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MATHEMATICAL MODELS OF PHYSIOLOGICAL SYSTEMS

FINAL REPORT

CONTRACT NAS9-16328

Prepared for

National Aeronautics and Space Administration
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MATHEMATICAL MODELS OF PHYSIOLOGICAL SYSTEMS

FINAL REPORT

1.0 INTRODUCTION

This is the final report for contract NAS9-16328 which was in effect from October 22, 1980, to December 1, 1982, with the National Aeronautics and Space Administration. The statement of work for this contract is contained in Appendix A of this report and involves work in five different but overlapping areas of physiological regulation and mathematical modeling. This report is structured to correspond directly to the items contained in the contract statement of work. Section 2.0 concerns calcium/musculoskeletal regulation, Section 3.0 concerns cardiovascular regulation, Section 4.0 concerns erythropoiesis regulation, Section 5.0 concerns fluid and electrolyte/renal regulation, and Section 6.0 concerns general modeling support and software development.

Most of the work discussed in this report is of one of two types. Either the work relates to new modeling developments, or to new analyses or simulations which have taken place during the contract period. In addition, in certain areas, an integrated picture of physiological events related to space flight is beginning to unfold, and this story is told where appropriate. A number of technical reports, meeting presentations, and scientific papers have resulted from the work expended on this contract and these are mentioned and referenced in the appropriate section of this report.

2.0 CALCIUM/MUSCULOSKELETAL REGULATION

2.1 INTRODUCTION

Over the last two years, work under this contract in the calcium/musculoskeletal area has resulted in five company reports detailing the progress which has been made in modeling whole-body calcium metabolism and in simulating the musculoskeletal effects of both space flight and bed rest (1-5). In addition, three presentations of preliminary results were developed and given at major scientific meetings (6-8). The calcium/musculoskeletal work itself falls into three categories. First, a significant amount of work has been done to complete and expand the mathematical model of the calcium regulatory system. Second, the model has been used in simulations of both bed rest and space flight, and the results of these simulations have shed light on certain of the relationships between bed rest and space flight and on some of the weaknesses of the present model. Third, additional work not required in the contract statement of work was expended in an analysis of the data arising from the San Francisco Public Health Hospital bed-rest studies. The work performed in each of these categories will be summarized in the following sections, which correspond to sections of the contract statement of work.

2.2 NEW MODEL DEVELOPMENT

The mathematical model of calcium metabolism which has been developed during this and prior contracts, is a compartmental, feedback model utilizing ordinary differential equations to describe the appropriate fluxes. The model itself is composed of seven subsystem models that are classified into four functional categories: three regulatory subsystems (parathyroid hormone, vitamin D, and calcitonin), two input/output subsystems (intestine and kidney), one distributing subsystem (plasma), and one storage subsystem (bone). All of the regulatory subsystem models were developed as original work by this contractor and were built from the ground up. The other subsystem

models were adapted from a similar overall model developed by Jaros, Coleman, and Guyton (9). This latter model will be called Jaros' first model in what follows.

Initially, Jaros' first model was coded in FORTRAN and the various subsystems were compared with those which had been developed or were to be developed by this contractor. Where actual model comparisons were required, they were performed using a specially designed program, named "CAL", which allowed subsystem models to be executed independently. It was found that the regulatory subsystems were more adequately described by this contractor's version of each control element, but that the other components of Jaros' first model were either equivalent or superior to the corresponding contractor version, as originally envisioned (10). Based on this analysis, it was decided to utilize Jaros' first model as a baseline model after making two major modifications. First, the original hormonal subsystem models of Jaros were replaced by those of the contractor. Second, the dependent variable representing ionized calcium in Jaros' first model was replaced by a dependent variable representing total calcium. This second change was made in order to compare model and experimental results more readily, as most investigators, including the Skylab investigators, utilize total calcium. This new model was named "STCAL", for short term, or soft tissue, calcium, and was the primary model which was used to produce most of the musculoskeletal tasks required by this contract.

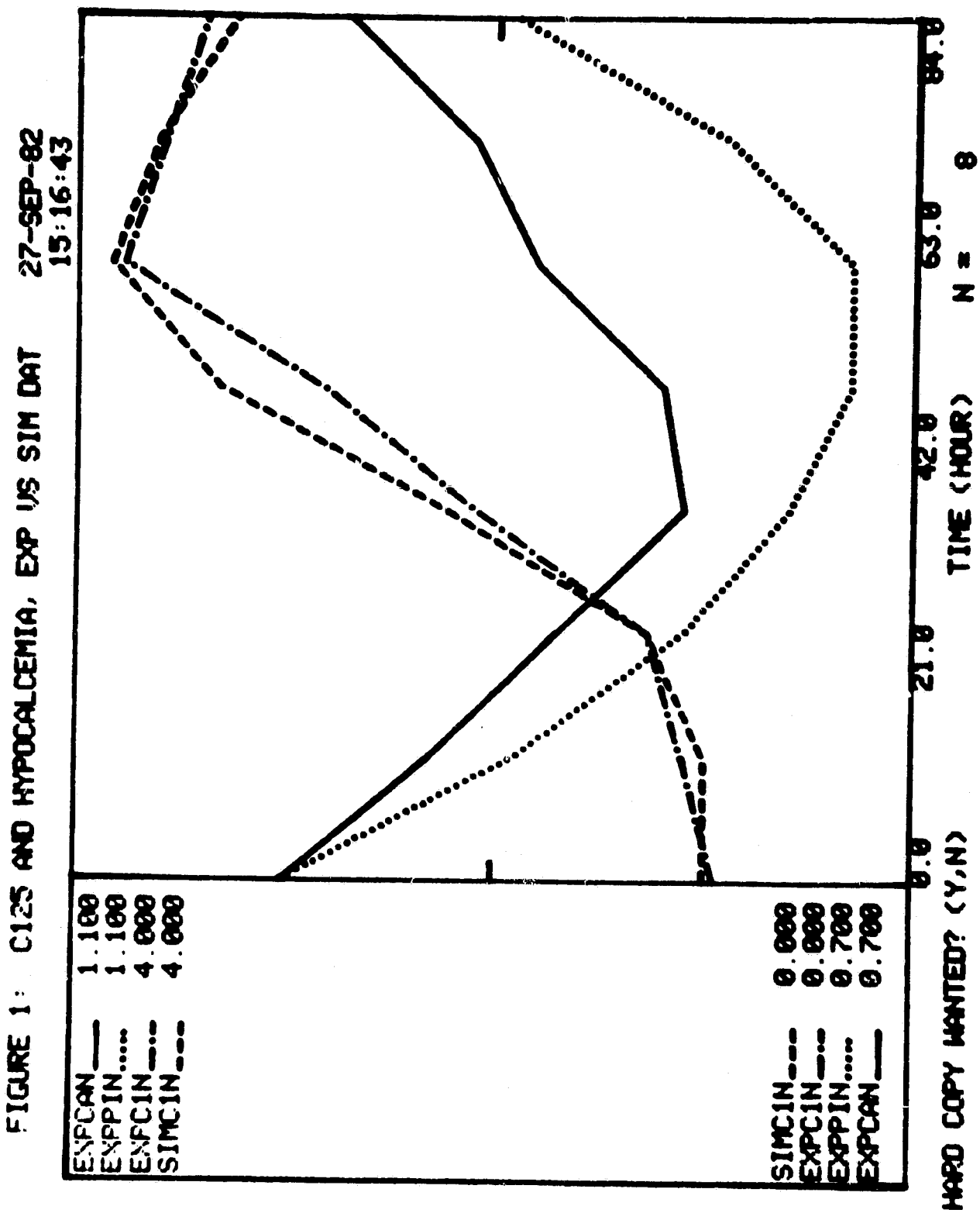
A number of additional minor modifications to the model "STCAL" have been made. Equations have been added which allow infusions of various types (calcium, EDTA, parathyroid hormone, calcitonin, and vitamin D and its metabolites) to be carried out in a simple way. Also, terms have been added which permit extracellular fluid levels and the major effect of gravitational stress on bone to be varied easily.

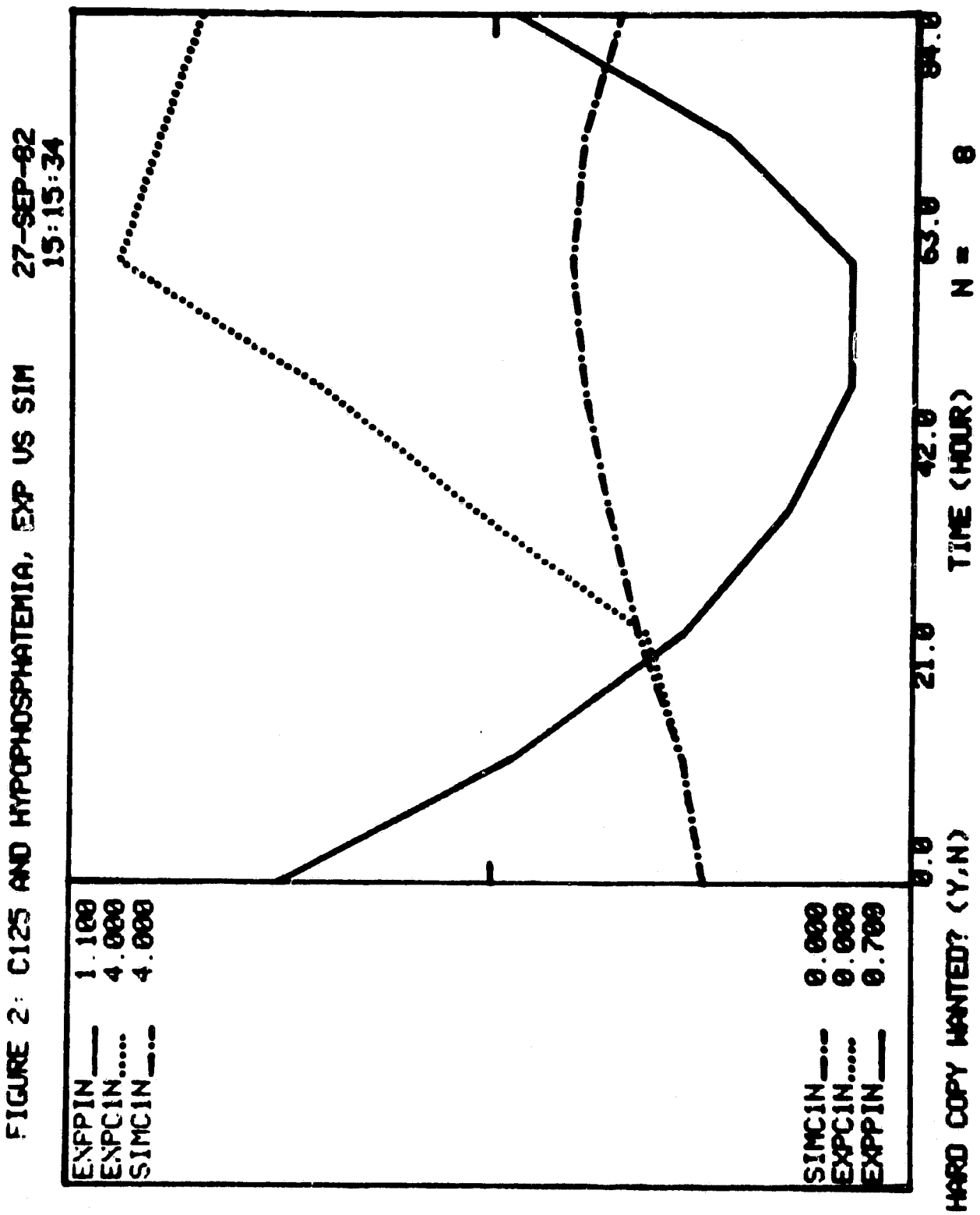
In addition, the operating systems used to actually perform the simulations have been improved extensively during this contract period; these improvements are discussed more fully in section 6.0 of this

report. Briefly, the improvements include the ability to call forth written summaries of the model and/or any subsystem, listings of variable names, values, and definitions by subsystem, and listings of particular subsystems or equations. The improvements also include full graphical capabilities, automatic input of variable data base changes, tabular output of simulation and experimental data in normalized form, and simultaneous plotting of simulation and experimental data. These modifications have resulted in a calcium model that is fast, easy to run, and yet provides a wide variety of frequently required user functions for the experienced or inexperienced user.

This contractor has conducted a wide variety of model validation studies using both the entire "STCAL" calcium model, and the individual subsystem models. These are presented in detail in the contractor's technical reports, particularly (1) and (3), but one example of such a study is presented here as an illustration. Figures 1 and 2 present the results of a study conducted with the contractor's vitamin D subsystem model (1). Bilezekian et al. (11) administered mithramycin to a group of subjects and measured the resulting plasma concentrations of calcium, phosphate, parathyroid hormone, and 1,25-dihydroxyvitamin D over a 120-hour period. Experimental values of serum calcium and phosphorus (shown on Figs. 1 and 2 as EXPCAN and EXPPIN, respectively, in terms of times normal) were used as forcing functions for the subsystem model. The resultant computed 1,25-dihydroxyvitamin D plasma concentrations (shown as SIMC1N on Figs. 1 and 2) were plotted on the same figure as the experimental 1,25-dihydroxyvitamin D plasma concentrations. The 1,25-dihydroxyvitamin D experimental (EXPC1N) and simulation (SIMC1N) data are almost identical in their time course and plasma concentrations. Both concentrations rise at the same approximate rate, peak at the same time and the same approximate concentration, and fall at nearly the same rate.

The experimental data does not determine the exact cause of the rise in 1,25-dihydroxyvitamin D plasma concentrations; plasma parathyroid hormone, calcium, or phosphorus could be responsible (11). Bilezekian et al. suggest that the regulators in this study are the plasma





concentrations of parathyroid hormone or phosphate; their assumptions are based upon intuition and correlation of the time courses of plasma calcium, phosphate, parathyroid hormone, and 1,25-dihydroxyvitamin D. Using the model, one may separate the various elements of regulation (controlling agents) and test the effectiveness of each one individually and then in groups. In fact, in the model, the effect of plasma calcium and parathyroid hormone (PTH) have been lumped together. This was done because PTH is itself directly regulated by plasma calcium and little is known about the dynamics of this closely coupled system. Figure 1 shows that when the model is used with calcium alone or both calcium and phosphorus as the controlling agents, the data from the model are almost identical to the experimental data. Figure 2 illustrates what happens to the model data when plasma phosphorus alone is used as the controlling agent. Then, the simulated 1,25-dihydroxyvitamin D plasma data have lower values than the experimental data. This suggests that the regulating agent in this particular study is calcium, parathyroid hormone, or both, because the degree of phosphorus regulation is too slight to influence the 1,25-dihydroxyvitamin D plasma concentrations appropriately. Ideally, the next stage of research would be to design one or more experiments that would test these predictive results of the model and determine whether or not phosphorus has any role in the changes in plasma 1,25-dihydroxyvitamin D concentrations. The results of these experiments could, in turn, lead to modifications and refinements of the model. This type of interactive support between model and experimental research seeks to continually improve the model, as well as the design of experiments and hypotheses.

The "STCAL" model has been modified and enlarged to include a phosphorus metabolic system and an expansion of the bone subsystem. Both of these additions were based on a second model developed by Jaros, Guyton, and Coleman (12). The name of this new calcium model is "LTCAL," for long-term calcium. Details concerning this model are contained in a contractor report (2), but this second model has not been tested as extensively as the first. Another program, called "BONE," has also been created. It contains all of the bone subsystems

of "STCAL" and "LTCAL" and allows the user to test and run each subsystem individually. The program has the same capabilities as the "CAL" program and will make simulations and modifications of the subsystems easier to test.

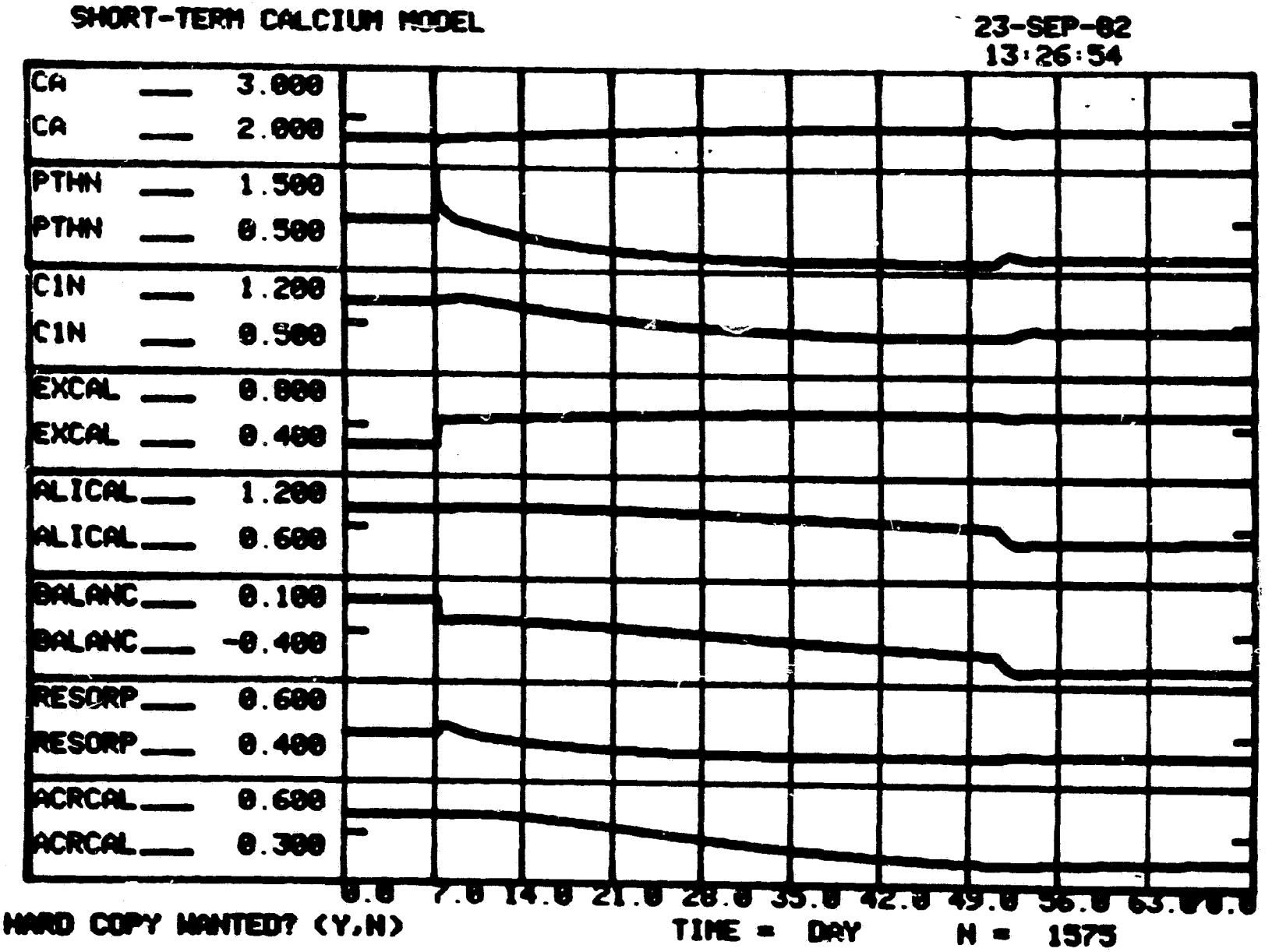
2.3 NEW ANALYSES AND SIMULATIONS

Following the development of the "STCAL" model discussed above, a simulation of the effects of weightlessness on the calcium system were carried out in the document entitled "Space Flight Simulations Using the Short-Term Calcium Model" (3). These simulations were designed to validate the model using actual space-flight data from Skylab, to improve the model, if required, and to provide preliminary testing of some of the hypotheses developed following the Skylab mission. Only a brief summary of this work is presented here.

Figure 3 presents the results of the initial simulation of weightless space-flight data using the "STCAL" model. The zero-gravity stress is initialized on day seven, and continues for nine weeks. It is hypothesized that this stress ultimately involves an increase in the rate of calcium efflux from the bone. No assumptions are made as to the cause of the increased calcium efflux. No other experimental stresses, such as dietary calcium increases, are assumed in this initial simulation. The variables, by row, are as follows: plasma calcium (CA, in terms of mmoles), 1,25-dihydroxyvitamin D (C1N, in terms of times normal), urine calcium excretion (EXCAL, in terms of mmoles/min), intestinal calcium absorption (ALICAL, in terms of mmoles/min), calcium balance (BALANC, in terms of mmoles/min), skeletal calcium resorption (RESORP, in terms of mmoles/min), and skeletal calcium accretion (ACRCAL, in terms of mmoles/min).

Most of the simulation results are qualitatively, and in some cases quantitatively, similar to the Skylab results. The plasma calcium concentrations and the urine excretion rates increase by the same approximate percentage. The assumed decreases in plasma 1,25-dihydroxyvitamin D concentrations, intestinal calcium absorption

FIGURE 3: SIMULATION OF THE SKYLAB DATA USING THE ' STCAL ' MODEL



rates, and skeletal osteoblastic accretion rates are also reproduced in the simulation. However, the plasma concentrations of parathyroid hormone and the rates of osteoclastic resorption predicted by the model do not agree with the Skylab results. These two variables decrease in the simulation rather than increase as the experimental data indicates. After careful examination of the data, it was decided that the secretion of PTH might be regulated by something other than plasma calcium levels. Examination of data from bed-rest studies suggested that this other agent might be plasma magnesium. Consequently, a magnesium term was incorporated into the parathyroid hormone subsystem model and the space-flight simulation was rerun (Figure 4). This time, all variables, including the parathyroid hormone concentrations and the osteoclastic resorption rates, agreed with the space-flight data, at least qualitatively.

