatched bar indicates the immersion response during the subsequent period using the same dietary regime as the control. The three curves on the right side of Figure 11 are derived from the bar graphs and represent the relative change between each control and immersion set of urine responses.
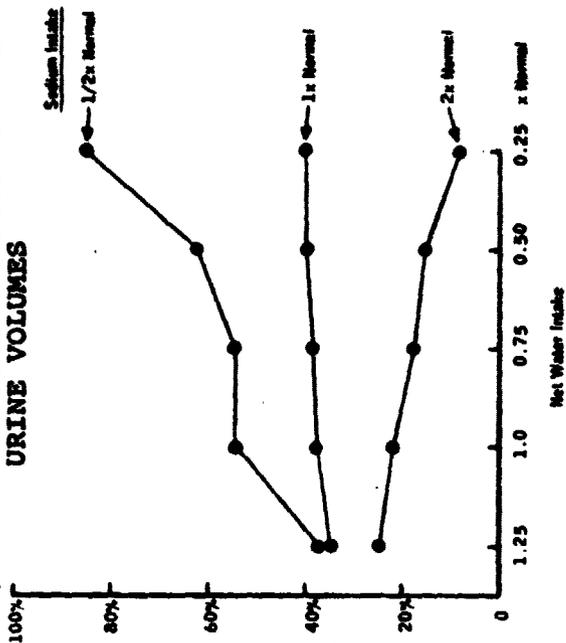
As expected, the absolute levels of urine flow decreases both during control and immersion as water intake decreases (see left side, Figure 11). Urine flow also decreases with reduced sodium intake, but the effect is much smaller than that due to changes in dietary water. In all cases studied, the urine flow during immersion increased in relation to its pre-immersion diet control; i.e., there was a relative diuresis. However, the degree of relative increase (shown on the right side of Figure 11) varied depending on the intake of water and salt. For example, if sodium intake is much lower than normal (upper curve on right) the relative diuresis actually increases when water

SIMULATED EFFECT OF WATER AND SALT INTAKE
ON URINE EXCRETION BEFORE AND DURING
WATER IMMERSION

FIGURE 11

intake is diminished. However, the relative urine change during immersion was apparently insensitive to changes in water intake when sodium intake was normal (middle curve on right).

How accurate are these model predictions? There have been no immersion studies performed which specifically attempted to measure the graded effects of simultaneous dietary water and salt disturbances on the immersion diuresis. However, by combining the results of several different studies it is possible to verify each of the generalizations discussed in the above paragraph. Specifically, the reader is referred to the immersion studies where subjects underwent overnight food and water restriction (Epstein, Pins, and Miller, 1975), normal and below normal water intake (Behn et al., 1969), normal sodium intake (Epstein, Katsikas, and Duncan, 1973), and 1/10 normal sodium intake (Epstein and Saruta, 1971).

Taken as a whole, these simulation studies on the effects of dehydration suggest that the relative proportions of water and salt in the diet could have a significant modifying effect on both the absolute, and especially, the relative diuresis found during water immersion. Although the model predicts that a relative diuresis will always be found irrespective of the water and salt load, it is possible to attenuate the immersion diuresis, by limiting water and salt in the diet, to an extent that it becomes less than a non-immersed control urine flow which is accompanied by a greater dietary intake. Therefore, it is possible that a diuresis which may be evident during the first few hours of immersion (or in space flight) could become obscured in a 24-hour pooled urine sample.

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Changes in Venous Pressure

A knowledge of the pressures in the low pressure side of the circulation (i.e., the central veins, the heart atria, and the pulmonary circuit) is of utmost importance in situations such as water immersion, head-down tilt, and weightlessness. The rise in these pressures accompanying headward fluid shifts reflects the magnitude of central hypervolemia (more so than pressures in the arteries), the degree of cardiopulmonary receptor stimulation which affects sympathetic and endocrine activity, and ultimately, the extent of homeostatic correction of the pressure disturbance by either volume reduction or increased vascular capacitance. In spite of the importance of this measurement, it is surprising that there is such a scarcity of data reflecting changes in the pressure of the venous circulation.

Two groups of workers (Arborelius et al., 1972; Echt et al., 1974) found a dramatic rise of 12-15 mm Hg in transmural central venous pressure at the onset of water immersion (Figs. 5 and 9). Following this initial increase there appears to be a slight, steady decline during the next three hours, the longest time for which venous pressure measurements are known in immersion. However, even after three hours, central venous pressure was considerably elevated. While a rise in venous pressure is in accord with the fluid-shift hypothesis presented earlier (see Fig. 1), the magnitude of this rise, and its dynamic behavior, is unexpected. According to an analysis of cardiac regulation performed by Guyton et al. (1973), an intravenous infusion of one liter of blood (similar to the 700 ml increase in central blood expansion measured in immersion) causes an instantaneous rise in central venous pressure similar to that measured in immersion. However, compensating mechanisms (e.g., reduced sympathetic activity, reduced resistance to venous return,

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stress relaxation and blood volume normalization) permit the venous pressure to return to normal within an hour or so. In addition, cardiac output following infusion rises much more sharply than measured during immersion, but then it also returns to normal. This is in contrast to the sustained increase during immersion of both cardiac output and venous pressure.

Other studies in which headward fluid shifts were induced were reviewed to help interpret the water immersion-venous pressure response. Unfortunately, no consistent story has emerged. In partial support of the immersion results are the findings from measurements of lower body positive pressure in monkeys (Kass et al., 1980) and in humans (Echt et al., 1974b). These results indicate an increase in central venous pressure that is maintained for several hours and possibly even several days (Moore-Ede, private communication). However, in head-down tilt studies lasting up to 24 hours in man (Gauer & Hull, 1954; Nixon et al., 1979), or up to 7 days in rats (Popovic, 1981), central venous pressure rises as expected, but in contrast to water immersion and lower body positive pressure findings, venous pressure (and cardiac output) then falls to control and, in some cases, below control. The possibility of venous pressure diminishing below control levels is of particular interest, because such a prediction was suggested from computer model simulations of bed rest some time ago (Fitzjerrell et al., 1975) and received confirmation by indirect pressure measurements during Soviet space missions (Yuganov et al., 1977). In addition to these observations regarding the dynamic behavior of venous pressure changes, it is also of interest to note that in none of the studies cited above do venous pressure measurements indicate increases of more than 3-5 mm Hg, in contrast to the increases of 12-15 mm Hg observed in water immersion. Computer model simulations support

the concept of a smaller change in venous pressure with an eventual decline below control (which occurs beyond the five hours shown in Fig. 8) as reflex compensation of vascular volume, capacitance, resistance, and flow takes place.