These studies with the "STCAL" model which attempted to simulate the Skylab and bed-rest calcium data resulted in small, but significant modifications to three subsystem models: bone, intestine, and parathyroid hormone. The first modification was the addition of two abstract, skeletal terms, which represent the flow of calcium into and out of the bone compartment during changes in mechanical, or tensile, forces. Changes in one of these terms initialize the model simulation of calcium metabolism upon entry into a zero-gravity environment, by stimulating the flow of calcium out of the bone compartment. The second modification involved the damping of the endogenous secretion rate in the intestine subsystem model. This secretion rate was a direct function of the plasma calcium concentration and, if not depressed, became too large and influential in the bed-rest and space-flight simulations. Therefore, the demand for intestinal secretion was delayed over a long time period to reduce and stabilize its influence upon the rest of the model. The third modification involved the insertion of a magnesium regulatory term onto the parathyroid hormone secretion rate, as explained above. Ideally, the next stage of research would be to design one or more experiments that would test these predictive results of the model and determine whether

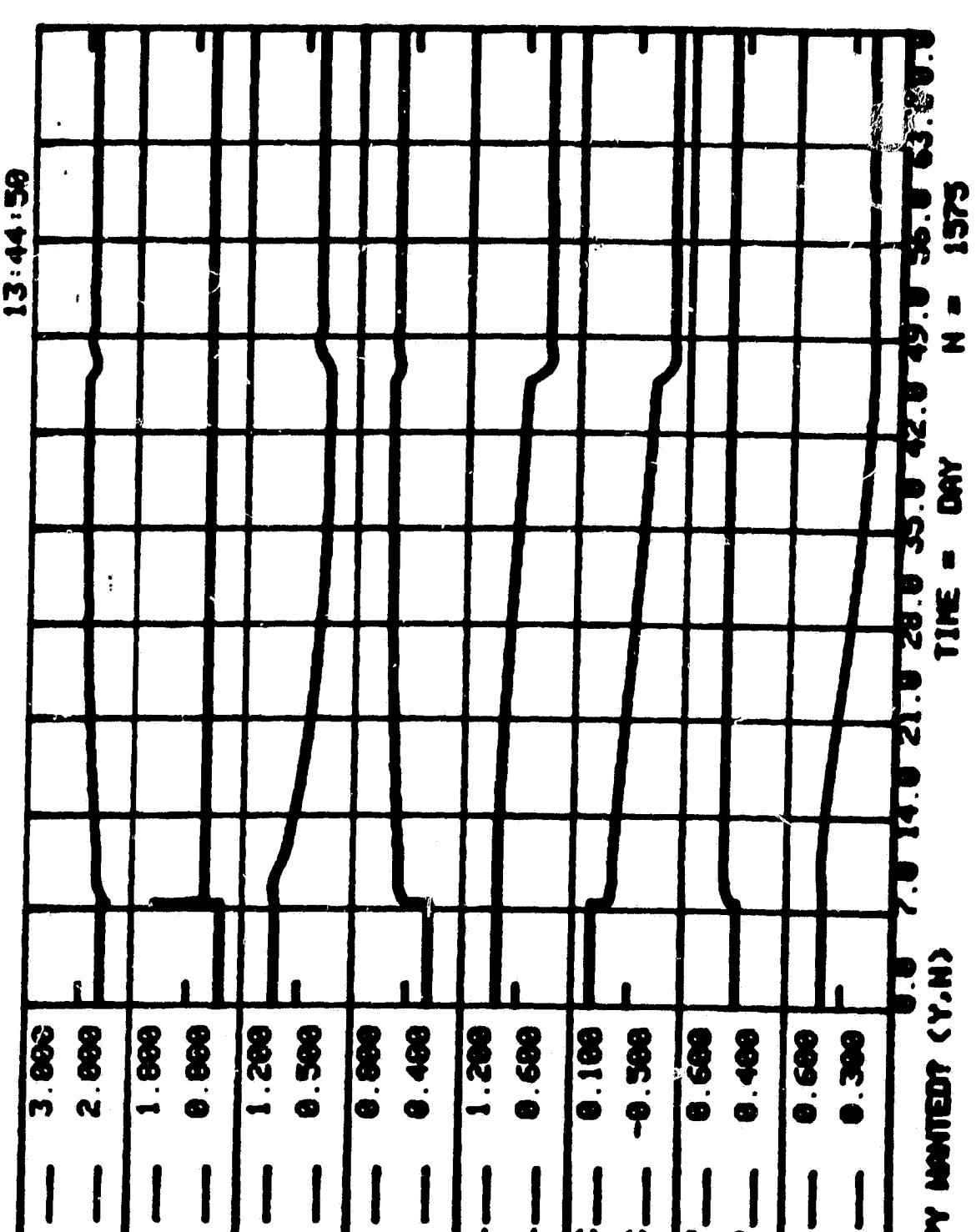


FIGURE 4: SIMULATION OF THE SKYLAB DATA USING THE 'STCAL' MODEL WITH A MAGNESIUM REGULATOR ON PTH SECRETION

or not magnesium actually has any role in regulating the plasma concentrations of parathyroid hormone during space flight.

2.4 ADDITIONAL WORK

Besides the work originally required for this contract, certain other work strongly related to the original tasks was undertaken and completed. This additional work, which was requested by the Technical Monitor, involved the analysis of the bed-rest data (with no additional treatments included) of the San Francisco Public Health Hospital, bed-rest studies. The purpose of this work was to develop a comprehensive understanding of calcium metabolism during bed rest, establish a working set of hypotheses, compare calcium metabolic responses during bed rest and space flight, and validate the calcium model. The work is reported in two company documents: "User's Guide for the BRASS (Bed Rest Analysis Software System) Program" (4), which describes the operation of the data-base retrieval and manipulation program, and "Report of the Bed-Rest Analysis. Treatment: Bed Rest Only." (5), which reports the results of the analysis.

The results of the bed-rest analysis confirmed many of the Skylab observations, provided support for some of the hypotheses developed from the space-flight data, and provided the first zero-gravity validations for the "STCAL" model. Basically, the bed-rest data bases are more complete than the Skylab data bases, not only by virtue of the consistent measurement procedures, but also because of phosphorus and magnesium metabolic measurements. (Unfortunately though, the hormonal analyses are weak in both the space-flight and bed-rest data bases.) The results and hypotheses of the Skylab data are supported and, in many cases, confirmed by the bed-rest data. The main difference between the two sets of data is that the magnitude and rate of variable responses are greater for space flight than for bed-rest stress. Whether these differences are due to a difference in the severity and rate of onset of the effect of true weightlessness during space flight versus that obtained with the bed-rest model, or whether they are due to dietary changes or other factors, is not known at this time.

3.0 CARDIOVASCULAR REGULATION

3.1 INTRODUCTION

Cardiovascular studies conducted during the last two years under this contract have concerned a comparison between various ground-based analogs of weightlessness and the true weightlessness of space flight. This section briefly summarizes a study which compares circulatory changes arising during bed rest, head-down tilt, and space flight, for both experimental data and values obtained from mathematical modeling and simulation. Water immersion, another ground-based analog of weightlessness, is not discussed with respect to cardiovascular studies, due to limitations of experimental data. It is discussed in an integrated fashion in Section 5.0 of this report; in addition, an analysis of circulatory, fluid, and electrolyte changes during water immersion may be found in a separate report (21). Work in the area of cardiovascular regulation has led to one technical report (13), two short papers (14-15), and one presentation abstract (16). In addition, the contractor was notified that two chapters concerning the modeling and simulation of cardiovascular regulation were set for publication (17-18).

3.2 NEW ANALYSES AND SIMULATIONS

The search for a suitable one-g analog of weightlessness for human studies began more than two decades ago, as the feasibility of manned space flights became apparent. Recently, Genin (19) has summarized the methods that have been used to predict the effects of true weightless exposure. Chief among these methods are the ground-based laboratory analogs of supine bed rest, water immersion, and head-down tilt. Many investigators have shown that these analogs produce functional changes that are qualitatively and, in many respects, quantitatively close to those that have been recorded in space flights. The analogs are used both to understand the behavior of physiologic systems under weightless conditions, and to develop and test countermeasures to the deleterious effects of weightlessness.

In human subjects, exposure to weightlessness or to a related one-g stress leads to deconditioning of the cardiovascular system. Such deconditioning is characterized by a reduction in exercise capacity and the development of orthostatic intolerance. Most of the studies of humans employing one-g analogs of weightlessness have been directed at describing the etiology of cardiovascular deconditioning. Further efforts to understand this multifactorial problem have been aided by computer simulations using mathematical models of the cardiovascular system (20). The objective of these computer simulation studies was to test the various hypotheses that have been advanced to explain the fluid, hormonal, and cardiovascular changes that occur in space flight, and to integrate changes in these various systems in order to develop a composite picture of the physiology of weightlessness. In this respect, the mathematical models serve, in a certain sense, as yet another one-g analog which can be used to study the effects of true weightless exposure.

Supine Bed Rest

Among the various analogs of weightlessness, supine bed rest has the longest history, dating back to the studies of Taylor (22-23) in the late 1940's. Immobilization has long been a medical problem of interest; however, there were only a few bed-rest investigations prior to the space-flight era that began in the early 1960's. Following the recognition that there are similarities between immobilization and the weightless state, a large number of bed-rest studies were begun, both in the U.S. and in the U.S.S.R. A list of all U.S., European, and U.S.S.R. human bed-rest studies may be found in the compendia by Greenleaf et al.(24-25).

The comparison analysis presented here began with a survey of the extensive literature on bed-rest investigations. A total of 64 different studies from which useful data could be extracted were selected. The breakdown of these studies between the U.S. and U.S.S.R. is indicated in Table 1, along with other pertinent discriminators.

Table 1: U.S. and U.S.S.R. Bed-Rest Studies Used in the Analysis

	U.S.	U.S.S.R.
Number of studies	48	16
Number of subjects	2-24,72	3-16
Age of subjects (Yrs)	17-46	21-40
Type of Subjects	Healthy, Male	Healthy, Male
Length of Bed-Rest	2-49 days 30-36 weeks	5-120 days

Studies or portions of studies that included countermeasures, drug effects, or other forms of stress were excluded from the analysis. Care was taken not to include any study more than once when different aspects of the same study were reported separately. Where data were not available in tabular form, they were extracted from published graphs or charts.

For many of the U.S. investigations done under NASA contract, individual subject data contained in the final contractor reports were found to be extremely useful. Inspection of these data permitted errors to be detected and questionable data points to be excluded from the averages. Information on incomplete tests, such as a post-bed-rest tilt test not completed due to symptoms of syncope, was useful in determining the exact number of subjects for each data point. Measurements obtained by new and unproven techniques were not taken into account. An example is the cardiac output determination by the single-breath method in the Methodist Hospital/JSC 28-day bed-rest study (26) in which a large increase in cardiac output was found, compared to the small decrease found in most other studies.

Although bed-rest studies ranging in duration up to 120 days have been reported by the Russian investigators, their publications, in many instances, have provided very little valuable quantitative information. For example, in a 62-day bed-rest experiment reported by Kakurin (27), the change in heart rate from pre- to post-bed rest was the only data that could be included in the present analysis. An exception to this was the recent Joint U.S./U.S.S.R. Hypokinesia Study (28-29); the availability of the final report of the USSR study provided individual subject data similar to the data gathered in U.S. studies.

Table 2 lists the cardiovascular variables that were tabulated from the 64 selected bed-rest investigations. Cardiac dimensions, although important, were not included, since techniques for their precise measurement have become available only recently. In addition, electrocardiographic changes were not considered, because our current models do not simulate electrical events of the heart.

The mean changes in the variables listed in Table 2 were computed by treating the reported value of each variable from each of 50 investigations as a sample. Each measurement was weighted with the number of subjects involved in the measurement. Such weighting yielded better estimates of means and standard deviations. The tables and charts containing individual and averaged data are included in a separate report (13). The data were found to have a large variability that was evident even from a cursory examination. For example, the change in resting heart rate from pre- to post-bed rest ranged from -2 to +24 in the 64 investigations. The distribution of the reported heart-rate changes is shown in Figure 5. The wide variability is evidently due to a large number of factors (absolute supine position, diet, circadian influence, to mention a few) that are difficult to control in a study stretching over several days.

The analysis revealed that the change in the circulatory variables due to bed rest did not correlate with the number of days of bed rest. A steady-state was assumed to be obtained within ten days of bed rest. This is borne out by the progression of the loss of plasma volume shown in Figure 6. This figure is similar to the one published by Greenleaf et al. (30), but has more experimental data points included. Much of the plasma volume loss occurs within the first few days of bed rest with only small decrements thereafter.

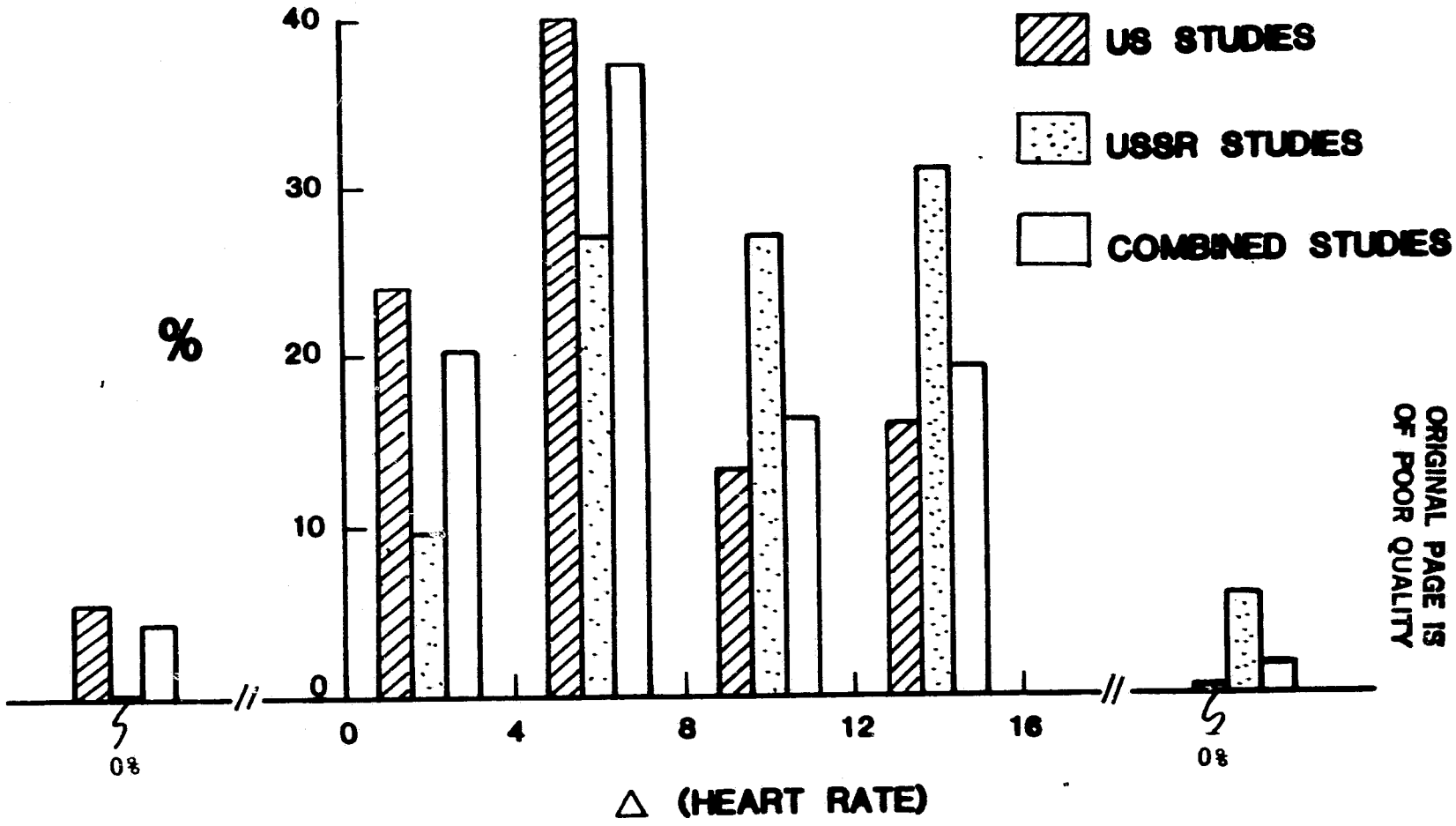
Head-down Tilt

Compared to the large number of supine bed-rest investigations, there have been only a few studies on head-down tilt. This is because the tendency for head-down tilt experiments to produce results that mimic the physiologic alterations of space flight came to attention only recently. To date, there are only three studies in which extensive measurements have been made and reported. These are the 24-hour study

Table 2: Cardiovascular variables analyzed. Tilt, lower body negative pressure (LBNP), and exercise responses are the changes measured from supine or control position during tilt (70^{o}), or LBNP (-30, -40, and -50 mmHg), or exercise (0-600 kpm)

Variable	Resting Value	Tilt Response	LBNP Response	Exercise Response
Heart Rate	X	X	X	X
Pulse Pressure	X	X	X	X
Mean Arterial Pressure	X	X	X	X
Cardiac Output	X	X	X	X
Stroke Volume	X	X	X	X
Total Peripheral Resistance	X	X	X	X
Leg Volume	X	-	X	-
Oxygen Consumption	X	-	-	X
Maximal Oxygen Consumption	X	-	-	-

FIGURE 5: DISTRIBUTION OF REPORTED VALUES OF CHANGES IN RESTING HEART RATE DUE TO SUPINE BED REST



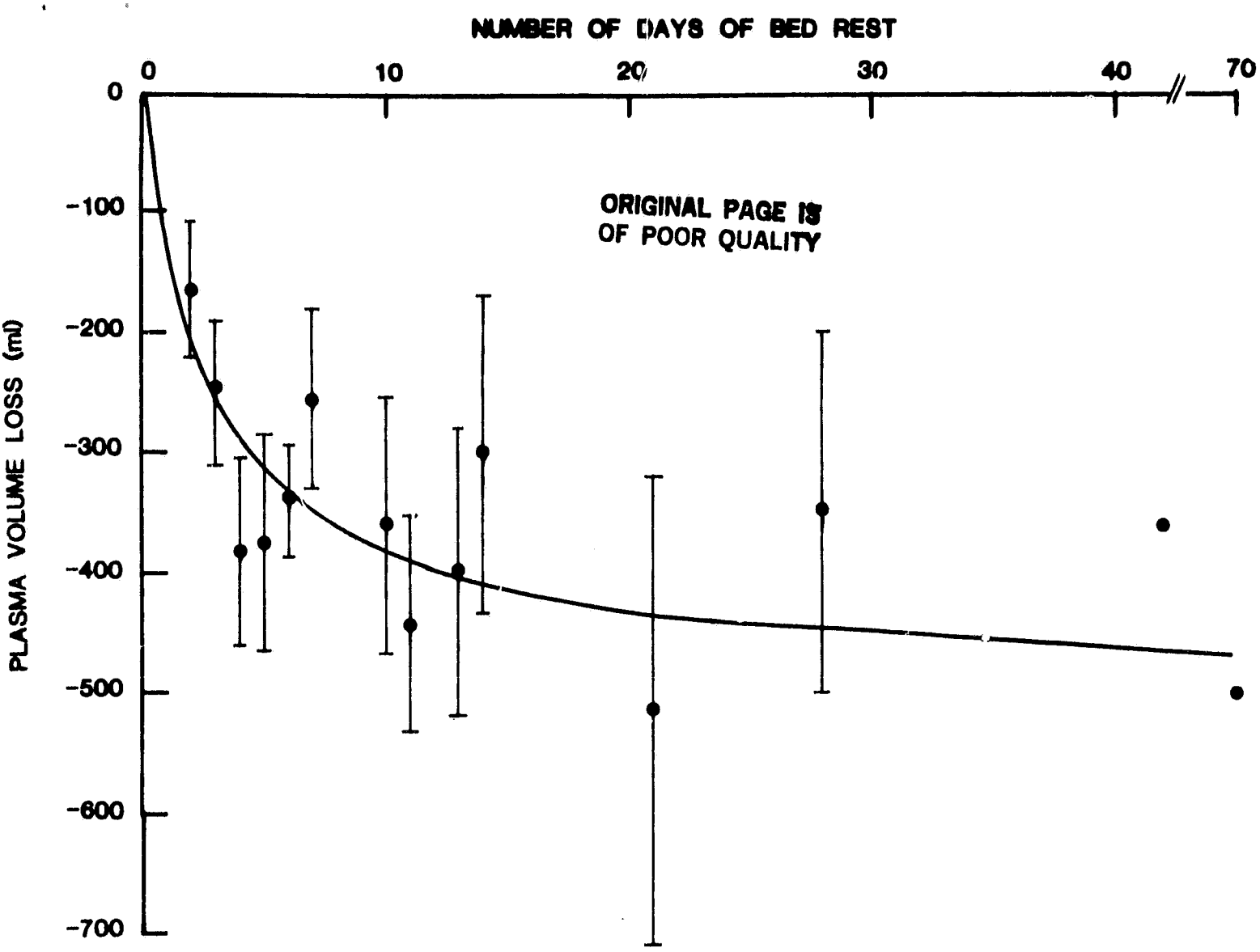


FIGURE 6 **PLASMA VOLUME LOSS DURING SUPINE BED REST.** Except for the last two data points on the right, each point is the mean of reported values from several studies, weighted according to the number of subjects involved. The bars represent the standard deviation of the reported means (inter-study variation). The mean curve is shown by the solid line.

by Nixon, Blomqvist, and their co-workers (31), and the seven-day Joint U.S./U.S.S.R. Hypokinesia Study which consisted of two separate studies, one by the U.S. (28) and the other by the U.S.S.R. researchers (29).