Thus, on the surface, it appears that the venous pressure response to water immersion is somewhat different than that observed for infusions, head-down tilt, and hypogravic maneuvers. It is possible that the central shift of fluids during immersion is large enough to cause much more severe increases in central venous pressure than occur with other stresses. However, measurements of the volumes of fluids shifted during these events are poorly documented. It is also possible that in water immersion to the chin, the 20 cm H_2O pressure exerted on the thoracic region is transmitted directly to the venous circulation and exaggerates the pressure response, although this is not likely. With regard to the dynamic behavior of venous pressure, it is possible that a return to normal pressure does occur within 10 hours of immersion (as suggested by the slow decline in measured central venous pressure and by the simulation model), but the necessary extended measurements have not yet been made. If that is the case, then the concept that all maneuvers that increase central blood volume (i.e., water immersion, lower body positive pressure, head-down tilt, supine bed rest, infusions, weightlessness) show a qualitatively similar reflex response becomes more tenable.

Control of ADH

Several investigators (Epstein et al., 1975; Greenleaf et al., 1980) have now documented the reduction in antidiuretic hormone (ADH) during water

immersion that was predicted some years ago by Gauer and Henry (1963). However, the factors which lead to the suppression of ADH are apparently still unclear. ADH is known to be responsive to two major types of control: volume control and osmo-control. Thus, inhibition of ADH can be expected in situations where central blood volume or pressure increases and where plasma osmolarity decreases. Inasmuch as one of the major characteristics of water immersion (and indeed all maneuvers which lead to headward fluid shifts) is the rapid increase in central venous volume, it would be expected, and is generally believed, that this pathway (i.e., Henry-Gauer reflex) is responsible for the measured reduction in ADH. However, several recent papers have suggested the importance of osmo-control of ADH during immersion (Greenleaf et al., 1981, Khosla and DuBois, 1979), underscoring the fact that this issue is not yet resolved.

The source of confusion in this instance may be summarized by the following evidence: a) increases in central venous volume and pressure during immersion have been measured and are believed to be sufficiently strong to suppress ADH (Gauer et al., 1970; Echt et al., 1974); b) several investigators have reported small but significant decreases in serum osmolarity and sodium concentration during immersion which could quantitatively account for the accompanying decreases in ADH (Greenleaf et al., 1981; Khosla and DuBois, 1979; Epstein et al., 1975); and c) despite the popularity of the Henry-Gauer reflex (which favors volume control of ADH) in the space life science community (Leach & Rambaut, 1977), more recent evidence has strongly suggested that blood volume changes are much less important than osmolarity in controlling ADH under physiologic conditions (Robertson, 1977). With regard to the last factor, it has been shown that ADH has a sensitive linear

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dependency on plasma osmolarity, while the corresponding sensitivity on blood volume is highly non-linear, showing little influence at small volume changes and a larger influence (larger than the sensitivity to osmolarity) at volume changes of about 15-20 percent of total blood volume (Dunn et al., 1973). It is important to note, however, that these measurements were not performed in humans. Furthermore, only the influences of low pressure and increased osmolarity on increases of ADH have been studied, and not the reverse situations leading to ADH suppression which is of prime interest in the immersion and acute weightlessness responses.

The mathematical model contains an ADH subsystem which is responsive to both plasma sodium concentrations and atrial pressure changes (see Fig. 12). In addition, there is a time-adaptive aspect to volume control contained in the model, whereby pressure changes, if maintained, exert a smaller and smaller influence on ADH. This is consistent with the concept that volume receptor tissues are elastic and adapt to changing pressures within reasonable periods of time (i.e., 24-48 hours) (Guyton et al., 1975). It is possible to vary the relative sensitivities of ADH to pressure and osmolarity, as well as the time period of adaptation. Therefore, this model becomes a useful tool for examining the ADH response to immersion when fluid volumes and electrolytes are in a highly dynamic state of flux. Using this model to simulate water immersion, our simulation results agree with the experimental findings that volume changes in the central circulation can instantaneously increase by about 700 ml (Arborelius et al., 1972), and that plasma sodium

DUAL CONTROL CONCEPT
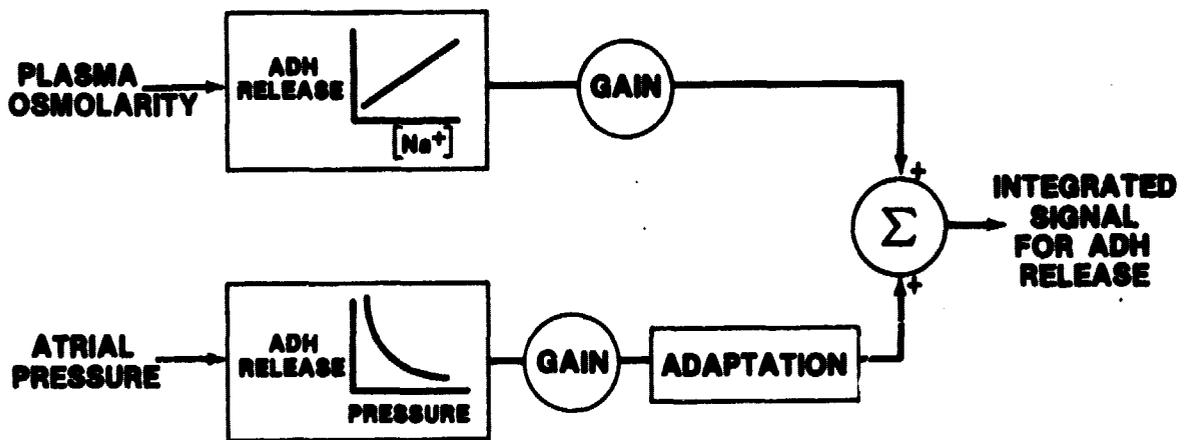# FOR ADH RELEASE
Osmo. vs Volume Control

FIGURE 12

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concentration can decrease by two percent (Greenleaf et al., 1981). Our model predicts that both of these changes are found to be sufficient stimuli for the suppression of ADH[*].

Inasmuch as the long-term dynamic behavior of venous pressure is not yet resolved, we have examined several different scenarios in order to predict potential effects on ADH. The results of these studies are illustrated in Figure 13. In all cases, it was assumed that hyponatremia develops upon immersion and that this has a suppressive effect on ADH. In addition, however, there is a venous pressure effect. It is assumed that venous pressure in one case remains elevated according to the predictions of Gauer and co-workers, or in another case returns to normal and perhaps below control according to the head-down tilt measurements of Blomqvist and co-workers. The conditions of volume receptor adaptation or no adaptation were also examined. In three of the five runs shown, ADH is predicted to remain below control throughout the simulated 24-hour period (longer than has been measured in water immersion) due to the effects of hyponatremia, elevated venous pressure, or pressure receptor adaptation. However, in two cases, it has been found that ADH could recover and possibly rise above control. This can occur in the situation where venous pressures fall and where the pressure/volume stimulus is controlling ADH (i.e., no receptor adaptation). If, in this same

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[*] The cause of the reduction in plasma osmolarity (i.e., hyponatremia) found in some studies of water immersion, as well as bed rest and space flight, is not known. It is not yet clear whether this is a characteristic typical of the prolonged hypogravic response. In our modeling studies, hyponatremia is produced as a result of a renal natriuretic agent. However, several investigators have hypothesized that during the acute stress of immersion there may be an influx of hypo-osmotic interstitial (and perhaps intracellular) fluid from the legs to the circulation (Greenleaf et al., 1981; Khosla and DuBois, 1979).

VARIOUS SCENARIOS OF ADH RESPONSE
DURING SPACE FLIGHT
(Assumes Hyponatremia)

A) VENOUS PRESSURE ELEVATED

B) VENOUS PRESSURE FALLS BELOW CONTROL

VENOUS PRESSURE

ADH

ADAPTATION

NO ADAPTATION

NO ADAPTATION AND VOLUME STIMULUS STRONGER
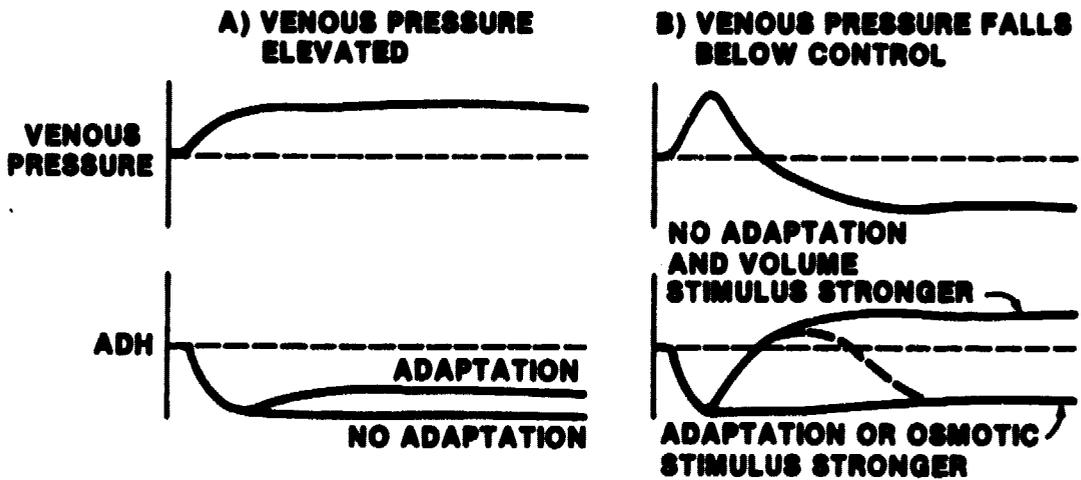
ADAPTATION OR OSMOTIC STIMULUS STRONGER

FIGURE 13

situation, volume receptor adaptation occurs, but is delayed, the model predicts a tri-phasic response. In this latter response, ADH first diminishes (under both pressure and osmo-control), then rises (under the control of a falling venous pressure) and, finally, falls below control as volume receptor adaptation occurs and osmotic stimuli take over regulation of ADH. This analysis suggests the importance of making careful measurements of blood pressure, serum osmolarity, ADH, and volume shifts during water immersion or space flight to distinguish between these several alternative scenarios.

Changes in Interstitial Volume

The reduction in plasma volume following immersion has been suggested to occur, not only via renal excretion, but also by outward filtration into the interstitium of the upper body (Gauer, 1975). It was possible, using computer simulation, to distinguish between depletion of the lower limb interstitium and expansion of the upper body interstitium, an analysis which would be experimentally difficult. The results were somewhat surprising.

If one considers the first four hours of immersion, a period during which plasma volume may not be significantly changing (Greenleaf et al., 1981), it is possible to compute the decline in body water and the contribution to this loss from the plasma and interstitial compartments. The results from the computer model and from one immersion experiment (Greenleaf et al., 1981) are shown in Table 3.