The above published data related to circulatory function were used in the present analysis to compute mean changes as described earlier in the analysis of the supine bed-rest data. Because there were five subjects in all three studies, it was immaterial to weight the reported measurement for obtaining averages. A complete analysis of the data from these studies including the fluid, electrolyte, and hormonal changes; a comparison of the experimental data with computer simulation results may be found in a separate report (32).

Computer Simulation

The simulation results presented in this section were obtained using a short-term pulsatile model of the cardiovascular system. It is a lumped-parameter model based on the assumption of a closed vascular system with no provision for fluid filtration into the extravascular space. It was originally developed to simulate exercise (33) and later modified to perform simulations of lower body negative pressure (LBNP) and tilt experiments under one-g conditions (34). It has been used in several analyses related to the Skylab data (35).

A normal set of values for the model parameters defined the condition prior to any hypogravic stress. The post-stress condition was obtained by alteration of certain of the parameters according to the following hypotheses:

1. A loss of blood volume as a compensatory response to proposed headward fluid shifts and central hypervolumia.

2. A redistribution of the diminished blood volume with resultant lower values of mean pressures and volumes in the leg veins and venules.

3. A higher resistance to flow in all parts of the circulation.

The last hypothesis listed above, which concerns the increase of flow resistance, is based on experimental data. A large increase in total peripheral resistance was calculated by Nixon et al. (31) in their 24-hour head-down tilt study. Many supine bed-rest studies have also indicated an increase of this circulatory variable. Postflight measurements in Skylab astronauts showed a decrease in cardiac output and an increase in mean arterial pressure, resulting in an average rise of resistance in the circulation. In the simulation, all resistance values were changed by +20 percent during post-hypogravic stress. This increase can be accounted for by the increase of viscosity due to hemoconcentration and some hormonal factors such as angiotensin.

There is little uncertainty regarding the loss of blood volume in all of the hypogravic stress situations considered here. The contribution of the various mechanisms that lead to this loss, apparently initiated by the headward movement of fluids upon exposure to weightlessness or a related condition, are now known with certainty. The blood volume loss assumed in the simulation was 10 percent or 500 ml. This figure is close to the weighted average value of 450 ml calculated using data from supine bed-rest studies (see Figure 6).

The second hypothesis relates to the plausibility of a portion of the blood volume loss being attributable to the loss of blood from venous compartments of the lower extremities. This hypothesis is supported by the reductions in leg volume observed in Skylab astronauts and in bed rest and head-down tilt studies. Comparison of the reductions in leg volume and total blood volume is shown in Figure 7. The space-flight data shown in this figure are the averages from the three manned Skylab missions. While the blood volume loss is approximately the same in all three cases shown, this is not true of the leg volume reduction. The huge leg volume reduction which occurs in weightlessness is a phenomenon that no one-g analog has been able to reproduce.

One of the results of leg volume reduction during the various hypogravic stresses is the diminution of mean pressures and volumes in

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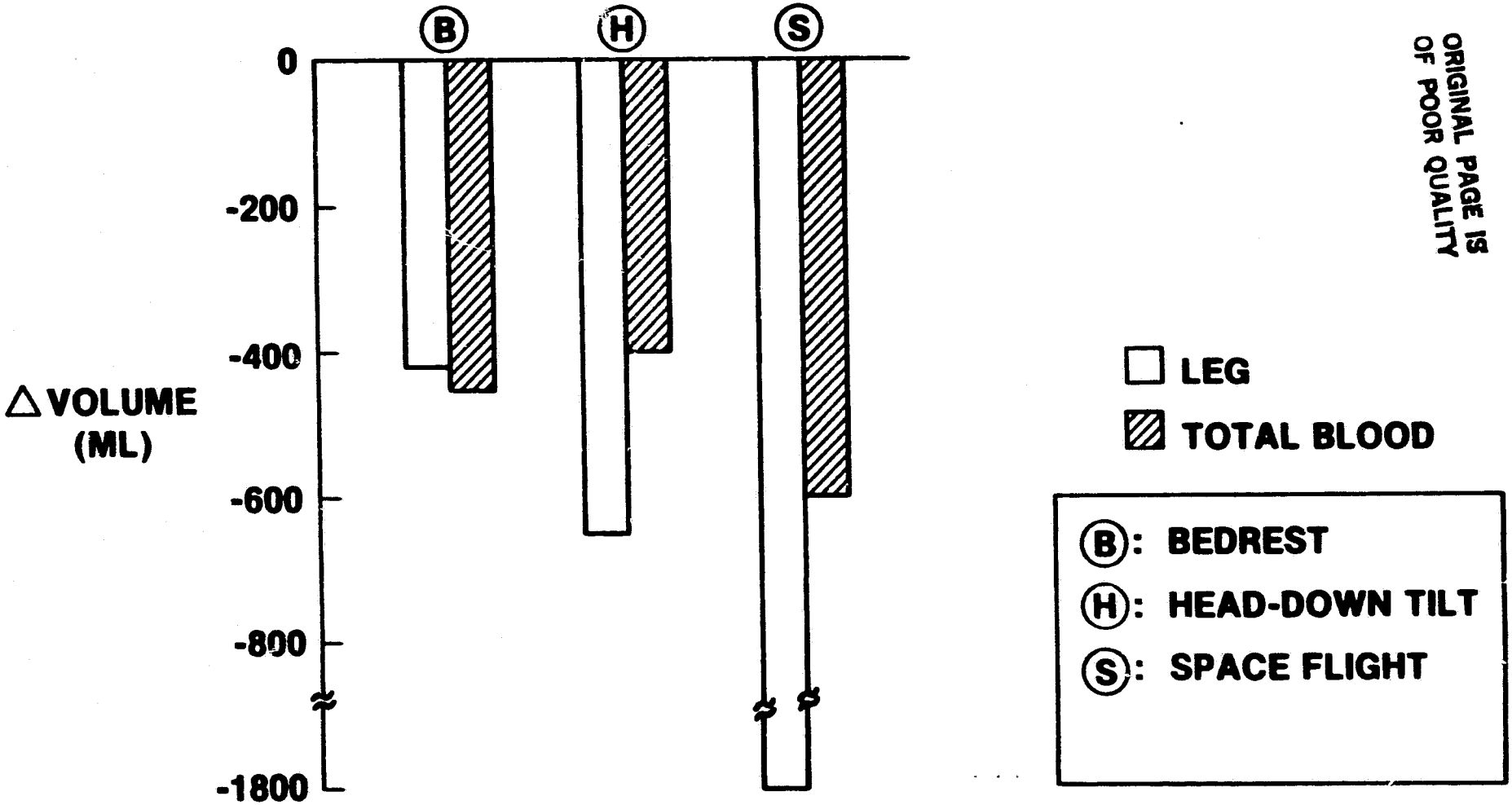
FIGURE 7

COMPARISON OF REDUCTIONS IN LEG VOLUME AND TOTAL BLOOD VOLUME



the lower extremities. The operating point on the pressure-volume curve must shift towards the lower left as shown on Figure 8. With a nonlinear pressure-volume characteristic, such a shift implies an increase in venous compliance without a fundamental change in the relationship between pressure and volume.

Results and Discussion

Two examples of simulation results are shown in Figures 9 and 10. Also shown for comparison are the average changes obtained from supine bed rest, head-down tilt, and Skylab studies. Cardiac output, stroke volume, and peripheral resistance are not shown for space flight as these variables have never been measured inflight.

As shown in Figure 9, the direction of change in heart rate, cardiac output, stroke volume, and peripheral resistance is the same in the various hypogravic stress situations considered here. The simulated data are in general agreement with experimental data in all of these cases. However, such is not the case for either mean or pulse pressure. While simulation and supine bed rest show similar changes in pressures in one direction, changes in head-down tilt and space flight are closer in the opposite direction. The observed changes in mean pressure are small and need not concern us. We do not know the reasons for the differences in pulse pressure changes.

The pre- and post-stress cardiovascular responses to -50 mmHg LBNP are compared in Figure 10. The increment in the heart-rate response is approximately the same in all cases. Simulation and supine bed rest show comparable decrements in pulse-pressure response as do head-down tilt and space flight. Again, the changes in mean pressure are well within measurement errors. It may be safely stated that the mean pressure is unaltered by any of the hypogravic stresses discussed here. The changes in cardiac output, stroke volume, and peripheral resistance are much larger in head-down tilt than in supine bed rest. Also, the pattern of the cardiac output and peripheral resistance changes is different in head-down tilt and supine bed rest. More experimental data are needed to resolve this difference.

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FIGURE 8

NONLINEAR PRESSURE-VOLUME CHARACTERISTIC

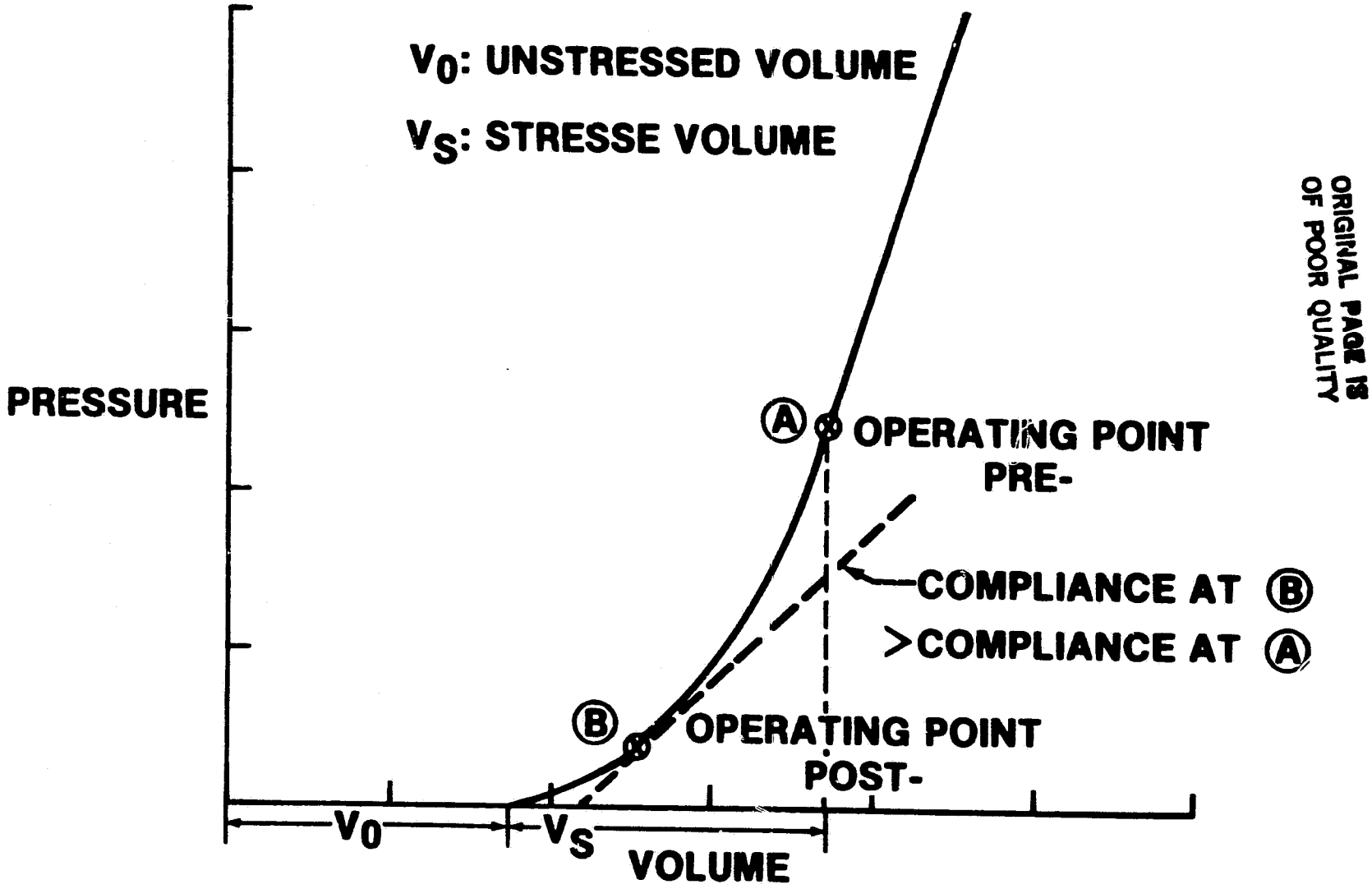

FIGURE 9

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COMPARISON OF CHANGES IN RESTING CARDIOVASCULAR INDICES DUE TO HYPOGRAVIC STRESS

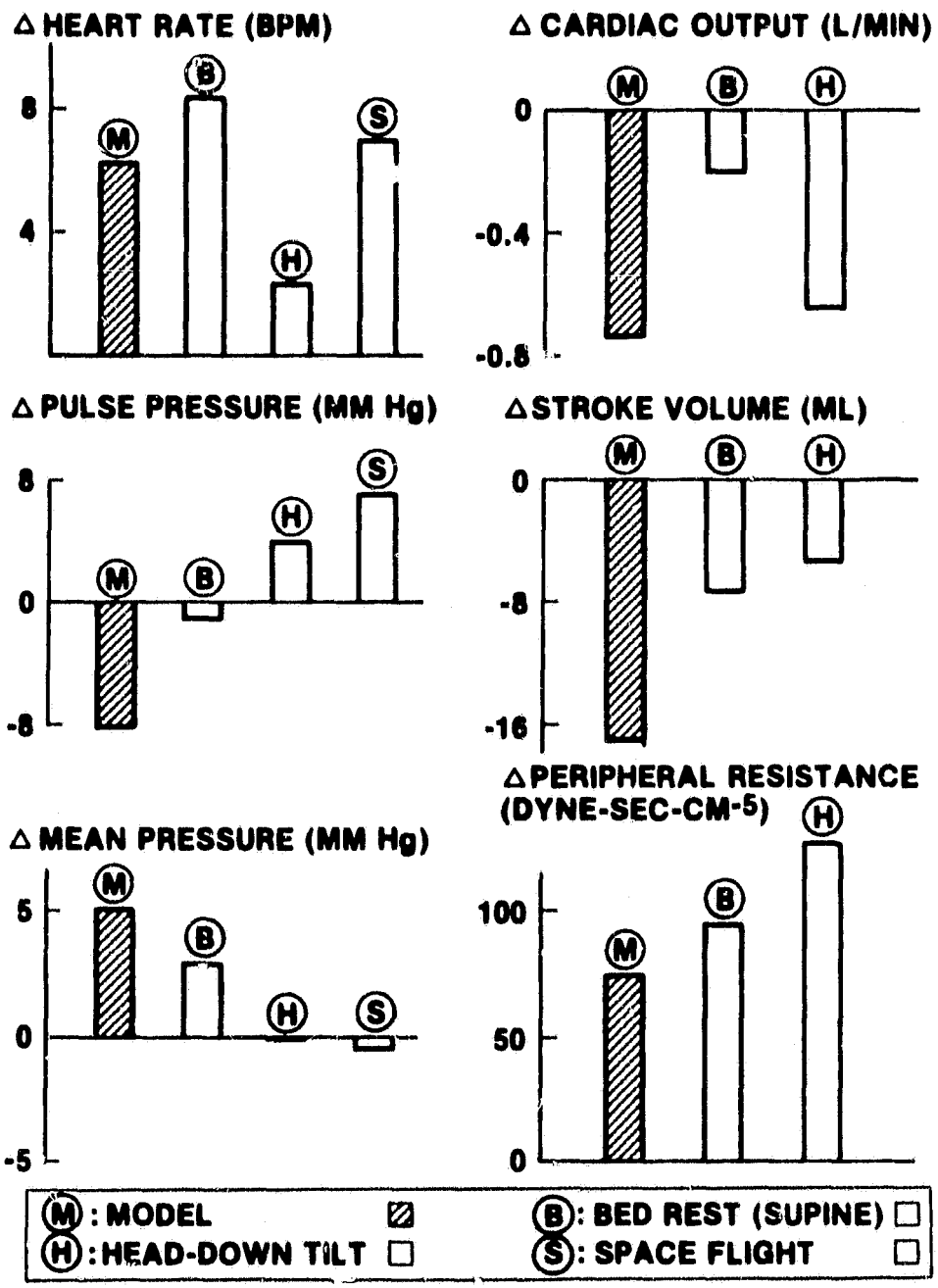
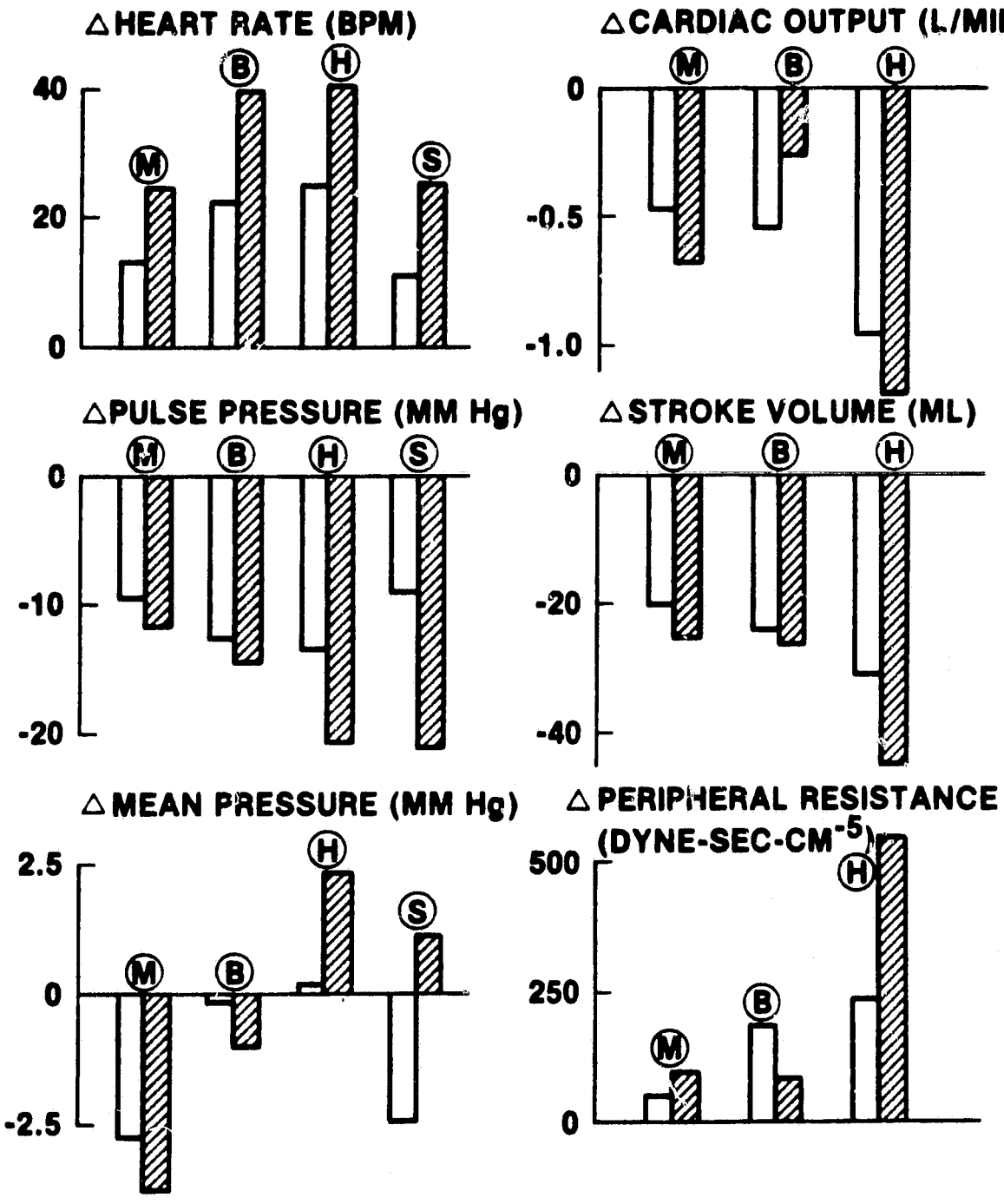


FIGURE 10

CARDIOVASCULAR RESPONSE TO LBNP (-50MM Hg): CHANGES DUE TO HYPOGRAVIC STRESS



The analysis presented here concerns two separate comparisons: (i) comparison of supine bed rest and head-down tilt with space flight, and (ii) comparison of model and experimental data. With regard to (i), the data on pulse pressure change support the contention that head-down tilt is a better analog of space flight than supine bed rest. With regard to (ii), the model data agree more closely with supine bed-rest data than with head-down tilt and space-flight data in some instances; the reverse is true in others. Apparently, the three major hypotheses used in our simulation are inadequate to simulate all three of the hypogravic stress situations. It appears to be necessary to include additional hypotheses involving myocardial and autonomic function changes. These changes were not considered here, as evidence clearly demonstrating their presence during hypogravic stress is lacking at the present time. The following conclusions are evident from the simulation studies:

1. The cardiovascular response to orthostatic stress following exposure to weightlessness or any of its analogs cannot be explained fully on the basis of blood volume loss alone.