TABLE 3

CONTRIBUTION OF PLASMA AND INTERSTITIAL VOLUMES
TO BODY WATER LOSS DURING 4 HOURS IMMERSION

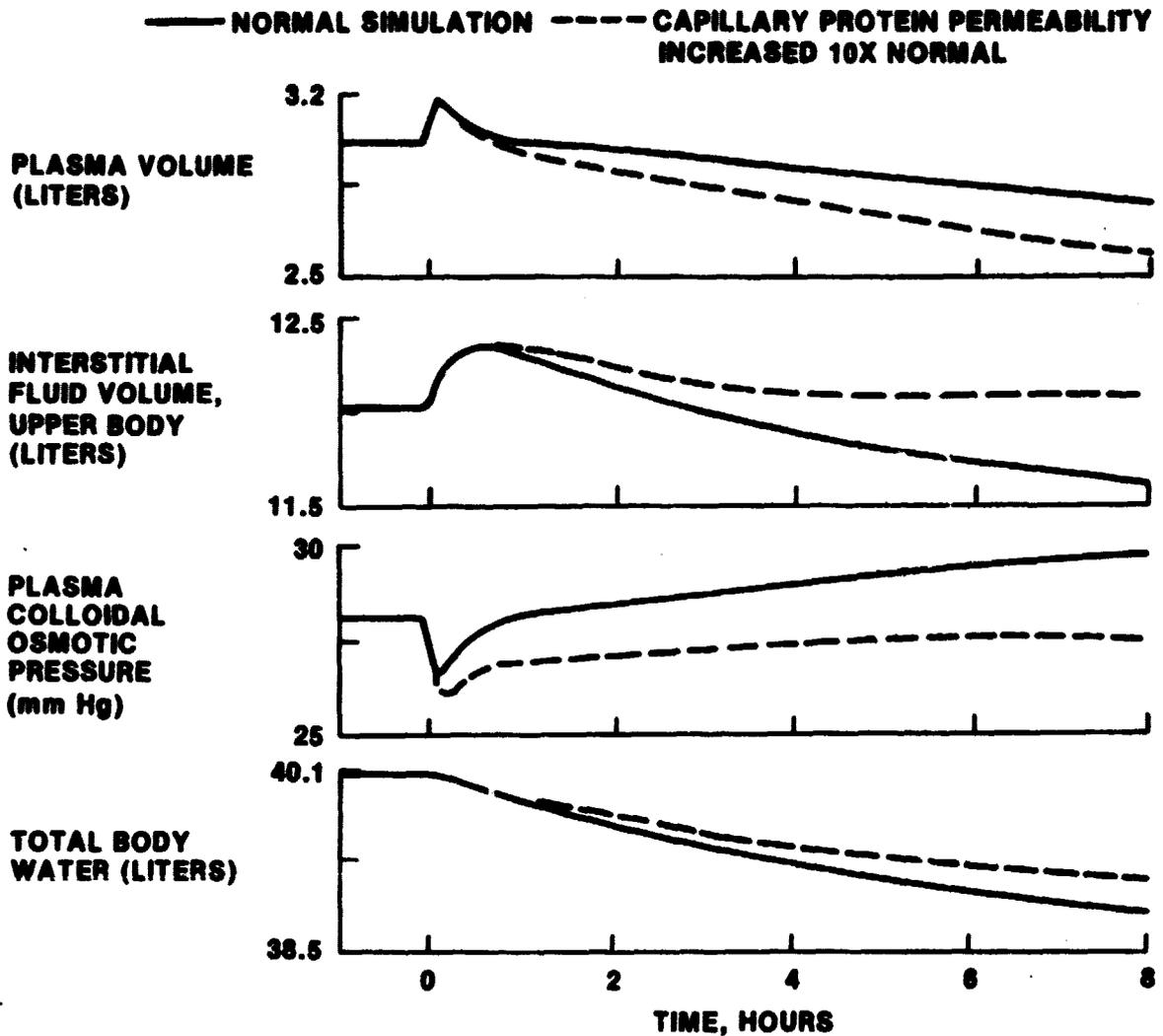|	Experiment	Model
PLASMA VOLUME	- 75 ml (15%)	- 123 ml (16%)
INTERSTITIAL VOLUME		
Upper Body	-	- 194 ml (25%)
Lower Limb	-	- 473 ml (59%)
Total	- 425 ml (85%)	- 667 ml (84%)
TOTAL BODY WATER	- 500 ml (100%)	- 790 ml (100%)

* Experimental data derived from Greenleaf et al., 1981

Although the absolute values of fluid losses derived experimentally are not identical to those predicted by the model, the percentage contributions of plasma and total interstitial volumes to total body water losses are quite similar to the observed values. Also, the experimental data and the simulation responses indicate that substantial amounts of water are removed from the interstitial fluid before plasma volume is largely affected. Furthermore, while the model predicts that most of the interstitial fluid loss originates from the lower limbs as expected, a significant fraction of fluid (25% of the total body water loss) is derived from the upper body interstitial fluid. This appears paradoxical in the sense that it is normally believed that plasma is filtered into these tissues and there is a net gain of tissue fluid (in the upper body) at the expense of plasma volume. However, while the model indicates that outward filtration into tissues does occur (see "upper body interstitial fluid" Figure 8), it is limited in time (about 2 hours) and in magnitude (about 300 ml). Also, the process quickly reverses because of increased plasma colloidal concentration as plasma is filtered through the renal tubules and the upper body capillaries. The model further predicts that if immersion were to continue beyond four hours, the upper body interstitial fluid would exhibit a net depletion of nearly the same volume lost from the leg tissues (about 500 ml), but would return to normal within 48 hours.

The concept that plasma shifts into the interstitium are self-limiting and even reversible due to the colloidal concentrating ability of transcapillary filtration has not previously been seriously considered in relationship to blood volume control during weightlessness. However, it is well known that the ability of plasma colloids to limit outward filtration is

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the basis for using them in plasma expanders as blood replacement substitutes. Furthermore, other analyses have demonstrated that in the face of a blood pressure elevation the interstitium is protected against edema by several safety factors. One such factor is the autoregulation of capillary pressure by pre- and post capillary resistance changes (Leonard and Abbrecht, 1973). Another factor is the normally low compliance of the tissue spaces, preventing large quantities of plasma from entering the tissues until capillary pressures rise significantly (Guyton et al., 1975). These safety factors apply only to the non-renal capillaries and not to filtration through the glomerular capillaries (i.e., urine formation), a process which promotes additional plasma colloidal concentration and acts as an additional safety factor.

The above arguments regarding limitations of filtration may be qualified to a degree if one considers that during water immersion there is a possibility that proteins are not perfectly filtered. That is, there may be an additional leak of protein across the capillaries as a result of pressure distension effects on the capillary membrane pores. This has been demonstrated, for example, during massive fluid infusions (Manning and Guyton, 1980). Such an effect would permit greater quantities of plasma filtrate to enter the tissue spaces. This possibility was examined by computer simulation with the results illustrated in Figure 14. Two cases were examined: a) a normal water immersion simulation identical to that shown in Figure 8, and b) a water immersion simulation in which protein permeability of the capillary membrane was increased by a factor of ten. Qualitatively, the two primary effects of increasing protein permeability are a reduced plasma colloidal concentration and an increased upper body interstitial fluid volume throughout the period of study. (A reduction in plasma protein concentration was also

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SIMULATION OF WATER IMMERSION: EFFECT OF INCREASING
CAPILLARY PERMEABILITY ON TRANSCAPILLARY FLUID EXCHANGE
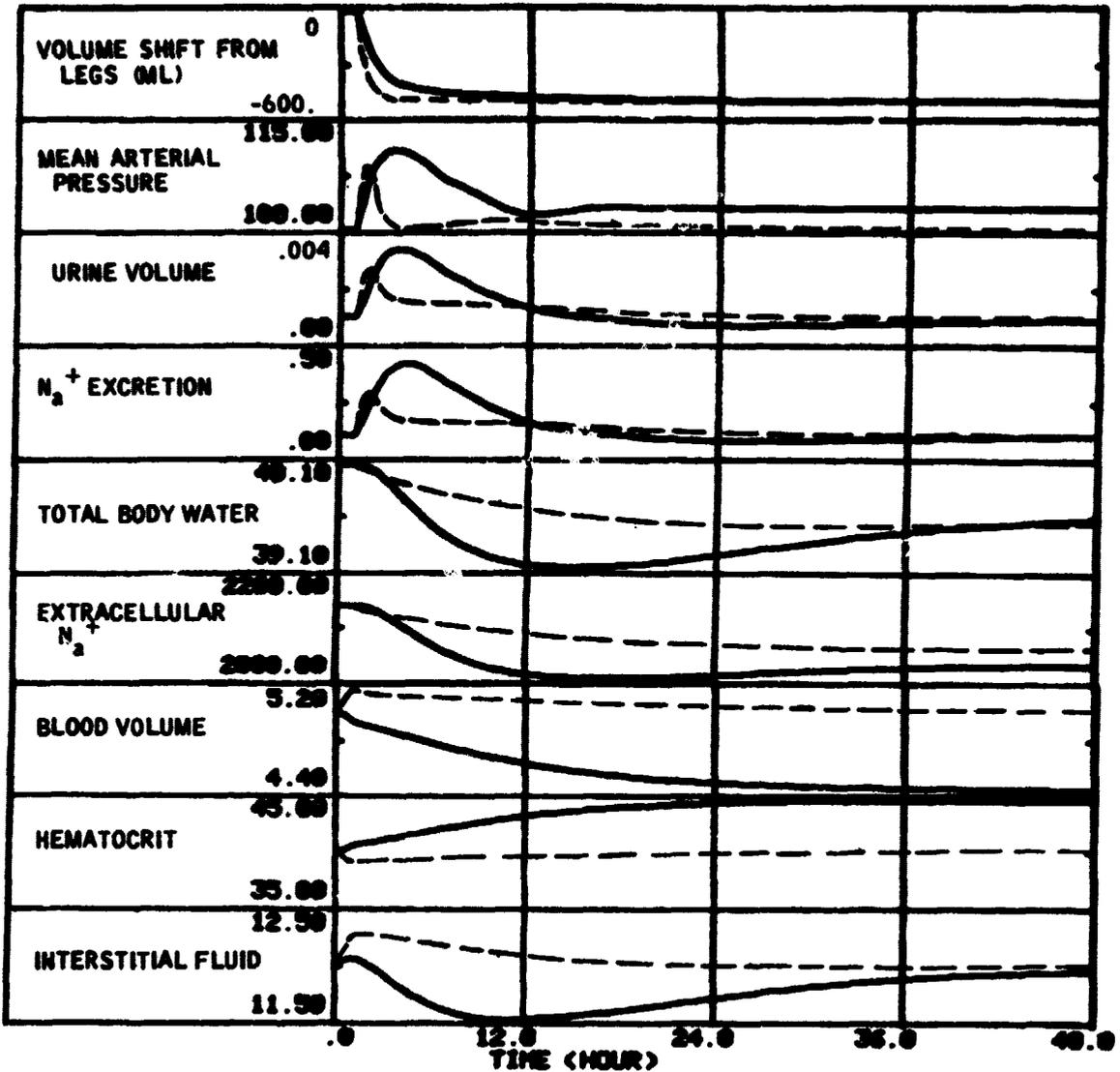
FIGURE 14

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reported by Greenleaf et al., 1981, in their water immersion study.) It should be noticed, however, that only the duration and not the magnitude of the simulated interstitial expansion was increased with increased permeability. This study also demonstrated that plasma volume reduction was nearly double for the case of increased protein permeability, while total body water losses were relatively similar in both cases. Taken as a whole, the assumption of increased protein permeability resulted in a more realistic simulation of the immersion experiments of Greenleaf and co-workers (1980,1981).

Blood and Interstitial Shifts to the Head

The fluid which is presumed to shift headward during the acute phase of hypogravic exposure consists of two components: a) blood originally pooled in the vessels (primarily veins) of the legs, and b) plasma filtrate pooled in the interstitial spaces of the legs. Although these two volume shifts occur simultaneously (as shown previously in the simulations of water immersion, Figure 8), it is possible to evaluate their effects separately using the mathematical model, an analysis not possible by experimental means.

For convenience we have assumed that one liter of fluid was shifted from the legs and that this amount was derived equally (i.e., 500 ml each) from vascular and extravascular sources. The model responses for each of these two volume shifts, one of interstitial filtrate, and one of whole blood, is shown in Figure 15, during a 48-hour period. In both cases, there is a reduction in leg volume and body water and salts, and increases in circulatory pressures and urine excretion. However, there are some basic and important differences

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CIRCULATORY, FLUID, ELECTROLYTE & RENAL RESPONSES TO:

(A) 500 ml BLOOD SHIFT FROM LEGS (————)
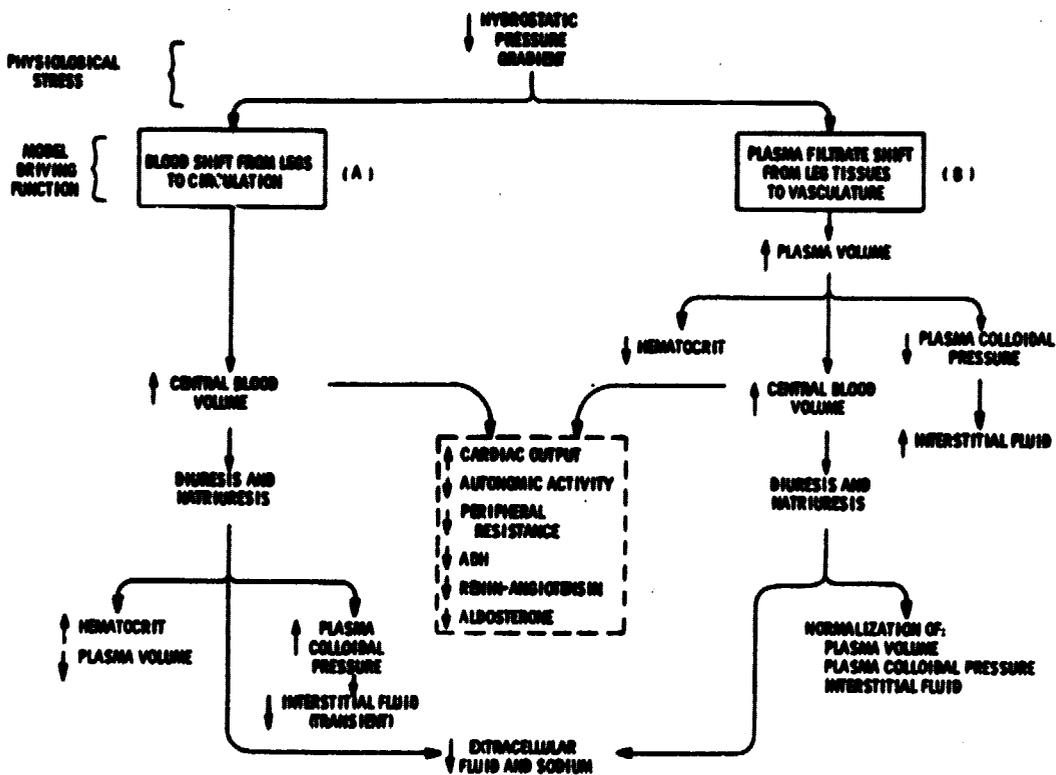
(B) 500 ml FILTRATE SHIFT FROM LEGS (— — —)

FIGURE 15

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between the two simulations which essentially are due to the fact that whole blood contains colloids and red cells while the plasma filtrate does not. These differences may be summarized as follows:

a) In the case of the filtrate shift, the original blood volume is initially expanded as leg tissue fluid enters the circulation. Intravascular red cells and plasma colloids are diluted by this filtrate. On the other hand, a shift of blood from the legs expands the central blood volume, but the total blood volume does not initially change; neither does hematocrit, nor colloidal osmotic pressure. The eventual reduction in blood volume occurs only in the case of a blood shift inasmuch as blood volume is restored to normal following the filtrate shift.

b) In both cases there is a tendency for the excess central blood volume to be eliminated via transcapillary filtration into the upper body tissues and into the renal tubules. However, in the case of the whole blood shift, this results in hemoconcentration and an increase in plasma colloids, but in the case of the filtrate shift, there is no net increase in red cell or colloidal concentration because the original inward shift from the legs did not contain these components.

c) Outward filtration from the central circulation to the surrounding tissues is enhanced by the dilution of plasma colloids in the case of the filtrate shift and attenuated by hemoconcentration in the case of the blood shift. Thus, in the former case, interstitial volume increases, but in the latter case there is a net decrease in

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interstitial fluid. In other words, with a pure headward blood shift, the model predicts a net inward filtration into the circulation from the upper body tissues (as discussed earlier in this report). This excess fluid is immediately excreted by the kidneys and, therefore, contributes to the diuresis. Thus, the magnitude of the blood pressure and renal responses may be more dramatic for the shift in whole blood compared to the shift in filtrate.

It is, therefore, apparent from Figure 15 that the responses of blood volume, hematocrit, and interstitial fluid are quite different for the two cases studied. These differences are summarized in Figure 16. In practice, the total response, as shown in Figure 8, is the sum of these two individual cases. However, these studies have suggested that the total response will depend in large measure on the total volume of fluid shifted as well as the ratio of filtrate/whole blood that is shifted. These factors are undoubtedly different for the various hypogravic maneuvers in use today, including water immersion, head-down tilt, bed rest, and space flight, because the initial stress on the legs are different. For example, total leg volume decrements have been reported to vary from about 500 ml during supine bed rest, to 900 ml during head-down tilt, to more than 1500 ml during space flight. Therefore, the acute responses of each of these stresses may be different, not because of some fundamentally different reaction, but merely because of the difference in tissue fluid volume mobilized compared to that for whole blood. Unfortunately, at the present time there is no practical means of measuring these differences directly. Note, however, that although the responses of the two

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HYPOTHESES FOR SIMULATION OF FLUID SHIFTS DURING FIRST DAY OF WEIGHTLESSNESS FROM (A) LEG VASCULATURE AND (B) LEG TISSUES

FIGURE 16

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cases in Figure 15 appear to converge at the end of 48 hours, there is still a wide divergence in their corresponding values at the end of six hours, the length of most immersion studies. This suggests that it may be possible, using parameter estimation techniques, to assess the filtrate/whole blood shift ratio by comparing model and experimental responses.

3.0 <u>DISCUSSION</u>

There is no doubt that water immersion experiments have provided a sound basis on which to predict early responses to weightlessness and to study underlying mechanisms. We have tried to demonstrate how mathematical models and computer simulation can complement these experimental studies. Quantitative models of the renal-endocrine-circulatory systems provide a common framework with which water immersion and space flight can be related. In this context, both water immersion and the computer simulation can be considered analogs of the weightlessness response, the former being an experimental analog and the latter a mathematical analog. However, inasmuch as models (or analogs) are imperfect representations of reality, it is useful to discuss the limitations of both of these approaches. We will discuss the shortcomings of water immersion and computer models in that order.

Limitations of the Water Immersion Analog

There are certain facets of the water immersion process that make this maneuver inherently different from the acute response to weightless space flight. Some of these differences will naturally limit our ability to extrapolate from the one-g situations to the zero-g environment. These limitations include the following:

a) Fluid is shifted from the legs in water immersion due to external water pressures, in contrast to the natural elastic tissue forces which are the primary drivers in weightlessness. As a result, the amount of leg dehydration and central hypervolemia may be different in the two situations. Gauer (1971) has suggested that the degree of relative engorgement of the heart and thoracic vessels in the weightless state is

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somewhere between that seen during bed rest as a lesser stimulus and that of water immersion as the more potent stress. This is a reasonable, but as yet, unproven contention. In space flight, it has been observed that the legs lose approximately 2 liters of fluid within several days (Thornton et al., 1977). This is a large volume relative to bed-rest observations and compared to normal postural changes in one g. Comparable values for water immersion, interestingly, do not seem to be available. Until more complete data are obtained from water immersion and acute space-flight periods, it will not be possible to assess their quantitative differences regarding the degree of leg emptying and central hypervolemia.

b) Because of operational difficulties and subject discomfort, water immersion has been most frequently used for experiments lasting less than about six hours. Short-term immersion should only be considered a reasonable approximation to similar periods of weightlessness (Howard et al., 1967). Therefore, longer term effects of weightlessness cannot be easily studied using the immersion technique.

c) Most workers immerse their subjects to the level of the neck in a sitting position, although other configurations (i.e., lying, standing, sitting in a reclining chair) are used. Inasmuch as the depth of the immersed tissues determines the hydrostatic forces which shift fluids toward the central circulation, it is often difficult to quantitatively compare different water immersion studies when the body posture varies.