2. Peripheral resistance changes appear to play a significant role in producing the observed cardiovascular responses.

3. The lowering of mean pressures and volumes in the legs seem to be more dominant than any fundamental change in leg venous compliance.

4.0 ERYTHROPOIESIS REGULATION

4.1 INTRODUCTION

Contractor work concerning erythropoiesis regulation involved both the development of species-specific models for the rat and the monkey and the analysis of model function for the man, mouse, rat, and monkey models. Certain additional studies related to erythropoietin control or to red cell dynamics were also conducted. During this contract period, work in this area has led to three publications (36-38), four technical reports (39-42), and two abstracts of presentations at major scientific meetings (43-44).

4.2 NEW MODEL DEVELOPMENT

Mathematical models representing the human and murine erythropoietic systems have been previously developed (36,37). These models have been useful in elucidating the mechanisms involved in the control of erythropoiesis under a variety of stress situations, including space flight. Recently, results of experiments concerning erythropoiesis regulation during both space flight and ground-based studies have been published. These studies utilize human subjects as well as the laboratory mouse, rat, and monkey. In order to analyze the data from these new experiments, relate experimental results among species, and address the problem of species variation, a uniform, species-independent modeling approach to the erythropoiesis system has been developed by this contractor.

The original erythropoiesis model (36) was developed to study the relative influence of the controlling factors of erythropoiesis on total red cell mass. This formulation was based on the concept that the overall balance between oxygen supply and demand regulates the release of the hormone erythropoietin from renal tissues sensitive to oxygen tension levels and which, in turn, controls bone marrow red cell production.

Renal oxygen tissue tension is influenced by several factors: hemoglobin concentration, lung oxygenation of hemoglobin, renal blood flow, and oxygen-hemoglobin affinity. A fraction of the oxygen reaching the kidney is extracted by the tissues, depending on the oxygen demand parameter. Oxygen enters the renal tissue by diffusion along an oxygen gradient between the venous capillaries and the tissue cells. A decrease in the oxygen supply in relation to the oxygen demand will reduce the tissue oxygen tension and result in an increased rate of erythropoietin release. Erythropoietin is released into the general circulation with its resulting concentration in the plasma being determined by its rate of release, volume of distribution, and the rate at which it is metabolized. The target of erythropoietin is the hemopoietic tissue. The production rate and release of red cells are determined by the plasma concentration of erythropoietin. There is a time delay between marrow stimulation and red cell release. The rate of red blood cell destruction is based on the life span of the cell and is assumed to be a fixed percentage of the red cell mass.

The problem of developing species-specific models was approached in the following manner. The equations from the original model of erythropoiesis were rederived to produce a minimal set of equations and parameters (38,39). In this mathematically reduced form, the model consisted of three non-linear differential equations and contained twelve parameters. The differential equations were scaled using the normal values of the three dependent variables (red cell mass, plasma concentration of erythropoietin, and red blood cell production rate). The twelve independent parameters were determined from the original model and each of these new parameters was a composite of several of the original physiological parameters. The physiological parameter values themselves are dependent upon the species of interest. Reducing the number of parameters and equations in this manner generalizes the form of the model and thus simplifies the analysis of model function. This new formulation of the model was ideal for studying interspecies variation, for once it was understood how the model functioned in general, species variation

aspects could be studied by simply changing the physiological parameter values, without altering the overall model structure.

In order to develop rat and monkey erythropoiesis models, an extensive literature search was performed in order to collect the necessary physiological data. Data were collected for the Sprague-Dawley rat strain and the squirrel monkey; these are the two species that are scheduled to be used as specimens in the hematology experiments onboard the Spacelab-4 dedicated Life Sciences shuttle mission. A description of the model reformulation, as well as the equations and parameters used in the model, can be found in a technical report (38). The actual parameter values used for each model, along with the rationale for the selection of those values, have been documented in a second technical report (40).

This appears to be the first time that a single model formulation has been used to represent (model) several different species. In the past, parameter values and experimental erythropoiesis data from one animal species have been used to estimate model parameters and to validate models, but they have never been used to develop separate models for each of several animal species. The present approach assumes that the basic concept of erythropoiesis control is identical among the species of interest; the overall model formulation is general. This does not necessarily imply that either the detailed physiology or the anatomical correspondence is identical. For example, all of the hemopoietic tissue is grouped into one compartment. This one compartment, however, may be anatomically equivalent to several different organs. In man, this compartment is equivalent to active bone marrow, while in the mouse this compartment may consist of two or more anatomical components (bone marrow, spleen, etc.). The significance of being able to simulate several different species using the same general model description is that, while there may be anatomical differences, the physiologies are governed by the same factors. This implies that one species can be used to study the physiology of another species.

4.3 NEW ANALYSES AND SIMULATIONS

The next phase of the erythropoiesis work was carried out in two parts: first, a detailed sensitivity analysis of how the model functions for each of the four species was performed, and second, the response of the four models to a variety of impulse and step stresses relevant to the space-flight program were studied. The details of this study have been documented in a contractor report (41). The following discussion highlights this species comparison study.

Sensitivity Analysis

Using the new model formulation discussed above, a comparative sensitivity analysis was performed using the species-specific models for the human, mouse, rat, and monkey. Because, in this new model, species-specific physiology enters through only the independent parameters, and because one of the primary issues related to model operation concerns the effect of parameter changes on the dependent variables, a detailed sensitivity analysis is the logical form for performing both a qualitative and quantitative comparison of the four species models. This analysis was performed on both the steady-state and dynamic versions of the models.

Steady-State Sensitivity Anaysis. The steady-state analysis consisted of parameter-variation studies and the direct analytical determination of steady-state parameter sensitivities. The parameter-variation study was performed by plotting the new steady-state solutions of the model equations that were obtained when each of the mathematical and physiological parameters were varied from 50 to 150 percent of their normal values for each of the four species ((39,41). Parameter sensitivities were also calculated for each of the mathematical and physiological parameters. The parameter sensitivities are the proportionality constants that directly relate changes in parameters to changes in variable values.

The results from this study showed that the model exhibits non-linear parameter dependence for all four species. However, it also showed that over the range of red cell mass that contains the physiologically meaningful information (50% of normalized red cell mass), the system responds in an approximately linear fashion. This is important because the parameter sensitivities which can be used to estimate new values of red cell mass and erythropoietin concentration for small changes (usually < about 5%) in a single parameter, or for small changes in combinations of parameters, can also be used to accurately estimate steady-state solutions for moderate changes (5 to 10%) in the parameter values without the need of an iterative solution scheme.

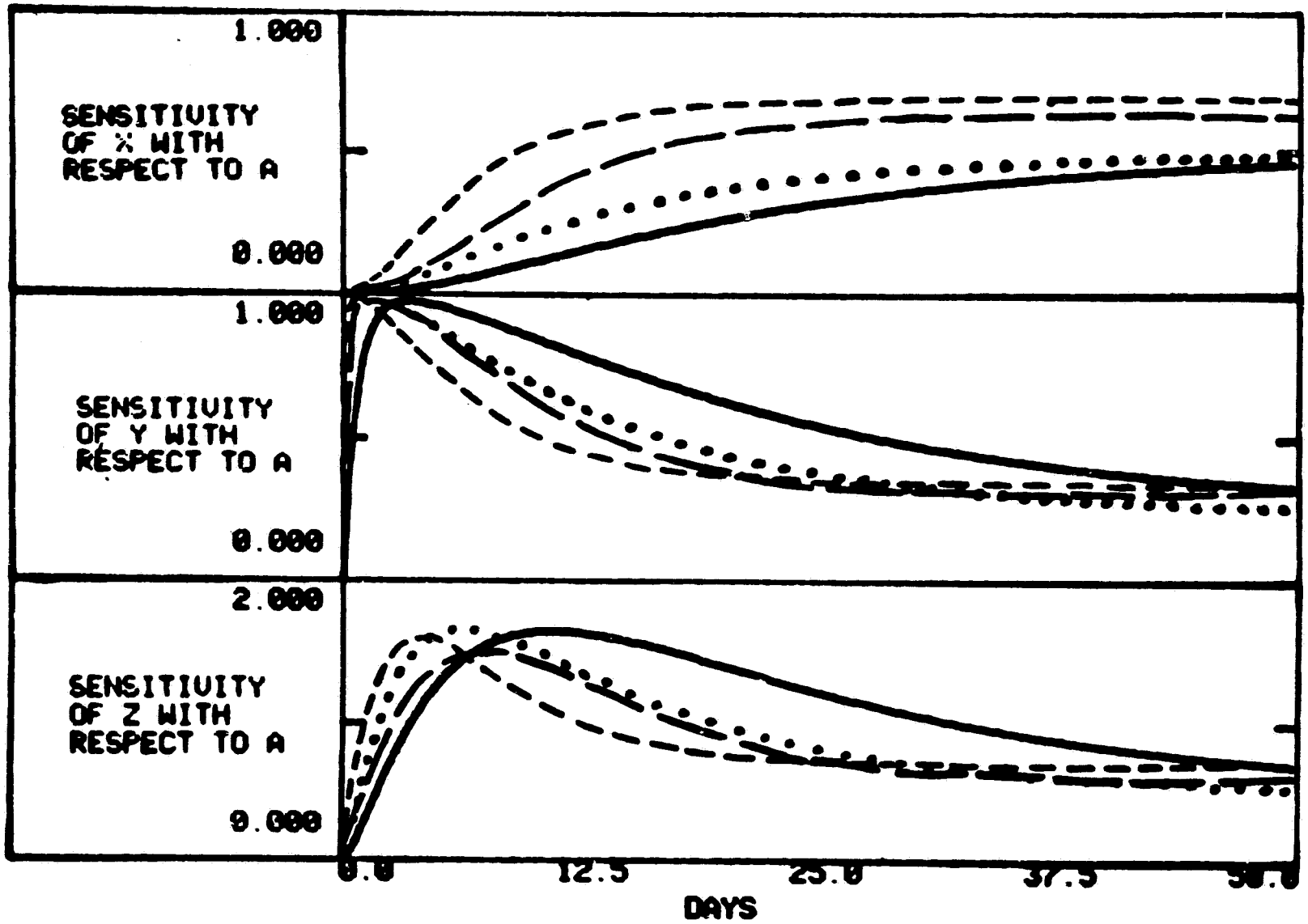
The steady-state sensitivity analysis also allows a ranking of the model parameters according to the impact that their changes have on the steady-state solutions, and of identifying how those solutions vary between species. If the erythropoietic systems show identical responses to parameter changes (that is, if the mouse, rat, and monkey are perfect models of human erythropoiesis), the mathematical parameters should be identical, even though the specific physiological parameters would be expected to be different. In fact, the mathematical parameters calculated for the four models are different, but within the same order of magnitude. The qualitative responses of the four models to independent variations in the mathematical parameters, while slightly different at the extremes of the parameter variation, are similar about the normal operating point. The parameter sensitivities for the four models are also slightly different; however, the magnitude and overall ranking of the mathematical parameters remain the same between the species. The interesting analysis from a physiological point of view is the species-to-species model response to changes in the physiological parameters. Changes in renal blood flow (Q), plasma volume (PV), and renal oxygen uptake (V_m) produce qualitatively the same results in all species. This is confirmed by the magnitude of the sensitivity coefficients for these parameters. However, the model response to changes in arterial oxygen tension (P_aO) and the partial pressure at

which hemoglobin is 50 percent saturated with oxygen (P_{50}) varies significantly among species. In fact, the curves actually change positions as body mass decreases (i.e., from man down to the mouse). This reverse in parameter sensitivities can be traced back to the species difference in the ratio of P_{50}/P_aO. This ratio aids in determining the shape of the oxygen-hemoglobin dissociation curve and the location of the operating point on that curve. A change in P_{50} will change the curve shape, a change in P_aO will change the location of the operating point, and a change in either will change the value of arterial oxygen saturation (S_aO) which is used to calculate several of the mathematical parameters.

The steady-state sensitivity analysis yielded the following two main results: 1) all four models qualitatively respond the same way to changes in the mathematical parameters, and 2) the models respond qualitatively the same way to changes in all of the major physiological parameters, except for P_aO and P_{50}. In the steady-state, the most interesting species difference lies in the model response to changes in P_aO and P_{50}.

Dynamic Sensitivity Analysis. The dynamic sensitivity analysis consisted of the calculation of dynamic sensitivities for all of the parameters, both "mathematical" and physiological. Dynamic sensitivities describe how the independent variable values change with respect to changes in parameter values as a function of simulation time. Figure 11 shows an example of how the sensitivities for red cell mass (X), erythropoietin concentration (Y), and red blood cell production (Z), each with respect to the mathematical parameter 'A', change as a function of simulation time for the human, squirrel monkey, rat, and mouse. The sensitivity curves for Y and Z show that the model is more sensitive to changes in parameter 'A' early in a simulation (0 to 25 days) where the sensivities peak in value, than later in a simulation where the sensitivities slowly decrease to the steady-state value. The sensitivity curves for Y peak sooner than the curves for Z. The sensitivity curves for X, with respect to 'A', however, show that the sensitivity increases

FIGURE 11 DYNAMIC SENSITIVITIES OF X, Y, AND Z WITH RESPECT TO THE MATHEMATICAL PARAMETER A FOR THE HUMAN (——), SQUIRREL MONKEY (····), RAT (– – –), AND MOUSE (— –).



slowly until it asymptomatically approaches the steady-state sensitivity value. Similar results were found for all parameters, both mathematical and physiological, for all four species. The only major difference is that some of the parameters have negative sensitivities. However, the trends for the sensitivities of the parameters with respect to X, Y, and Z remain the same. The trend for Y and Z to be more sensitive to parameter changes early in a simulation, and for X to be more sensitive to parameter changes at the end of a simulation are related to the time constants K_1, K_2, and K_3 which are associated with the equations for X, Y, and Z, respectively. The K_1 values for all species (variable X) are at least an order of magnitude smaller than the K_2 and K_3 values (variables Y and Z). The K_3 values are within the same order of magnitude as the K_2 values, but are consistently smaller. These constants correspond to the time frames associated with the physiology of the three variables, X, Y, and Z. Changes in variable Y (K_2), erythropoietin concentration, can take place in the order of hours; changes in Z (K_3), red blood cell production, occur within days; while changes in X (K_1), red cell mass, occur only after many days.

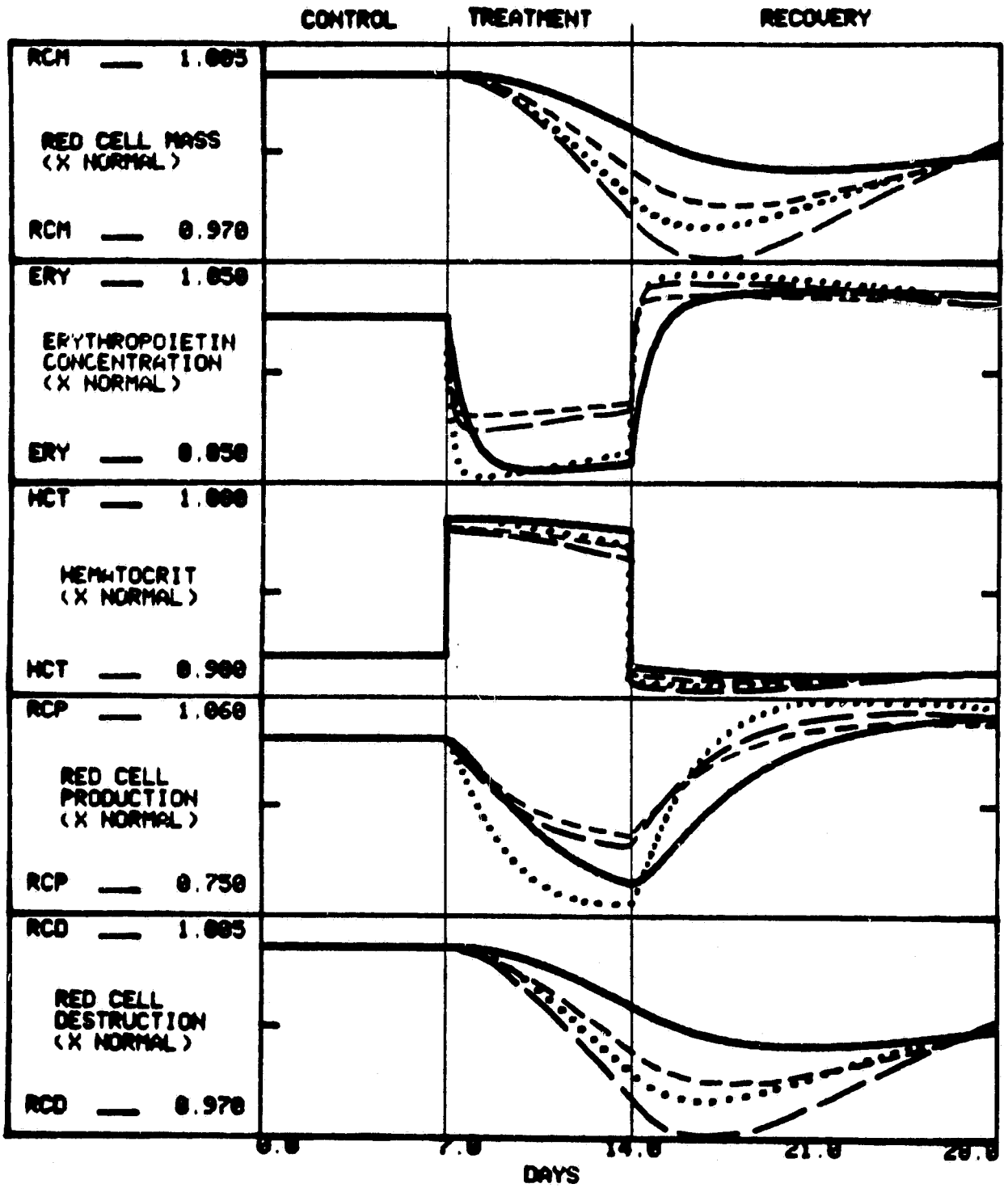
Species Response to Identical Hypoxic Stresses

A series of comparative simulations were performed using the four species models. These simulations were performed in order to study the species-to-species response to the following stresses: altitude hypoxia, descent from altitude, loss of red cell mass, red cell infusion, and plasma volume depletion. For each of these simulations the two gain factors in the model (G_1, the gain of erythropoietin control function and G_2, the gain of the marrow red-blood cell production-control function) were held constant at the same values for all species. This was done in order to examine how the species differences in the physiological parameters affect the model operation. The detailed results from these simulations can be found in a separate report (41). The following discussion describes the results from one of these comparative simulations.

Plasma volume depletion simulations were performed for the human and also for the mouse, rat, and squirrel monkey, in order to compare the animals as analogs of human erythropoiesis control during space flight. Plasma volume depletion has been modeled previously to simulate the effects of space flight on the erythropoiesis system. The simulation used consisted of seven days of control, followed by seven days of plasma volume depletion followed by 14 days of recovery. These time periods were selected as being representative of a one-week Spacelab mission. The plasma volume was decreased by 10 percent for each species the first inflight day, held at this level for seven days, then returned to normal at the end of the seventh day. Figure 12 shows the results of this simulation for all four species. The data shown are for a selected set of hematological variables for each species. The values for the variables shown in Figure 12 have been scaled to represent changes from normal, where RCM = red cell mass, ERY = erythropoietin concentration, HCT = hematocrit, RCP = red blood cell production, and RCD = red blood cell destruction.

The qualitative response of all four species to a 10 percent decrease in plasma volume is approximately the same. All four show gradual decreases in red cell mass and red blood cell destruction, along with more dramatic decreases in erythropoietin concentration and red blood cell production during the treatment phase. These decreases are all caused by the increase in hematocrit due to the plasma volume depletion. The species differences that are observed have to do with the magnitude and the rate at which the changes take place. As can be seen there is no uniform ranking between the species as to how they respond to the stress for each of the variables. This is due to the fact that for the selected combination of parameters for each species there is not a consistent ranking between species for the steady-state sensitivities (magnitude of response), nor for the time constants (rate of responses). However, the simulations do show that the qualitative response to the stress is consistent between the species; that is, all of the variable values respond in a similar fashion for all four species.

FIGURE 12 7 DAY 10% PLASMA VOLUME DEPLETION IN MAN (——), SQUIRREL MONKEY (• • • •), RAT (- - -), AND MOUSE (— —).



The examples described above demonstrate the utility of performing sensitivity analyses in conjunction with model formulation. They clearly demonstrate the role and importance of parameter values in interpreting and understanding the functioning of the model.

4.4 ADDITIONAL WORK

Effects of Hematocrit and Blood Volume on Blood Flow and Oxygen Transport

An additional task completed during the contract period involved the development of a subsystem model to describe the effects of hematocrit and blood volume on blood flow and oxygen transport. This task was initiated by performing a review of the relevant literature to determine the relationships between blood flow, blood velocity, and blood volume. The review included previously collected material as well as a literature search for reports on recent investigations.

The general relationship between blood flow and hematocrit and between blood flow and blood volume were studied, and different functional forms were developed to describe the observed relationships between these variables. By using simple linear functions to relate blood flow, blood volume, and oxygen concentration to hematocrit, it was possible to reproduce reasonably well the family of curves representing the maximum amount of systemic oxygen transport as a function of the hematocrit level at different blood volumes.

While these results were encouraging, they pertained only to acute changes. The remaining work that was performed under this task involved identifying and defining the problems of hematocrit and blood volume variations for long-term changes, and the effects of both short-term and long-term changes in hematocrit and blood volume on renal circulation. The detailed results of this study have been documented in a separate contractor report (42).

Effects of P_{50} Shifts on Erythropoiesis Model Operation

P_{50} values have been shown to shift (increase or decrease) under certain erythropoietic stresses such as hypoxia. However, the direction and magnitude of these changes have been the subject of much investigation and controversy (45-47). In addition, there is disagreement as to whether a P_{50} shift to the right (increase) or a shift to the left (decrease) from normal is more beneficial to the body during hypoxic stresses. Since hypoxic stresses are used quite frequently to help understand the physiology and operation of the erythropoietic system, a study was performed to learn how changes in P_{50} values affect the operation of the erythropoiesis model.

One of the most important relationships in the regulation of erythropoiesis (and in the formulation of the model) is the oxygen-hemoglobin dissociation curve (ODC). The ODC relates arterial oxygen tension (P_aO) to the percent saturation of arterial blood with oxygen (S_aO). This relationship can be characterized by its shape, quantitatively expressed by the slope, n, of the Hill equation, and by the position of the curve, usually designated by P_{50}. The position of the ODC can be shifted by changes in blood pH, temperature, and organic phosphate concentration. Due to the complexity of the compensatory responses of the body to hypoxia, there is considerable uncertainty about whether these changes result in left or rightward shifts in P_{50} and whether or not these shifts are of any benefit.

The current formulation of the erythropoiesis model uses a formulation of the Hill equation to describe the percent saturation of arterial blood (S_aO) and the venous oxygen tension (P_vO). The model was used to address two different aspects of P_{50} shifts. The first aspect studied concerned the effects to the model of instantaneous changes in P_{50} (that is, how the model responds to changes in P_{50} before the red cell mass begins to adapt to the new conditions). Because the model was formulated using the concept of a renal tissue oxygen sensor for the release of erythropoietin, renal

oxygen tension (P_tO) was selected as the parameter that would be used to determine if instantaneous P_{50} shifts would be beneficial; thus, increases in P_tO would be considered beneficial. This first part of the study was performed using those portions of the model equations which describe P_tO. P_tO was determined as a function of P_{50} at several different values of arterial oxygen tension (P_aO). These results, which can be seen in Figure 13, show, over the range of physiologically meaningful P_{50} values from 10 to 50 mmHg, that for moderate hypoxia ($P_aO > 40$ mmHg), rightward P_{50} shifts always cause an increase in P_tO. However, for severe hypoxia ($P_aO < 40$ mmHg), there are specific P_{50} values which will yield the highest optimal values of P_tO. Whether or not these optimal P_{50} values constitute right or leftward shifts from normal depends on the severity of the hypoxic stress.

The second part of this study involved extending the simulation to see how instantaneous P_{50} shifts affected the new steady-state model solutions that would be obtained at different levels of P_aO (that is, how the model would respond to changes in P_{50} after the red cell mass began adapting to the new conditions). To accomplish this goal, the steady-state sensitivity analysis of the erythropoiesis model discussed in the last section was extended to include P_tO. The effects of parameter variations on P_tO values, as well as parameter sensitivities, were determined at different levels of P_aO. The results from this study are presented in Figures 14 and 15. Figure 14 shows how the new steady-state values of P_tO will change as P_{50} is varied from 50 to 200 percent of the normal value. For moderate hypoxia ($P_aO > 40$ mmHg), P_{50} shifts to the right will result in increases in P_tO. However, for severe hypoxia ($P_aO < 40$ mmHg) maximum P_tO values are observed and left or right shifts in P_{50} about those maxima will not be beneficial. Figure 15 shows a plot of the sensitivities of P_tO with respect to P_{50} as a function of P_aO. The center line on the graph separates the regions where rightward versus leftward P_{50} shifts would be beneficial. That portion of the curve above the line (positive sensitivities) indicates where rightward shifts would be beneficial, while that part of the curve below the

FIGURE 13 INSTANTANEOUS VALUES OF RENAL OXYGEN TENSION AS A FUNCTION OF P50 AT DIFFERENT LEVELS OF ARTERIAL OXYGEN TENSION (PAO).

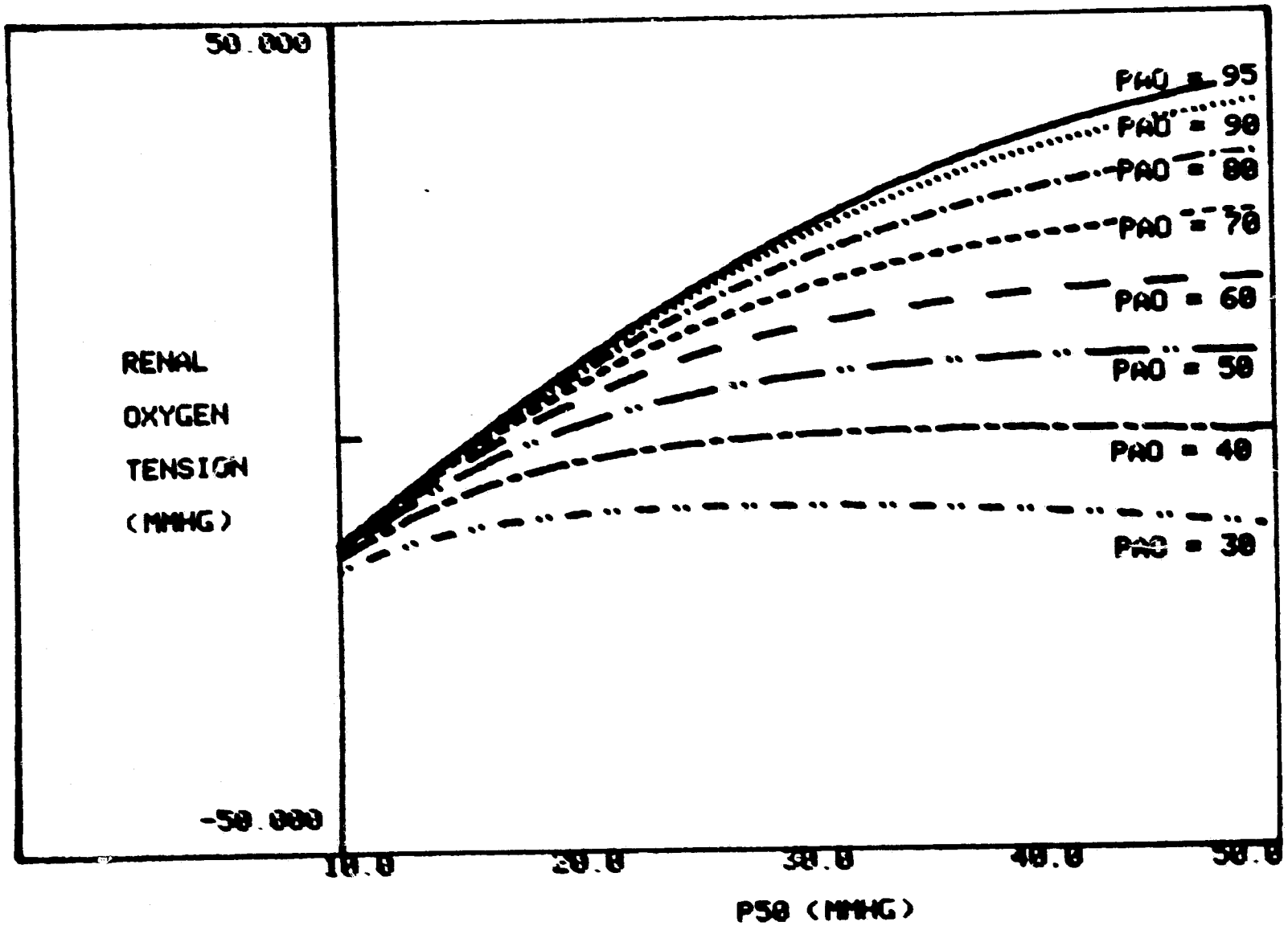


FIGURE 14 OXYGEN TENSION AS A FUNCTION OF P50 AT VARIOUS LEVELS OF ARTERIAL OXYGEN TENSION (PAO)

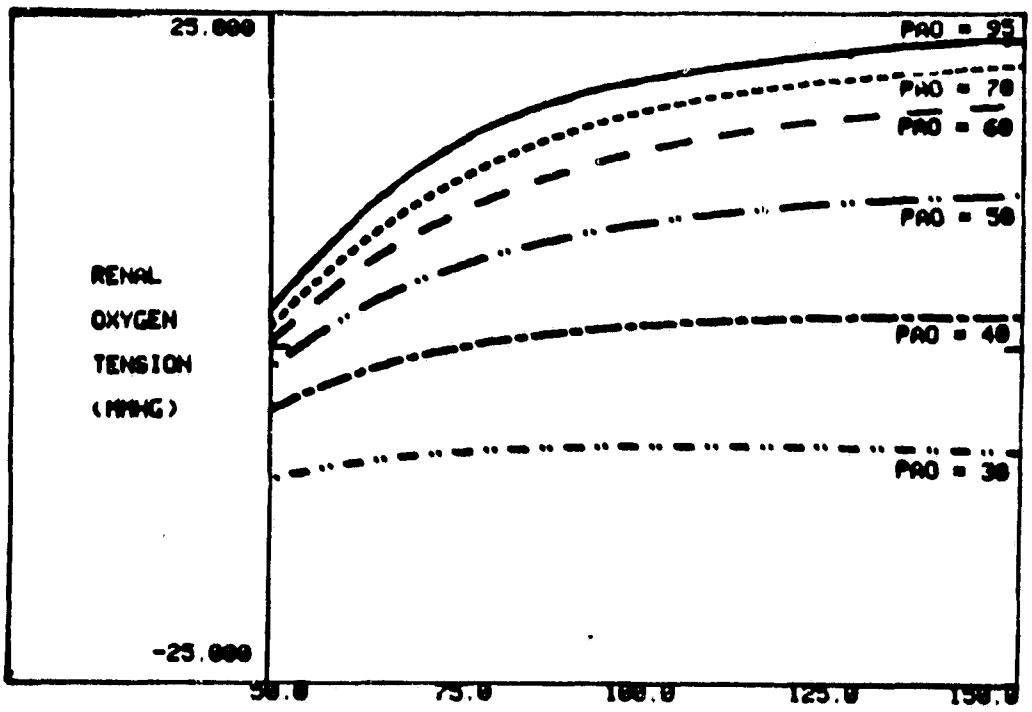


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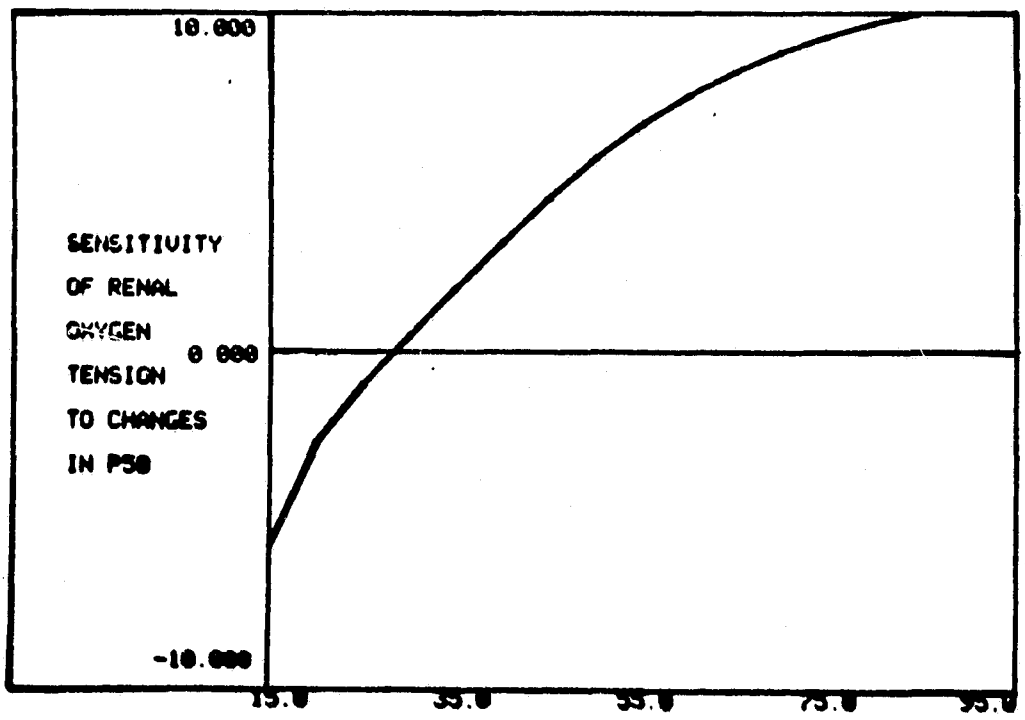
FIGURE 15 STEADY STATE SENSITIVITY COEFICIENTS OF RENAL OXYGEN TENSION WITH RESPECT TO P50 AS A FUNCTION OF ARTEPIAL OXYGEN TENSION



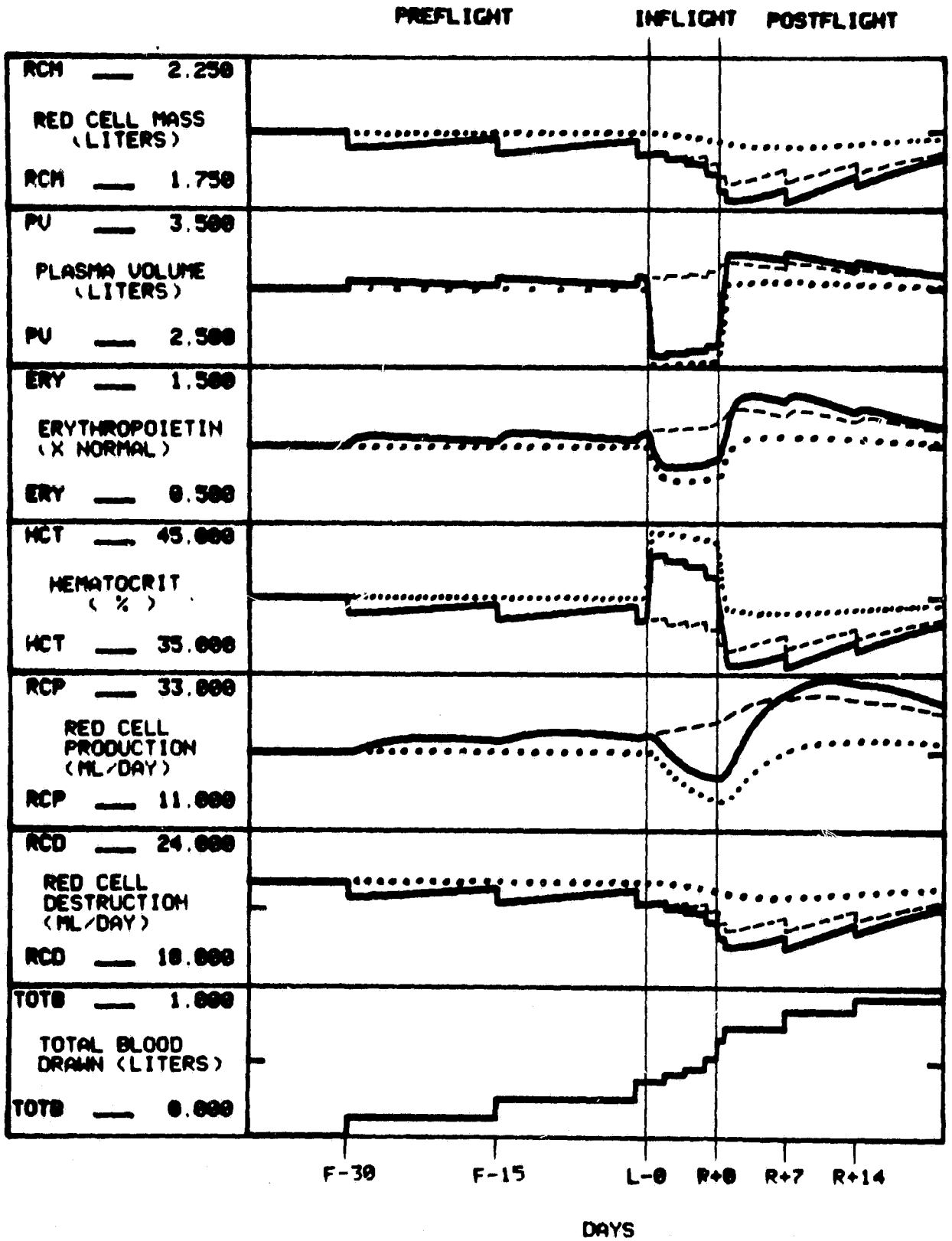
center line (negative sensitivities) represents that region where leftward P_{50} shifts would be beneficial. The point where the plot crosses the line indicates the P_aO value at which neither left nor right P_{50} shifts would be beneficial. This value is approximately 28 mmHg in the human, but in the mouse the value is closer to 42 mmHg. These P_{50} shift differences between man and the mouse are caused by the different P_{50}/P_aO ratios for the two species. This ratio determines both the shape of the oxygen-hemoglobin dissociation curve and the location of the normal operating point for the animal on that curve. Thus, for studies of the effects of P_{50} shifts at altitude, this indicates that animal experiments could yield different results than could human experiments.

According to the current formulation of the erythropoiesis model, increases in P_{50} would be beneficial for moderate hypoxia ($P_aO > 40$ mmHg). However, for severe hypoxia ($P_aO < 40$ mmHg) there is a single maximum P_{50} value which is most beneficial; this value could represent either a right or left-ward shift from the normal P_{50} value, depending on the severity of the hypoxic stress and the species being studied.

Simulation of the SL-1 Blood-Draw Protocol

A series of simulations were performed to study what effect, if any, the proposed SL-1 blood draws might have on the physiology of the participating crewmembers. The erythropoiesis system should be one of the most sensitive of the body's systems to any artificial alterations in red cell mass and plasma volume (that is, to blood draws); therefore, it was decided to use the erythropoiesis model to perform this study. The following three simulations were performed to examine the effect of blood draws: 1) zero-g stress simulation only (no blood draws), 2) SL-1 blood-draw stress simulation only (no zero-g stress), and 3) combined zero-g and SL-1 blood-draw stress simulation. The results from these simulations are presented in Figure 16. In each of these simulations, the total blood volume was assumed to be constant (either 5000 or 4500 ml depending on the

FIGURE 16 SIMULATION PESULTS FPOM: 1) ZERO-G STRESS ONLY (·····), 2) SL-1 BLOOD DRAW PROTOCOL ONLY (- - - -), AND 3) COMBINED ZERO-G STPESS AND SL-1 BLOOD DRAW PROTOCOL (———)



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simulation), and the plasma volume was assumed to automatically adjust to compensate for any changes in the circulating red cell mass due to blood draws.

Simulation 1: Zero-g Stress Only. The first simulation concerned the effects of zero-g stress only (see dotted lines, Figure 16). In this simulation, the total blood (plasma) volume was reduced by 500 ml linearly over a 12-hour period beginning at the time of launch, so that the total blood volume was reduced from 5000 to 4500 ml by the end of the first inflight day. The total blood volume was maintained at this reduced value until the beginning of reentry (seven days following launch), at which time the blood volume was allowed to return to the preflight value of 5000 ml linearly over a 24-hour period (that is, complete blood-volume recovery at the end of the eighth day following launch). The simulation was continued to include three additional weeks, in order to show the postflight response of the erythropoietic system to zero-g stress.

Simulation 2: SL-1 Blood Draws Only. The second simulation concerned the SL-1 blood-draw protocol only and involved no space-flight stress (see dashed lines, Figure 16). The blood draws begin 30 days before the scheduled flight and continue 14 days postflight. Table 3 presents the frequency and volumes of the proposed blood draws.

Simulation 3: Combined Zero-g and SL-1 Blood-Draw Stresses. The third simulation concerned a combination of the zero-g and SL-1 blood-draw stresses described above (see solid lines, Figure 16).

This SL-1 blood-draw protocol study addressed two main questions: first, 'Does the SL-1 blood draw protocol seriously perturb the erythropoiesis system?', and second, 'Does this perturbation amplify or attenuate any potential space-flight changes?' As can be seen in Figure 16, both the zero-g stress (dotted lines) and the SL-1 blood draws (dashed lines) will each have a significant impact on the erythropoietic system as it is currently modeled. In fact, the two

TABLE 3. SL-1 BLOOD-DRAW PROTOCOL

Day		Blood Volume (ml)
Preflight (Flight minus X days)		
F-30		127
F-15		123
F-1		123
	Preflight total	373
Inflight (Mission Day X)		
MD2		48
MD4		32
MD6		71
	Inflight total	151
Postflight (Recovery plus X days)		
R+0		127
R+1		80
R+7		114
R+14		84
	Postflight total	405
	Experiment Grand Total	929 ml

stresses have opposite effects on some of the system parameters during the inflight phase of the simulations, as can be seen in the curves for plasma volume (PV), erythropoietin concentration (ERY), hematocrit (HCT), and red blood cell production (RCP). The model predicts that the zero-g stress is the dominate stress, as can be seen by the fact that the combined simulation (solid lines) qualitatively resembles the zero-g simulation rather than the SL-1 blood-draw simulation. The blood-draw protocol is predicted to "attenuate" the expected inflight changes and "amplify" the expected postflight changes for ERY, HCT, and RCP. However, when the data are presented as percent changes from the preflight average (i.e., average data that would be obtained from the preflight blood draws), then the results obtained from the combined simulation are no longer in qualitative agreement with the results obtained from the zero-g simulation. Table 4 presents the percent changes from preflight averages for the combined simulation (left-hand column) and the zero-g simulation (right-hand column) for the last inflight blood draw (MD6) and the second postflight blood draw (R+1). On MD6, for the combined simulation, the percent changes from preflight averages for hematocrit and red cell production would be attenuated and those for erythropoietin, red cell mass, and red cell destruction would be amplified when compared to the zero-g simulation. On R+1, however, for the combined simulation, the hematocrit, red cell mass, and red cell destruction values would be amplified while erythropoietin and red cell production values would be attenuated when compared to the zero-g simulation. In fact, the erythropoietin values measured in the combined simulation would indicate an increase over the preflight values, while from the zero-g simulation one would expect to see a 10 percent decrease. These results highlight the problem of using the subject's own preflight values as controls for that subject's inflight and postflight treatment periods. This is especially true if the sampling technique causes large changes in the system being studied. The simulation results indicate that to more accurately follow and interpret the experimental results, a ground-based blood-draw study should be used as the control for the space-flight experiment.