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d) Immersing a subject to the neck or chin results in negative pressure
    breathing because the force exerted by the water on the surface of the
    body has no counterbalance in the airways. Negative pressure breathing,
    or the positive pressure breathing equipment used to counteract this
    effect, may interfere with all the circulatory, renal, and hormonal
    responses that are under examination (Epstein, 1978).

e) During immersion, there is a marked decrease in evaporative water loss.
    While this simplifies the interpretation of water balance and renal
    alterations (e.g., the predominant route for fluid losses is via the
    kidney), it does not permit exact extrapolation of renal responses to the
    weightless condition in which skin losses are a significant fraction of
    overall water balance. The total quantity of urine voided during
    immersion might, therefore, be expected to be somewhat higher than that
    achieved during weightlessness, assuming all other parameters were
    identical, because the kidneys are the major avenue of water loss in the
    former case.

f) The pressure on the walls of the thorax from the hydrostatic forces of
    water external to the body is an effect that is not present in
    weightlessness and can lead to higher intrathoracic pressures than would
    be observed in space flight. This transthoracic pressure gradient and
    compression of submerged tissues is probably responsible for the
    sustained hyperkinetic circulatory state reported during immersion
    studies (Begin et al., 1976; Rehn et al., 1969). As a result, immersion
    may lead to a larger reduction in blood volume than would be expected in
    zero g and a masking of any reflex relaxation effects of peripheral
    capacitance vessels (Nixon et al., 1979).

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Limitations of the Computer Simulation

These simulations did not consider the effects of evaporative water loss, which are reduced to a minimum during immersion. Neither did they account for a difference in the degree of headward fluid shift between the hydrated and dehydrated cases. It can be argued that the magnitude of the fluid shift from the legs in response to immersion would be less in previously dehydrated subjects compared to well hydrated subjects. The divergence in the theoretical response between hydrated and dehydrated cases would be expected to be even more marked if these factors were considered in the simulation.

Several questions were raised as a result of the simulation studies which suggest either modification of the model or a more detailed examination of the water immersion response. For example, the model consistently exhibits a stronger diuresis response as a result of immersion than is shown by human subjects. Experimental results also suggest a greater dissociation between the immersion diuresis and natriuresis responses than is indicated by the model. In addition, significant differences in urine flow between the normally hydrated and dehydrated cases are observed in the model over a 24-hour period, but not during the first few hours of immersion as has been shown experimentally. It is not clear just which renal elements in the model require modification. Both the model's propensity for producing a pressure diuresis, and the elementary form of the algorithm describing natriuretic factor release should be reexamined.

Another area of disagreement involved the failure of the model to demonstrate the magnitude of central venous pressure changes as shown experimentally. The tentative conclusion reached in this study was that a

reevaluation of the experimental venous pressure response is warranted, especially extending the period of experimental study beyond 3 hours. Also, the effects of external water pressure on the thorax need to be accounted for in the model.

The simulations demonstrated that the role of volume control of ADH needs to be reassessed with regard to dynamic behavior of atrial pressure, adaptation of the volume receptors, and relative sensitivities of ADH to plasma osmolarity versus central venous pressure. Finally, the role of transcapillary filtration control in plasma volume regulation during immersion was not shown by the model to have the importance ascribed by some investigators. Additional experimental findings are necessary to evaluate this model prediction, including the suggestion that the transcapillary permeability to plasma proteins is increased during water immersion.

4.0 CONCLUSIONS

Aside from the limitations discussed above, these studies, experimental as well as theoretical, have proved valuable for understanding the nature of the short-term response to the fluid redistribution of hypogravity. It has been demonstrated that a mathematical model, based on current concepts of fluid volume regulation, can simulate dynamic responses to water immersion, and by inference, the acute effects of weightless space flight.

A model, once validated, becomes a research tool for subjecting particular responses to detailed scrutiny and testing hypotheses that might be diffficult to experimentally evaluate. In this analysis, for example, it was possible to study the differences between the hydrated and dehydrated responses, to distinguish between the changes in interstitial fluids of the lower and upper body, to separate out the effects of intravascular and extravascular headward fluid shifts, and to examine the osmolarity vs pressure regulation of ADH. Most of these issues have not yet been adequately addressed, either during water immersion, or during space flight. The results of this study can, therefore, be applied to predicting the range of responses during future space-flight studies.

Some of the more significant acute measurements which are currently planned for Shuttle Spacelab research include venous pressure, cardiac output, plasma endocrine levels, renal clearances and excretion rates,, and plasma volume. The current study has provided a theoretical basis for interpreting these data, once it has been collected. In addition, predictions of the model for each of the most significant physiological quantities of interest have been documented. In certain cases, however, it was demonstrated that some

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uncertainty exists regarding the expected space-flight results. Thus, special attention was devoted to the effects of dehydration on the renal response, the variability in venous pressure responses, the possibility of altered transcapillary protein permeability, and alternative responses of ADH. As a result of the analysis, one can predict that a diuresis in space flight should be observable during the first several hours of flight. The probability of demonstrating this response decreases as subjects become dehydrated, as their fluid intake diminishes, and/or if urine voids are pooled during the first 24 hours.

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APPENDIX

DESCRIPTION OF THE MODEL OF CIRCULATORY, FLUID, AND ELECTROLYTE REGULATION

The mathematical model employed in this project was originally developed by Guyton and co-workers (Guyton et al., 1972) as a representation of overall circulatory regulation. However, an understanding of circulatory dynamics also requires a quantitative assessment of many other complex and interrelated systems. Therefore, this model contains descriptions of about 18 major subsystems, shown in Figure A-1, each describing some important physiological aspect of circulatory, fluid, and electrolyte control.