TABLE 4. COMPUTER SIMULATION

SL-1 HEMATOLOGY EXPERIMENT

Percent Change From Preflight Average
MD-6 Value

	With Blood Draws	Without Blood Draws
Hematocrit	+ 8.2	+ 11.0
Erythropoietin	- 21.4	- 14.0
Red Cell Mass	- 4.5	- 1.0
Red Cell Production	- 19.3	- 28.4
Red Cell Destruction	- 4.4	- 1.0

Percent Change From Preflight Average
R+1 Value

	With Blood Draws	Without Blood Draws
Hematocrit	- 6.0	- 1.1
Erythropoietin	+ 2.2	- 10.1
Red Cell Mass	- 8.8	- 1.6
Red Cell Production	- 18.7	- 30.8
Red Cell Destruction	- 8.8	- 1.6

This study shows the benefits that can be obtained from simulating experimental protocols using mathematical models. In addition, it demonstrates how models can be used to help analyze experimental results, and refine experimental protocols. The results of this simulation study and the absence of appropriate and pertinent experimental data in the open literature point out the need for new experiments which would more fully investigate this problem.

5.0 FLUID AND ELECTROLYTE/RENAL REGULATION

5.1 INTRODUCTION

Past work in this research area has resulted in the production, over the past two years, of six technical reports (21,32,48-50), two major scientific papers (20,51), and three abstracts of meeting presentations (34,52,53). One of these papers (20) was honored as the outstanding technical paper at the 15th International Conference on Systems Science held in January of 1982.

The work reported in this section concerns recent investigations by the contractor in the area of hormonal control of fluid and electrolyte changes which occur during hypogravic states. This task was accomplished by first organizing the most significant experimental findings regarding fluid-electrolyte disturbances into logical groupings that would lend themselves to the study of common control mechanisms. Examples of such groups are: acute fluid disturbances, long-term adaptation, renal effects, hormone behavior, metabolic balance, etc. One or more hypotheses regarding those mechanisms which might account for the observed findings were then formulated. Computer simulation techniques were then applied to test these hypotheses and assess their plausibilities.

Hypothesis evaluation is not amenable to a rigorous process at this stage of our knowledge of space-flight physiology. In the simplest case, it involves a comparison of data with model response. However, because the data are often incomplete or lacking entirely, complementary and indirect evidence is often sought. For this reason, it was imperative to draw upon the results of ground-based studies, in particular, water immersion and head-down tilt. In other cases, it was important to reanalyze space-flight data in a new light so as to permit an easier interpretation, or to provide a superior format for comparison with model simulation output. Thus, by using a combination of space flight, head-down bed rest, and water immersion data within the framework of a mathematical model of physiological function, it was

possible to assess the importance of potential mechanisms and hypotheses by a "plausibility" criteria. The most plausible of these results then should become a starting point for designing validation experiments in the laboratory.

5.2 NEW MODEL DEVELOPMENT

During the course of this contract, this contractor used a modified version of A.C. Guyton's large-scale model to study the hormonal control systems regulating antidiuretic hormone (ADH), aldosterone, and the natriuretic factor. These studies were then compared with the hormonal control systems in the very latest research version of Guyton's model. This latest model, obtained privately from Professor Guyton, has a significant number of differences from the version currently in use by the contractor. Many of these differences result from the fact that Guyton has developed a new and significantly enlarged renal subsystem model, and has utilized this new kidney model in his overall circulatory/fluid model. Because the new kidney model functions in a different way from the older version, many of the hormone systems which have an impact on the kidney required modification. The salient features of some of these new systems will be summarized in what follows.

The present ADH system regulates the ADH level directly through three factors: extracellular sodium concentration, right atrial pressure, and autonomic stimulation. The low pressure receptors adapt with a time constant of about one day, and the baroreceptors adapt as well. The new version includes direct effects on ADH from both angiotensin and arterial pressure. In addition, in the case of right atrial pressure, the control law is modified from a linear one to a power law. Both the old and new versions contain an ADH effect on drinking and urinary output, but the new version contains an effect on renal sodium reabsorption in addition. Finally, the dose-response curve relating ADH level with effect was changed from an exponential form to a rational form.

The present aldosterone control system regulates aldosterone level through three factors: arterial pressure, angiotensin level, and the extracellular potassium-to-sodium concentration ratio. The new model utilizes only angiotensin level and extracellular potassium concentration. In addition, the old model utilizes a product format while the new model utilizes a power law format. In the old model, aldosterone had a direct effect on potassium excretion and an inverse effect on sodium excretion and urinary output. In the new model, aldosterone has no direct effect on urinary output; however, aldosterone has a direct effect on renal excretion of potassium, a different-sized direct effect (six times larger) on sodium reabsorption by the kidney, and it directly influences the equilibrium level of intracellular potassium. Additionally, in the new model, the level of aldosterone itself exerts the regulating influence, while in the original model, an exponential dose-response curve relates level to effect.

Similar changes exist in the new Guyton model in the systems regulating angiotensin or the natriuretic factor. The examples of ADH and aldosterone suffice to illustrate the following facts. First, the model selected to represent one system in the body (a hormone system) can be strongly related to the model selected to represent a second system in the body (the kidney). For example, if a hormone affects peritubular capillary uptake or distal tubular reabsorption of a substance, different models would be required with kidney models of various types. Second, a complete evaluation of a new renal system for the Guyton model is a large and significant undertaking and without such an evaluation, any new hormone system should be used with caution. Dr. Guyton himself is not ready to release his new model at the present time because his evaluation is still in progress.

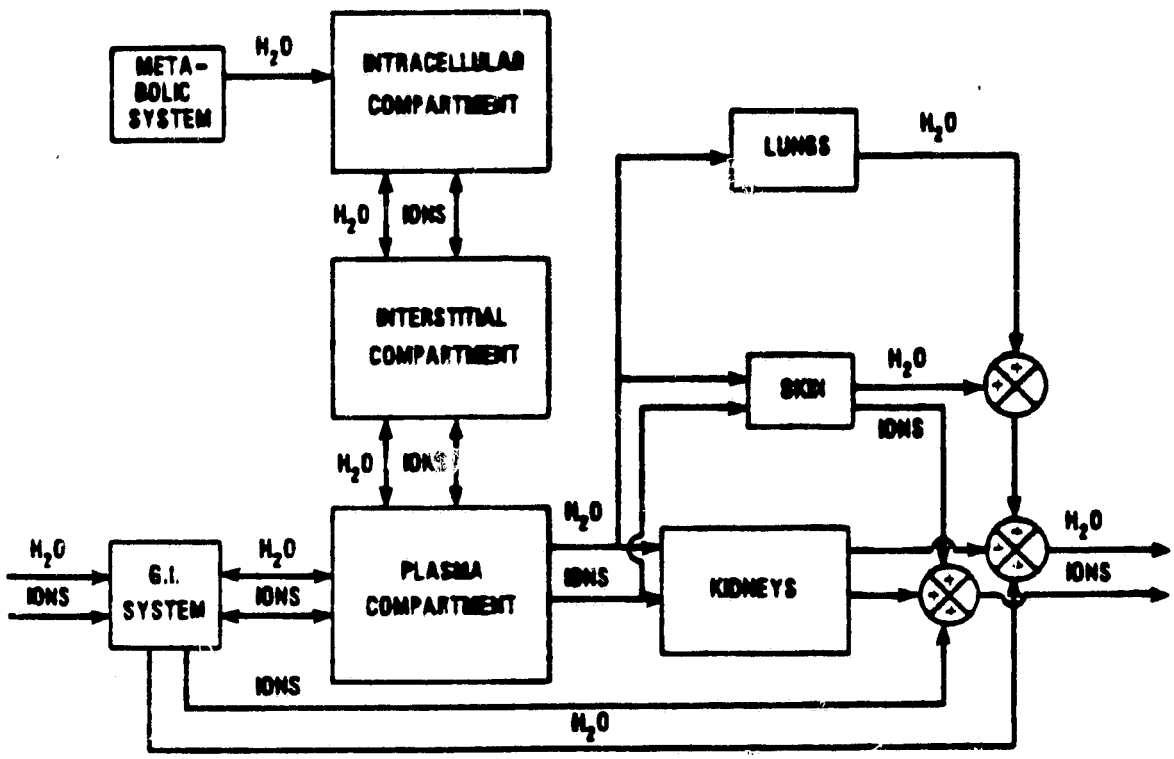
Thus, taking into consideration all of the above factors, it was decided not to make major adjustments in the hormonal control systems presently in use. The particular, detailed version of these control sytems did not preclude conducting the appropriate analyses related to space flight or its hypogravic analogs.

5.3 NEW ANALYSES AND SIMULATIONS

The fluid and electrolyte system, as indicated in Figure 17, may be characterized by the volume of several fluid compartments (plasma, interstitial, and intracellular compartments), the electrolyte concentrations (primarily sodium and potassium) in these and the metabolic input and output flowpaths for water and ions (dietary inputs, metabolic water generated, fecal loss, urine excretion, evaporative loss). In addition, a more complete description should also include the major physiological mechanisms that regulate these volumes and fluxes. An example of such regulatory mechanisms is illustrated in Figure 18 which indicates the hemodynamic, neural, and hormonal elements involved in controlling the volume and composition of the extracellular compartment.

For a number of years, the present contractor has been involved in an effort to describe and characterize the changes in these fluid-electrolyte systems which occur during prolonged space flight. This task has included a number of different elements and has led to several different categories of results which include: (1) complete partitional metabolic balances for water, sodium, potassium, nitrogen, and energy, (2) time-continuous profiles of the various volumes, concentrations, metabolic fluxes, and regulating agents such as those shown in Figures 17 and 18, (3) a quantitative explanation of body weight loss in space flight showing dynamic behavior of body water, body protein, and body fat, and (4) an interpretation of all of these events in terms of an holistic theory of body fluid-electrolyte regulation as it is affected by weightlessness.

This challenging task was confounded by the lack of adequate data in some cases, and by an incomplete physiological epistemology in other cases. Several novel approaches were required. For example, a new technique for computing cumulative-material balances was devised; this technique was based on combining metabolic balance and whole-body measurements of various constituents in such a manner as to determine



MAJOR ROUTES OF FLUID-ELECTROLYTE METABOLISM

FIGURE 17

FIGURE 18

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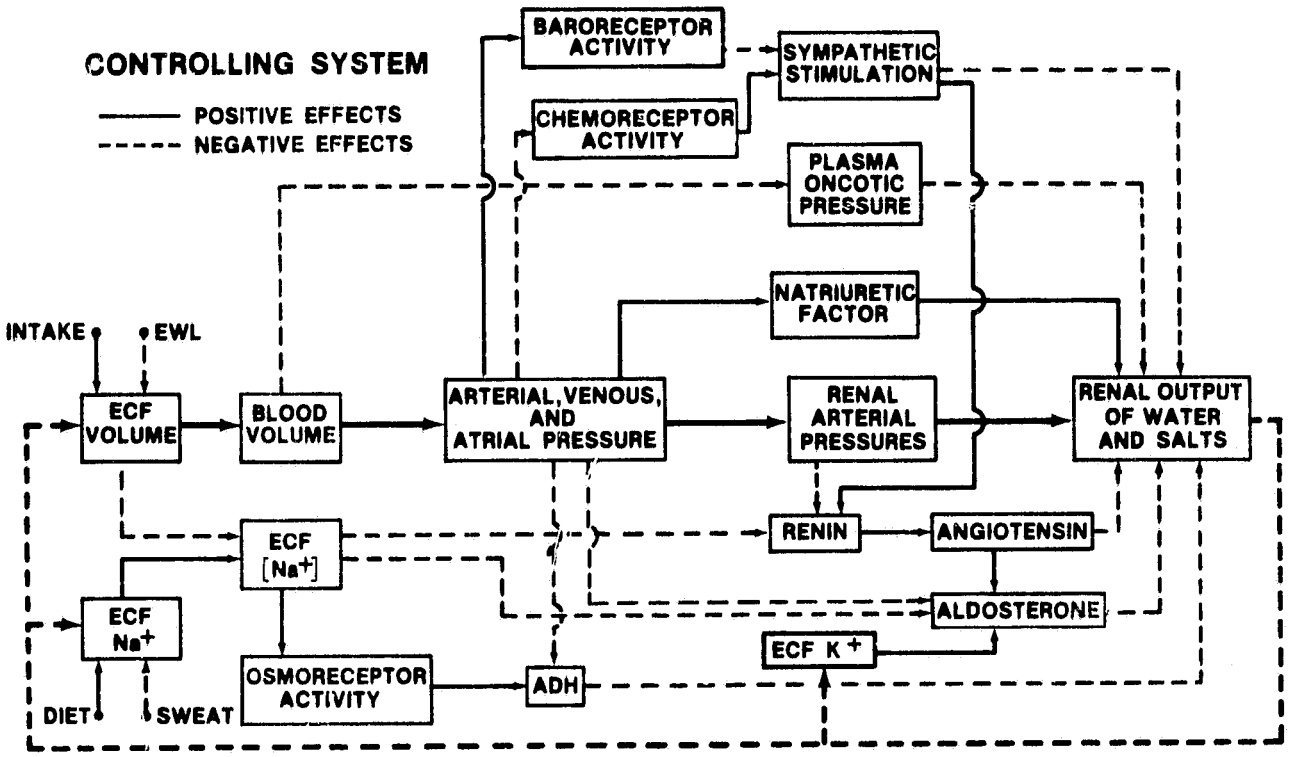
MODEL REGULATION OF EXTRACELLULAR AND CIRCULATORY DISTURBANCES



cumulative balances without accumulating the large statistical errors that usually occur when cumulative-material balances are computed. This approach permitted time-varying estimates of inflight changes in quantities which were not measured directly. A second innovative technique that was employed involved the use of a mathematical model of whole-body fluid-electrolyte regulation. This model was used for a computer simulation of a weightlessness state. The simulation was driven by the crew's recorded dietary intake of water and salts, and it resulted in plausible estimates of several parameters: daily changes in the major fluid compartments, evaporative losses, electrolyte concentrations, and renal excretion. Even more importantly, the modeling approach allowed specific hypotheses related to the mechanisms which control fluid-electrolyte regulation to be tested. Modeling allowed a more complete utilization of the space-flight data base and enhanced the understanding of the processes of adaptation to weightlessness.

Use of Ground-Based Analogs and Mathematical Models

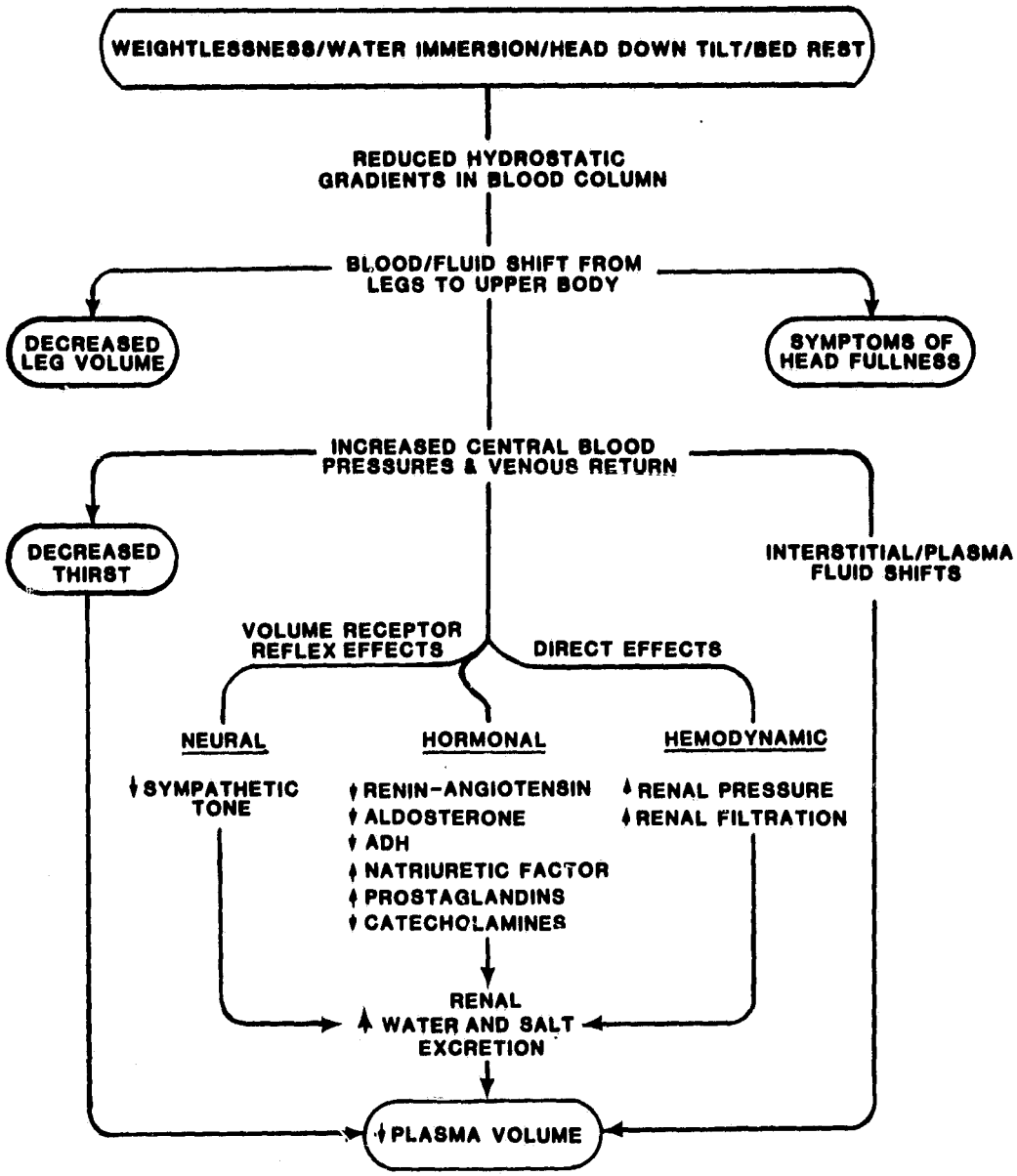
The fluid-electrolyte responses to zero-g can be conveniently divided into an acute phase (hours to days) and an adaptive phase (days to weeks). Ground-based studies often provide more abundant data than space-flight investigations, especially for the acute phase of stress. Over the course of this and preceding contracts, each of the more useful ground-based analogs has been reviewed, and simulations of each have been successfully performed. These include simulations of postural changes (54-56), supine bed rest (54,55), head-down bed rest (32), and water immersion (21). The last two reports cited were prepared during the current contract period. All of these stresses share the characteristic of 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 of space flight 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; the unraveling of their individual influences should lead to a better understanding of the longer term fluid-electrolyte responses.

A suitable mathematical model should be able to provide one means to systematically examine these stresses and should provide a framework for the study of their commonalities and differences. Such a model was developed some time ago by Arthur C. Guyton (57,58), and modified by this contractor for application to space-flight stresses (55,59). This model contains many elements which represent the dynamic interactions between acute and long-term adaptive control of the body fluids and the cardiovascular system. The modeling approach used by this contractor has led to a tentative description of the complete spectrum of temporal responses resulting from exposure to weightlessness and has explained the relationships among many of the time-dependent observations (60,61).