The fluid system of the model is divided into four major compartments: blood, interstitial, intracellular, and pulmonary fluid. Exchange of fluids (water and proteins) and electrolytes (extracellular sodium and intracellular potassium) occurs between compartments via diffusion, active transport, transcapillary exchange, or lymph flow. A complex algorithm of renal function permits a realistic description of fluid volume and electrolyte regulation. It is these features which permit simulation of such stresses as fluid and salt loading and water immersion. The circulation is subdivided into seven compartments composed of arteries, veins, heart chambers, and lung segments. Heart function is represented by basic cardiac function curves modified by the effects of autonomic stimulation, arterial pressure afterload, and hypertrophy, or deterioration of the heart.

Most of the above characteristics of the model can be viewed as the controlled system (see Figures A-1 and A-2), while the controlling system consists of three major components - local control, hormonal control, and autonomic control (see Figures A-1 and A-3). The inclusion of such elements as hormonal metabolism, autoregulation, baroreceptor adaptation, erythropoiesis control, protein formation and destruction, venous stress relaxation, and cardiac conditioning factors clearly indicate that the Guyton model was developed to study long-term adaptive responses.

The model's complexity precludes an easily understood detailed pictorial representation of its entire system (White, 1973). 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 responses of the model to water immersion, 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.

In addition to water immersion, many varied experiments have been simulated with this model, including infusions of water, electrolytes, and plasma, congestive heart failure, loss of kidney function, nephrotic proteinuria, and angiotensin infusions. Some important modifications were performed to permit the model to respond appropriately to gravity-dependent stresses, including orthostasis and weightlessness ((Leonard and Grounds, 1977; White, 1974; Leonard et al., 1978). These modifications included gravitational hydrostatic gradients, additional leg compartments, and improved subsystems for erythropoiesis, hormones, autonomics, and local circulatory control.
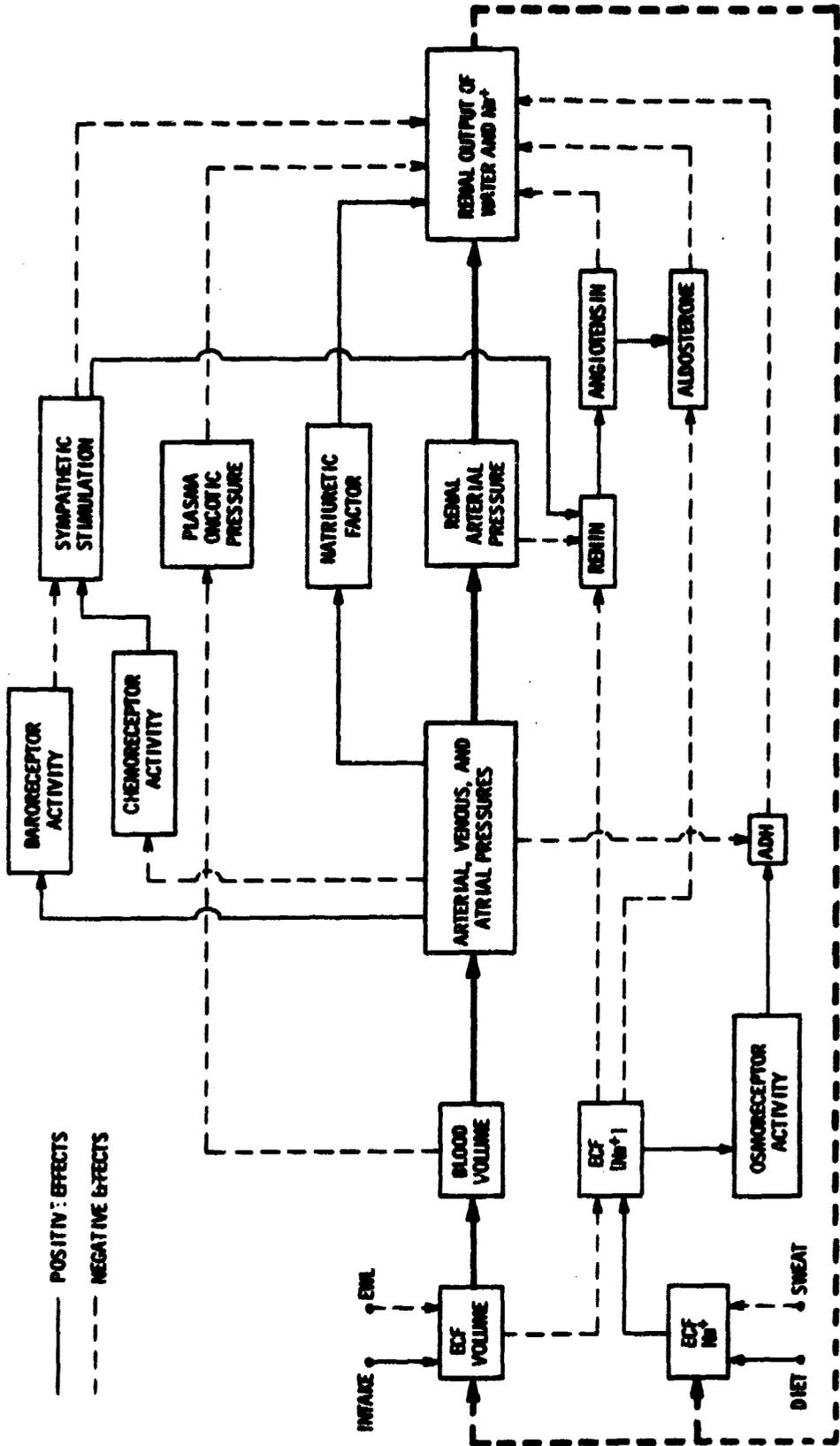
FIGURE A-1

CONTROLLED SYSTEM

CIRCULATORY AND FLUID COMPARTMENTS IN MODIFIED GRAVITY

DEPENDENT MODEL OF CIRCULATORY, FLUID AND
ELECTROLYTE REGULATION

FIGURE A-2

CONTROLLING SYSTEM

MODEL REGULATION OF EXTRACELLULAR AND CIRCULATORY DISTURBANCES

FIGURE A-3

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