Acute Fluid Volume Regulation

There is unequivocal evidence that hypogravic stresses result in significant fluid redistribution within the body. The removal or reduction of the hydrostatic pressure in the blood column, coupled with the normal tissue elastic forces and muscle tone of the lower body, results in shifts of blood and tissue fluid from the lower body to the intrathoracic circulation. The consequences of this event are widespread and long lasting, as suggested by Figure 19, and lead to a loss of plasma volume. According to this description, reconstructed from model simulations 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 this diagram. 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 separated into three groups, mediated by neural, hormonal, and hemodynamic factors. Although the pathways connecting these factors

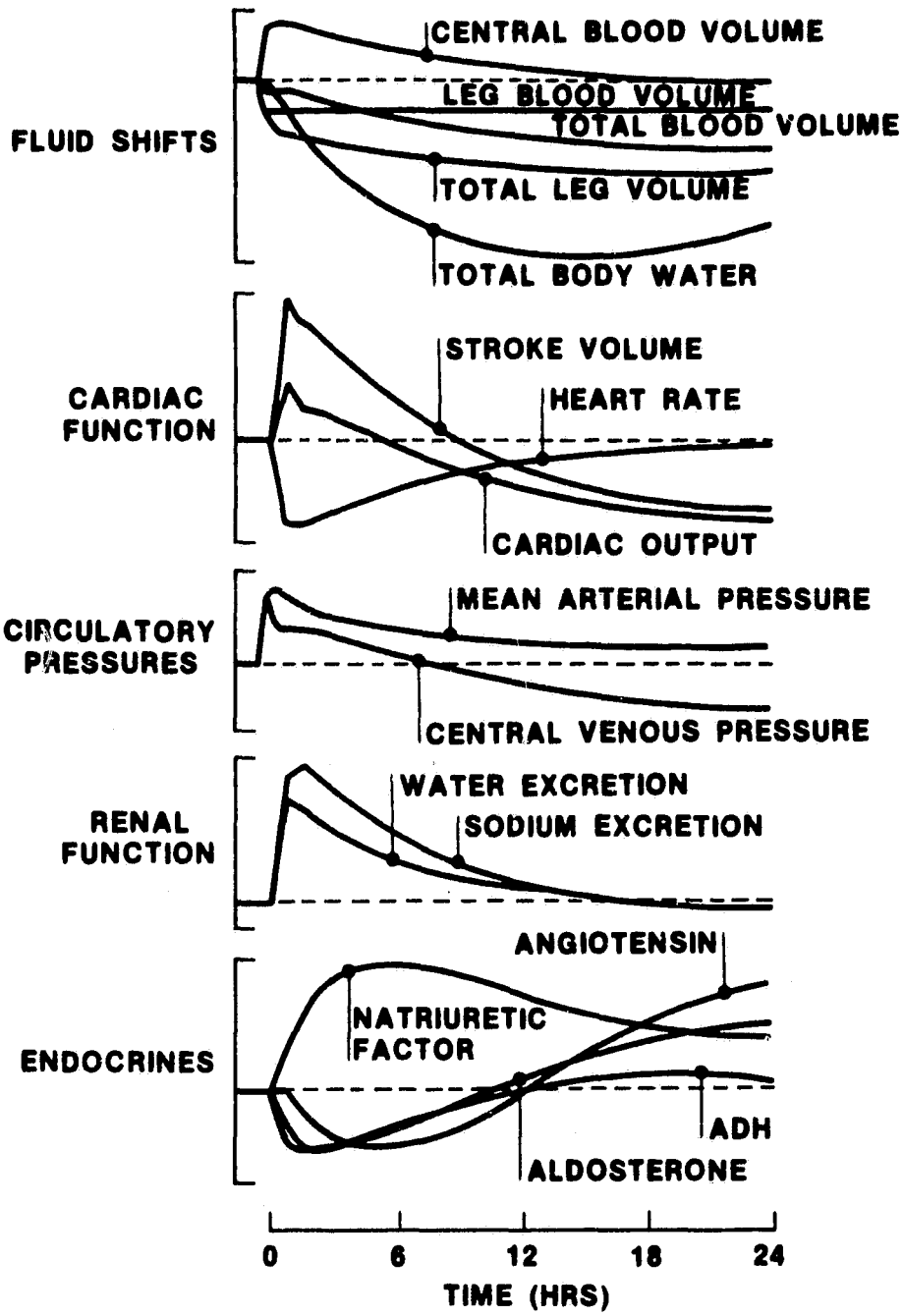


FLUID - SHIFT HYPOTHESIS

FIGURE 19

are not indicated, they are embedded in Guyton's mathematical model, and are highly interrelated and tightly coupled. Theoretically, it is possible for a reduction in plasma volume to occur by any one of the three major pathways shown. In practice, it appears that each pathway's contribution depends on its unique characteristics and the circumstances of the experimental study. For example, on Skylab most of the fluid losses can be accounted for by deficit drinking, while during water immersion studies, fluid losses are related to a renal diuresis. One of the important findings from the simulation studies is that a diuresis may occur during the first few hours of space flight, but that it can be obscured by the pooling of urine into 24-hour aliquots, especially if the subjects are dehydrated. The role of transcapillary fluid shifts was also assessed by model simulations; these revealed, surprisingly, that this pathway is self-limiting as a means to relieve central hypervolemia, because plasma colloidal concentration increases as fluid is filtered into the interstitium. Simulation studies demonstrated that even if capillary permeability to proteins increases dramatically (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 are the principal avenues of fluid regulation during weightlessness. That renal-volume controllers are involved is also suggested by the failure of plasma volume to return to normal during prolonged flight, even though fluid intake is adequate.

Computer simulations of the first 24 hours of head-down tilt, as shown in Figure 20, demonstrate the capability of the model to realistically portray the response to acute hypogravic stress. These responses are in excellent agreement with the results from experimental head-down tilt studies in human subjects (31,62). Within the first several hours there is a marked decrease in leg volume, and the resulting behavior of fluid volumes, hemodynamics, and renal-endocrine function is in essential agreement with the hypothesis diagram of Figure 19. Following this early phase, nearly all variables examined, with the exception of the fluid volume changes, exhibit a transient biphasic behavior, with a return to baseline, or even an overshoot beyond



SIMULATION OF HEAD DOWN TILT (-6°)

FIGURE 20

control by the end of 24 hours. This simulation indicates that the hypothesis diagram of Figure 19 (typical of those found in the literature) represents only a static picture of the earliest responses, while a more realistic dynamic analysis indicates secondary changes that 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.

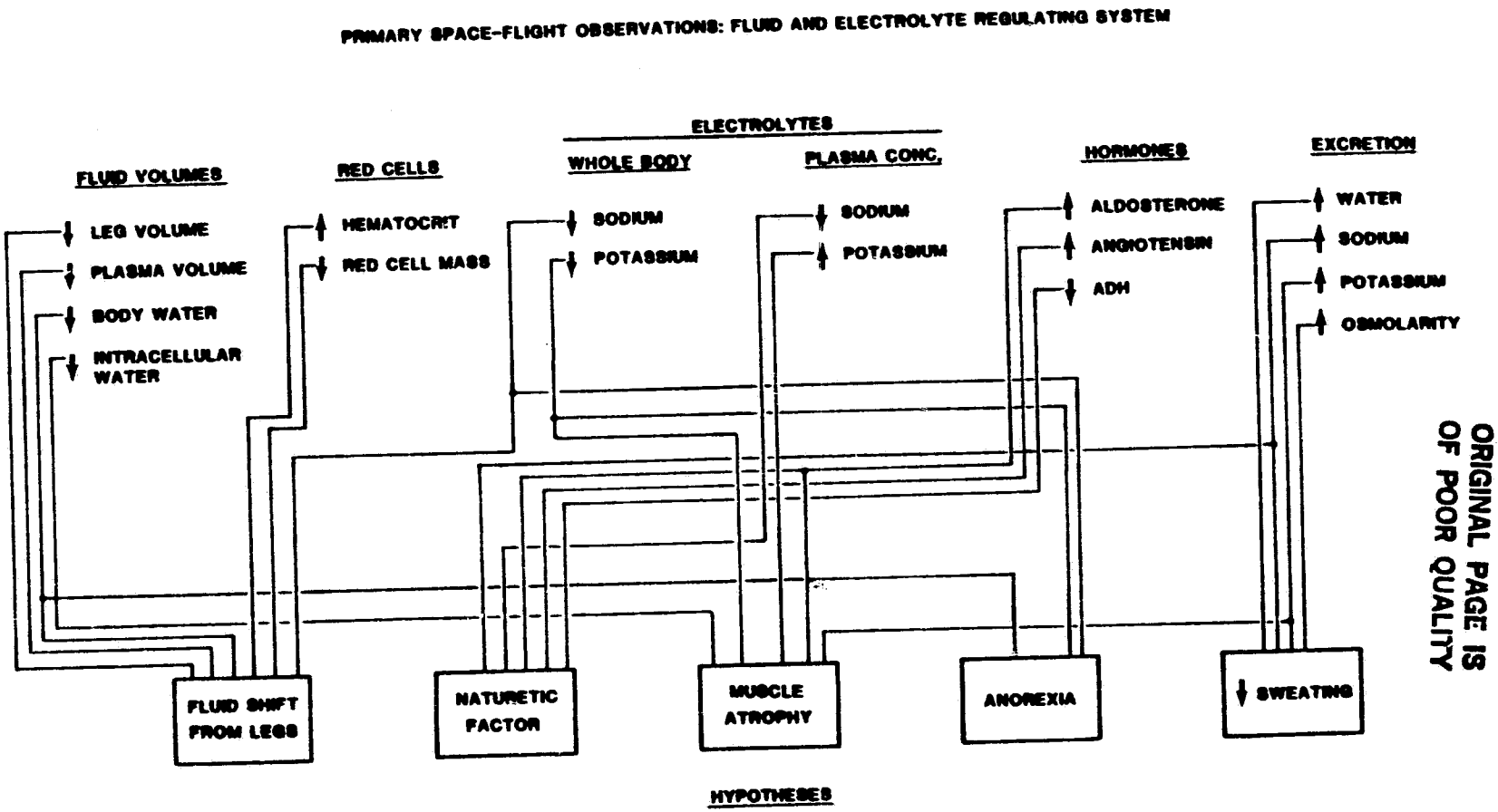
Longer-Term Fluid-Electrolyte Adaptations

During prolonged space flight (i.e., Skylab), and after the major acute fluid disturbances have stabilized, a number of alterations in the fluid-electrolyte status have been observed. Some of the more significant observations have been summarized in the top part of Figure 21. 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.

Most of these disturbances occur gradually, are of a more subtle nature than the acute changes, and are, therefore, more difficult to characterize and understand. Though there is a generalized theory to account for the acute fluid disturbances (i.e., Figure 19), none exists to account for these 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 (50,60,63,64.) These hypotheses and the observations they account for are shown schematically in Figure 21.

According to the description in Figure 21, the headward fluid shifts from the legs account for a number of critical changes involved with loss of fluid, sodium, and red cells. However, this hypothesis does not explain many other findings, some of which can possibly be attributed to small disturbances in diet, evaporative and skin losses,

FIGURE 21 HYPOTHESES WHICH ACCOUNT FOR SPACE-FLIGHT OBSERVATIONS OF THE FLUID-ELECTROLYTE SYSTEM



intracellular mineral losses (muscle atrophy), and to 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 (64). The findings of excess renal excretion of water and sodium probably reflects this reduction of evaporative water and electrolyte loss from the skin. Potassium loss occurs more gradually than water and sodium and is undoubtedly secondary to atrophy of lean body mass. Cellular potassium loss (muscle atrophy) may have widespread consequences, accounting for the findings of enhanced aldosterone levels, increased potassium renal excretion, elevated plasma potassium, decreased intracellular fluid, and decreased body potassium (32,60).

Hormone levels are influenced significantly by electrolyte concentrations (primarily sodium and potassium). Alterations in body-fluid electrolyte concentrations can arise from changes in the basic metabolic pathways (i.e., dietary intake, renal excretion, fecal excretion, sweat loss, cellular loss). The modest changes in plasma sodium and potassium-producing hyponatremia and hyperkalemia appear to explain, in part, long-term trends in hormone levels during the three-month Skylab missions (60). 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 theory describing control of the renal-regulating hormones (50,52). This new 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. 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 22, 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 (Na) or potassium (K) concentrations). The volume stimuli may provide control only during acute disturbances, because of the existence of several types of adaptive mechanisms indicated in Figure 22, or because the volume disturbances are corrected by volume-regulating mechanisms. However, the influences of the electrolyte disturbances are not known to be corrected by adaptive mechanisms.

During hypogravic stress, therefore, acute headward fluid shifts lead to an initial suppression of hormone levels (see Figure 20) 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. Similar hormone changes were observed in a recent one-week head-down bed-rest study, with the exception of aldosterone which was depressed. According to the simulations of this study, shown in Figure 23, the long-term changes in aldosterone, 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 simulated endocrine responses of Figure 23 exhibits a multi-phasic response which reflects the effects of competing and time-varying stimuli. As indicated in Figure 22 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 atlerations, control of endocrine secretion shifts from pressure control to electrolyte control. Dynamic variations of endocrine levels can,

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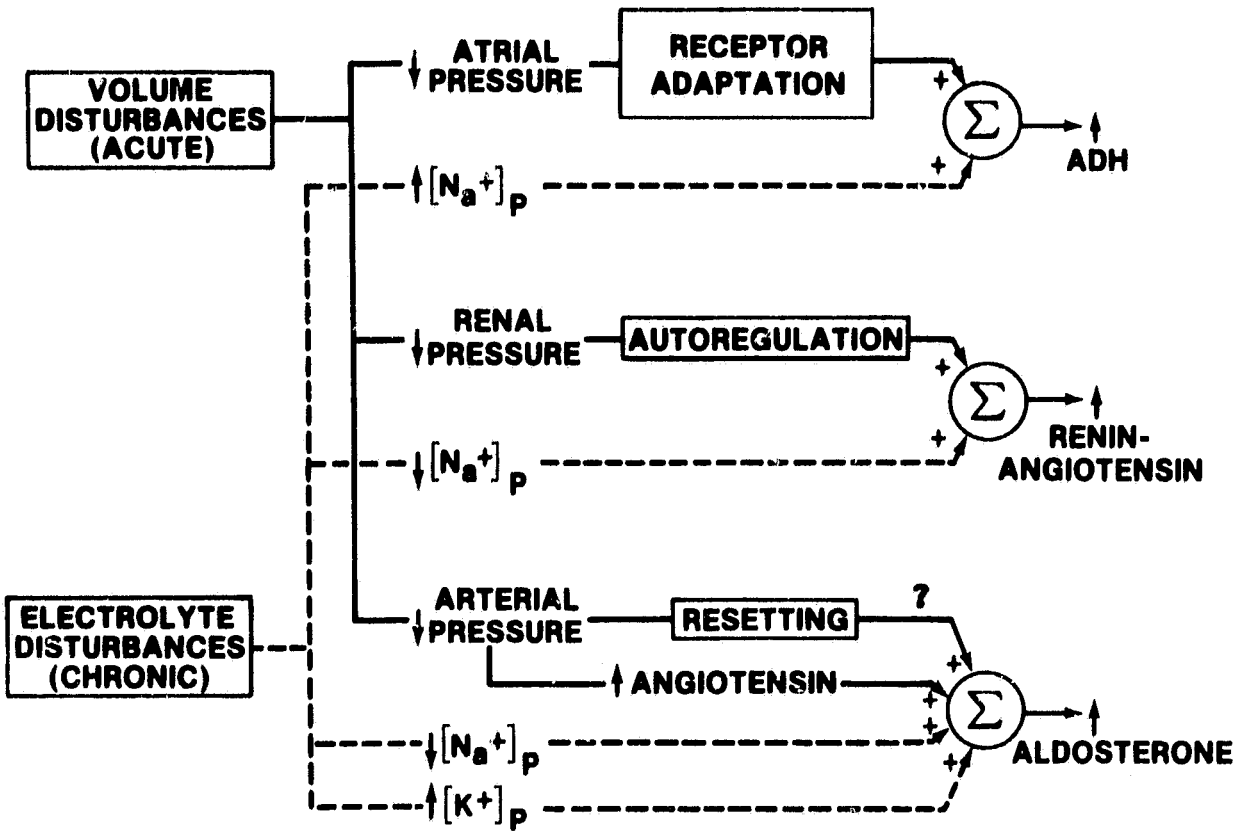

INFLUENCE OF VOLUME(——) AND ELECTROLYTE(-----) CONTROLLERS ON HORMONAL SECRETION

FIGURE 22

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FIGURE 23

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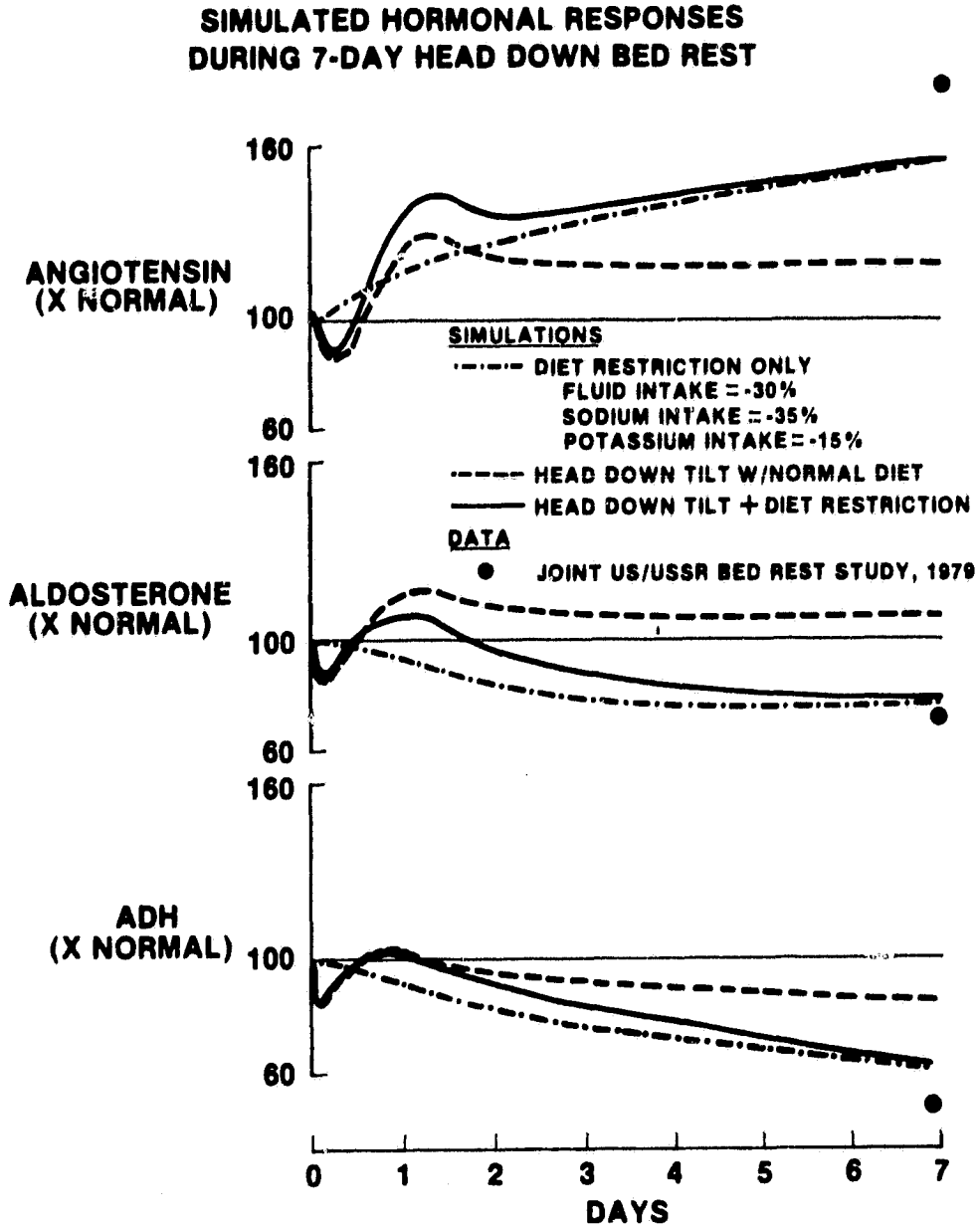

therefore, be considered a normal response to hypogravity and/or dietary influences, and thus may account for discrepancies often reported between different studies, subjects, and test conditions. These analyses are fully described in several reports and papers (32,50,52).

Energy Balance and Body Composition

The quantitation of body composition changes in prolonged space flight has been an additional, ongoing goal of the systems analysis effort. Prior work done by the contractor has resulted in analysis of water balance (63,65), sodium and potassium balances (66), and energy utilization (67,51). During the present contract period, a study was completed resulting in the most definitive description to date of energy balance and the composition of weight loss in space flight (48). In addition, a manuscript based on previous work was submitted and accepted for publication (51). A brief description of the energy balance-body composition study follows.

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 been inferred from tests performed postflight. However, by developing new techniques for analyzing conventional metabolic-balance data, it was possible to derive estimates of inflight changes of body composition. Body mass is considered to be composed of body water and body tissue solids (protein and fat components). In Figure 24, 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. Comparison of these two flights reveals several interesting aspects of 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 Figures 19 and 20. The larger loss of mass and water in the crew of the 59-day mission was apparently a result of space sickness. Over the next few weeks, a portion of this depleted fluid was replenished on the 59-day mission.

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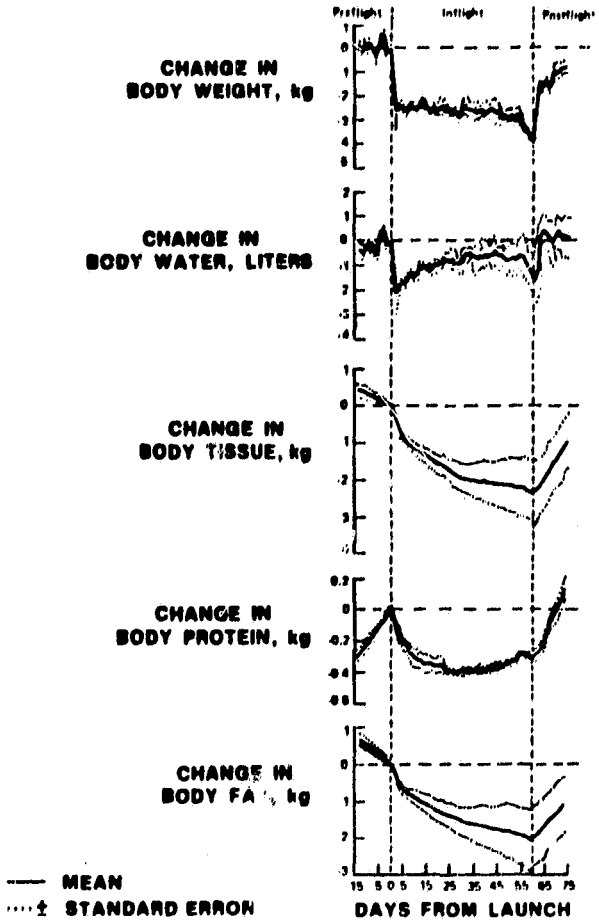
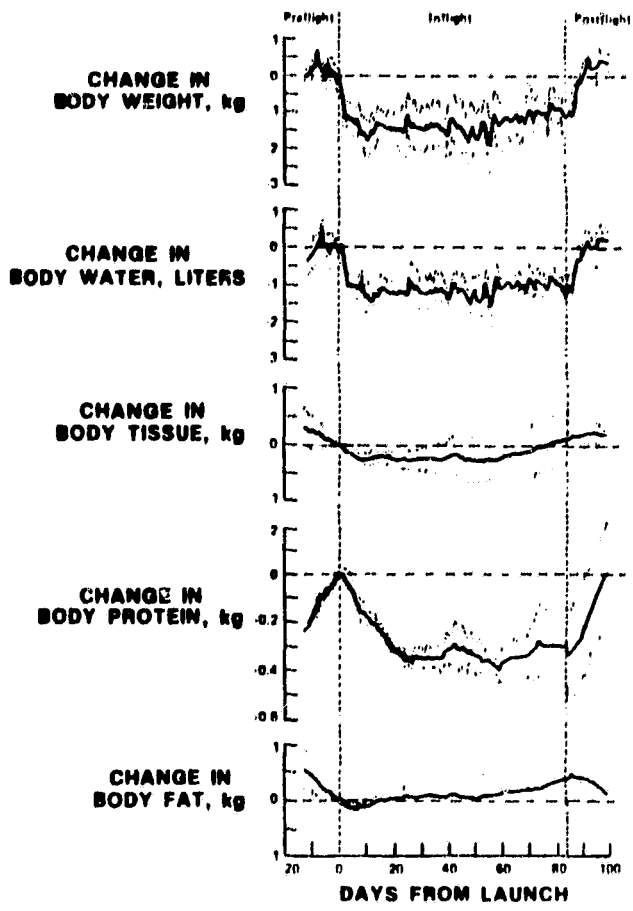
FIGURE 24

CHANGES IN BODY COMPOSITION DURING SPACE FLIGHT

59 - DAY MISSION



84 - DAY MISSION



However, body mass continued to decline gradually as a result of body fat and protein losses. 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 the longer mission, presumably because caloric intake was adequate. On both missions, body protein appeared to diminish over a three-week period before stabilizing. Perhaps this reflects a decrease in mass of postural muscles (due to disuse) and is independent of the diet and amount of exercise, both of which were somewhat different on the two flights.

In summary, these metabolic-balance simulation and modeling 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 (or extrapolating) beyond the observed results and showing 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 identifying and 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.

6.0 GENERAL MODELLING SUPPORT AND SOFTWARE DEVELOPMENT

6.1 NEW SOFTWARE AND SUPPORT TASKS

Program Conversion From the UNIVAC System to the VAX System

Prior to the present contract period, life sciences modeling and simulation work at Johnson Space Center was carried out on a UNIVAC computer system located at that facility. During 1980, the Medical Sciences Division at Johnson Space Center purchased a Digital Equipment Corporation (DEC) Virtual Address Extension (VAX) 11/780 computer system, and it was necessary, as part of the present contract, to transfer the various existing models and data base files from the new Univac system to the new VAX computer. For many programs this was a simple matter, since the FORTRAN used in a number of programs was compatible with that accepted by the VAX system. In such cases, a set of standard, baseline simulations were generated using both the Univac and the VAX systems, and these were compared to check error propagation and stability in the two systems. On the other hand, some programs were written in Univac assembly language, and these had to be rewritten for use on the VAX system. In order to avoid such problems in the future, all newly developed or rewritten programs were coded using American National Standards Institute (ANSI) standard FORTRAN IV to the maximum extent possible. In addition, programs were developed to replace the Univac library subroutines as required.

To accomplish the task of transferring the required programs and data files from the Univac system to the VAX system, a program was written which would read a source file from the Univac system and generate an ASCII VAX readable tape. A second program to read this tape was created for the VAX system. After a set of Univac programs were transferred to the VAX system, the actual conversion process began. To begin with, a FORTRAN program was developed to read the Univac-generated multiple element file on the VAX system and then to recognize element end mark. A separate file was created for each element; this program reduced the conversion time by approximately 45 working days. In this way, all Univac source elements were separated and made ready for actual conversion. Only source programs were

treated in this manner; assembly level programs, such as the plot interface program, were completely rewritten in ANSI FORTRAN.

Two steps were involved in converting the FORTRAN programs from the Univac to the VAX system. First, all program elements were analyzed line-by-line, and coding unacceptable to the VAX system was replaced by new standard coding which was VAX compatible. Second, after the replacement of unacceptable coding, there were lines of code which, though acceptable, required minor modifications (e.g., nonstandard read statements). These were easily modified, and compilation and verification of the entire program followed.

Following this conversion process, the process of model verification was carried out. To begin with, baseline simulations were generated using the Univac system for all of the models of interest. Then, a second baseline simulation using the same model and the same conditions was produced using the VAX system. The results of these two separate executions were compared for error propagation and system stability. In a number of cases, the results were different because of the structural difference between the two systems (Univac has six bit/byte while VAX has four bit/byte). In each case, the source of the error was resolved and the conversion was completed. Comment lines and other user-oriented coding was added to each program, so that its function could be determined easily and quickly.

Development of Special Purpose Numerical Algorithms

Due to physiological homeostasis, the maintenance of a constant or stable internal environment, mathematical models of physiological control systems are typically characterized by stability matrices. The matrix A is said to be a stability matrix if, and only if, each eigenvalue of A has a negative real part. Because physiological control is often complex, with some variables subject to control by more than one mechanism, mathematical models of physiological control usually result in stiff systems of differential equations. A system of differential equations is said to be stiff if the absolute values of

its eigenvalues differ by orders of magnitude. Mathematical models in physiology frequently result in non-linear systems of differential equations, due in part to the complex interaction between various control systems. Thus, the mathematical modeling of complex physiological control often leads to a stiff system of non-linear differential equations characterized by a stability matrix.

Because it is usually very difficult to solve non-linear systems of differential equations by analytic techniques, mathematical models of complex physiological control systems are usually solved using numerical integration techniques and high speed computers. The numerical solution of a stiff differential system poses an interesting dilemma. How does one achieve both accuracy and computational efficiency when solving stiff differential systems using numerical integration techniques? Shampine and Gear (68) discuss the problem at length. They point out that explicit numerical methods fail on stiff problems because of the severely restricted step size. When very small step sizes are used throughout a computer simulation, efficiency suffers due to the large number of computations required, and accuracy may be limited due to roundoff error resulting from many computations. Implicit numerical methods permit larger step sizes, but usually require many computations per step to either invert a matrix or to iterate in order to find a suitable solution at each step. Again, efficiency and accuracy may be sacrificed.

In the modeling of many physiological control systems, high order accuracy is not required since the values of many of the parameters are not known with great precision. It is, therefore, desirable to have an efficient numerical integration method for use in physiological simulations. The order of accuracy of the method is not of primary importance. The method should be easy to implement in a computer simulation; hence, a subroutine to do the numerical integration is desirable. The method should be capable of recognizing and following rapidly changing transients wherever they occur and should be capable of using a large step size when the system is at, or very near, steady state. Efficiency precludes iteration and/or matrix inversion at each step.

A simple, variable step-size method based upon Euler integration which possesses all of the above traits has been devised for use in a large class of simulations of physiological control. This method is discussed more fully in a contractor report (69), and was used to accomplish the tasks outlinied in Section 4.0 of this report.

Development of Special-Purpose Statistical Analysis Software

Work in this area was carried out to support the analysis of bed-rest data gathered at the U.S. Public Health Hospital in San Francisco, and to support the analysis of data used in parallel line assays. The first set of statistical routines is discussed in detail in two technical reports (4,5), while the second is published (70).

The Bed Rest Analysis Software System (BRASS) package is a retrieval, statistical, and graphical system designed to be used in conjunction with an extensive data base related to bed rest and calcium metabolism. The package was developed in ANSI FORTRAN and contains 33 subroutines which comprise four different files. This package utilizes a separate graphics system developed by this contractor and reported in a separate document (71).

The parallel line assay program provides a rapid, convenient, and accurate procedure, with a high level of operator interaction, with which to perform the somewhat cumbersome mathematical manipulations necessary for the evaluation of parallel line assay results. The availablity of this program should overcome one of the problems which frequently prevents the complete analysis and validation of the results of parallel line assays.

Development of Master Model Operating System

In the past, mathematical models representing physiological systems of interest were developed one at a time, and each one of the models was coded for computer implementation in as efficient a manner as seemed practical. The resulting programs were designed to take special

advantage of certain non-standard features of the particular computer system available in order to enhance operating characteristics, even though the models themselves were all written using the FORTRAN programming language. Some of the software systems evolved with time, with later models having access to improved versions of some software elements, such as special graphics tools.

The sequential development of a large number of mathematical models over the past ten years created the need for a computer system just to document the configuration and function of the programs which are available to users. Because of the way that the models were developed, it was difficult to maintain enough documentation to lead the user through the execution of the program. For each model, there were several input/output (I/O) programs to choose from; a user wanting to use three different models would have to learn the responses to three separate I/O programs. All of this required the user's time and access to someone else who was familiar with the model and who could lead the user through it's execution. Furthermore, having many I/O and graphic programs increased user disk space and frequently caused a shortage of this resource. As a result, models and other software were often resident on tape and had to be unloaded and loaded back into the main system memory. All of these problems, and others besides, required time and effort for their solution.

Based on these needs, a new master operating system, SUPER, was designed and implemented on the VAX 11/780 computer system. This system is described in a separate technical report (72), and its operation will only be summarized here. This package provides the user with access to all of the available models developed by the present contractor during the last few years. The user is provided with a list of the available models and is allowed to choose one. The user can obtain a a brief description of the model as well as a list of some of the major types of simulations that can be performed by the model. The user then has the options of observing a sample simulation run automatically, running his own simulation, modifying the model and running simulations using the modified model, or selecting a different

model to analyze. For any particular model, the user can examine subroutine variable definitions along with initial data values.

SUPER has a number of other features worth mentioning. First, the system itself contains several levels of documentation on each program or element available. These levels range from brief summaries to extensive operating instructions. Second, all models and all data bases are usable in conjunction with any of the separately produced and maintained input/output processors, and graphic packages. Thus, modeling and data base studies can always use the most recently developed software programs. Third, the use of standard input/output processor and graphics interface programs in this package facilitates rapid learning, since the input/output and graphics are not dependent on the particular model or data-base system used, but are general and apply to all models and data systems. This means if a user learns to execute a single model, then that user is able to run any other model available in the SUPER package without outside help from either the model, a systems programmer, or other group members. Fourth, the use of these standard systems reduces the effort required to develop new models or data bases, because the peripheral software are handled quite separately. Fifth, since common blocks and data files are constructed in an orderly and alphabetized manner, variables can be easily located and modified in a single copy rather than through many common blocks in separate subroutines and data files. Sixth, the software package which was developed includes an editor system which allows the user to modify any desired model temporarily and to dynamically compile, link, and execute the new version. Finally, SUPER includes both a manual and a dynamic interrupt mechanism which allows the user to halt the execution of the model temporarily and activite any desired options.

SUPER Structure

Figure 25 presents the model configuration for SUPER. In this figure, each rectangular block represents either a subpackage or a model, while each ellipse represents a main driver subroutine of a given model. As

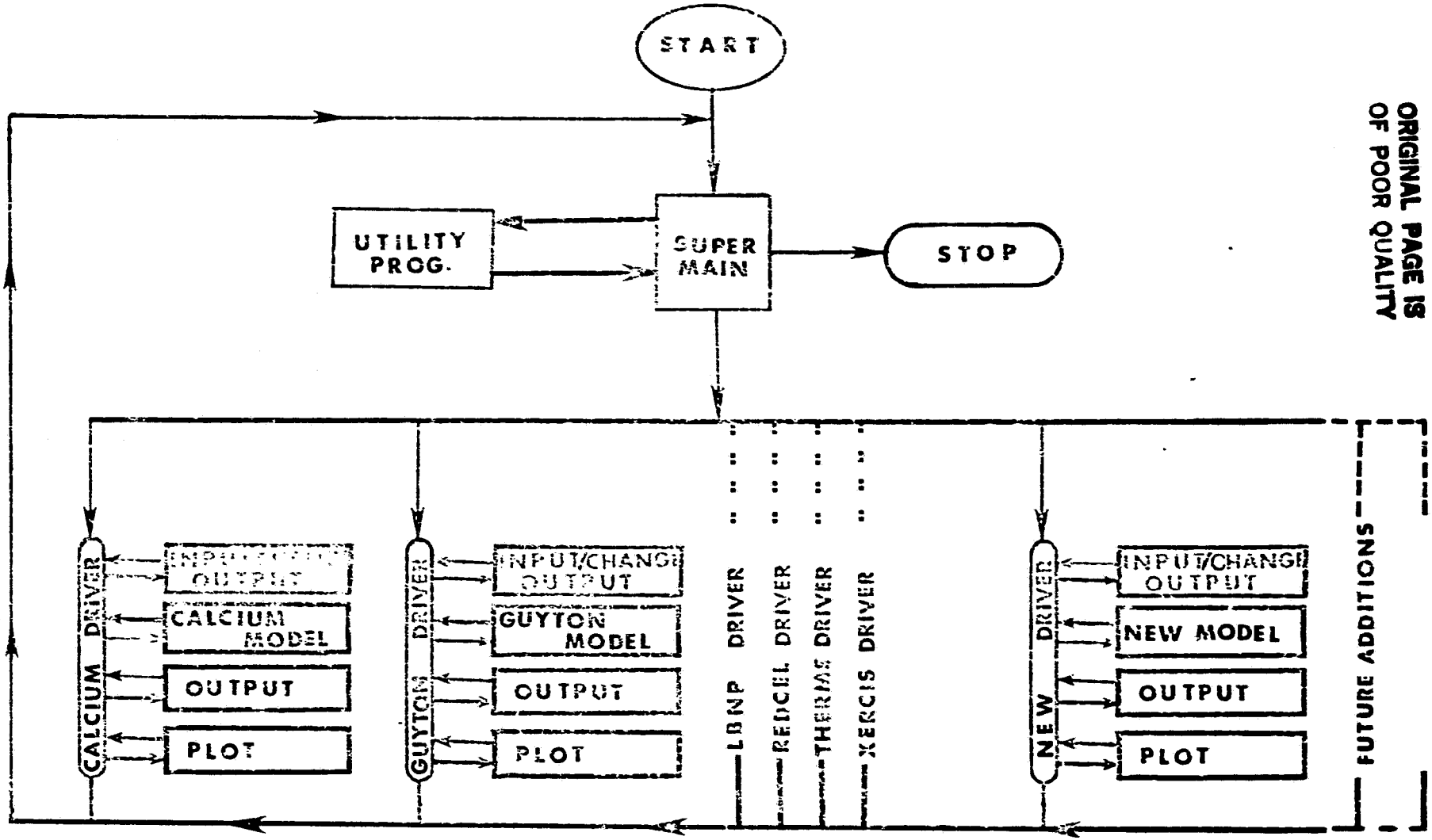


FIGURE 25 SUPER MODEL CONFIGURATION

NOTE:
THE SAME I/O, CHANGE AND PLOT PROGRAM IS USED IN EVERY MODEL.

the SUPER configuration illustrates, every sub-element or model has basically the same structure. First, the driver subroutine calls the input routine to read the data files. Then, it allows the user to make all initial modifications, and produces the headings and starting values. After these calls, the initialization of all local parameters takes place. Then, the main loop begins the execution and calls the particular model desired. After each return from the particular main model selected, the driver routine calls the output program to print the latest calculated values at the requested time intervals. After the final calculations, the graphics package is called to accomplish the plotting of the desired parameters.

6.2 ADDITIONAL WORK

Two additional models were obtained and added to the model systems available for use. These include MACPUF, a model of the human respiratory system, and HUMAN, a model of overall human physiological function. MACPUF was designed by C.J. Dickinson and K. Ahmed and was obtained through McMaster University (Canada), while HUMAN was designed by T.G. Coleman and was obtained from the University of Mississippi Medical Center.

The HUMAN model was modified for interactive use on the VAX system, and a report was written which described the use of the resulting model in some detail (73). This new version of HUMAN has been given the name MATHMAN.

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APPENDIX A

STATEMENT OF WORK

MATHEMATICAL MODELS OF PHYSIOLOGICAL SYSTEMS

1.0 OVERVIEW

Work has been done to develop mathematical models of various human body systems. Systems alrerady developed include: Calcium/musculoskeletal regulation; cardiovascular regulation; erythropoiesis regulation; and fluid and electrolyte/renal regulation. These models can be used to predict changes that may be anticipated during space flight, and to integrate data from complex experiments encountered during future missions. The contractor will continue to provide development of these models by fulfilling the following tasks.

2.0 CALCIUM/MUSCULOSKELETAL REGULATION

2.1 SUMMARY

Preliminary analyses of the musculoskeletal space flight data have demonstrated losses in total body calcium skeletal density and lean body mass. Work previously done has demonstrated that the space flight responses probably result from a series of feedback mechanisms in a highly complex and interactive musculoskeletal system.

2.2 NEW MODEL DEVELOPMENT

2.2.1 The contractor shall complete the calcium model. This includes developing and validating several of the soft tissue and the bone subsystems. The remaining subsystems shall be validated individually, integrated into one model, and the feedback loops incorporated. The model should be capable of simulating calcium metabolism in the normal adult and in particular pathological states.

2.2.2 The contractor shall expand the calcium model. The present calcium model does not yet include several components which may play a role during the removal of gravitational stresses. As these elements are probably located in the bone compartment, this compartment shall be modified and expanded. Particular elements to be considered are mechanical stress, piezoelectric fields, and new hormonal agents.

2.3 NEW ANALYSES AND SIMULATIONS

2.3.1 The contractor shall run simulations of experiments done during Skylab. From these simulations, he will develop as necessary, further modifications of the model. He will also use such Skylab data to validate the model for space flight responses.

3.0 CARDIOVASCULAR REGULATION

3.1 SUMMARY

Without gravitational orientation, the fluid nature of the vascular system is distorted from its normal distribution, causing subsequent cardiovascular responses which alter virtually all other organ systems. Changes observed during space flight resulted from both the direct and reflex effects of the acute cephalic shift of fluid and from the chronic influences of the fluid pooled in the upper body. Several cardiovascular disturbances were noted, including decrease in blood volume, decrease in plasma volume, orthostatic intolerance, and reduced post-flight exercise capacity. Possible aspects of long-term adaptation to hypogravity may include autonomic control mechanisms, arterial and low-pressure mechanoreceptor resetting, peripheral vascular changes in autoregulation of tissue blood flow, and changes in venous compliance and capacity.

3.2 NEW ANALYSES AND SIMULATIONS

3.2.1 The contractor shall provide detailed comparisons of water immersion, bed rest, head-down tilt, and space flight to determine which is the best analogue of space flight. The contractor shall also determine whether extrapolation from these analogues to space flight is valid, based on present data and, if so, shall use this to add further predictive capability to the model.

4.0 ERYTHROPOIESIS REGULATION

4.1 SUMMARY

The most significant hematologic observation in manned space flight has been a consistent reduction in circulating red blood cell mass. The variability seen among the individual astronauts in the decrease of their red cell mass and observation of the complicated post-flight recovery mechanisms suggest that there is a complex relationship between the red cell mass loss and the duration of the exposure to weightlessness. This loss in red blood cell mass was accompanied by a reduction in plasma volume, which apparently occurs early in the mission, and, along with other changes in blood distribution and flow, is maintained throughout the flight.

4.2 NEW MODEL DEVELOPMENT

4.2.1 The contractor shall develop species-specific erythropoiesis models for the rat and monkey. These specific animal models will be used not only to support actual experimental work on such animals, but also to extrapolate the experimental results from such animals to man.

4.3 NEW ANALYSES AND SIMULATIONS

4.3.1 The contractor shall perform a comparative sensitivity analysis of the species-specific models for man, the rat, the mouse, and the monkey. The results from this study will be used to qualitatively define, and then to quantitate, the differences between the various models.

5.0 FLUID AND ELECTROLYTE/RENAL REGULATION

5.1 SUMMARY

It has been demonstrated that the physiological response to weightlessness includes a wide spectrum of significant and complex changes of body fluid volumes, electrolytes, endocrine secretions, and renal behavior. The systems analysis effort is useful in understanding the short- and long-term adaptive processes that are operative in the weightless environment.

5.2 NEW MODEL DEVELOPMENT

5.2.1 The contractor shall develop new subsystems, or modify existing subsystems, to account for antidiuretic hormone (ADH), natriuretic factor, and aldosterone. Such development shall consider that recent research has indicated that the short-term regulation of these factors may be different from the long-term regulation.

5.3 NEW ANALYSES AND SIMULATIONS

5.3.1 The contractor shall analyze the control mechanisms to determine which of them are predominant during space flight. Although the major fluid and electrolyte changes can be presently simulated, those feedback control mechanisms which are actualy responsible for the observed changes have not been identified.

6.0 GENERAL MODELLING SUPPORT AND SOFTWARE DEVELOPMENT

6.1 NEW SOFTWARE AND SUPPORT TASKS.

6.1.1 The contractor shall review all existing programs for utility and shall either edit or rewrite them, as necessary, to implement them on the VAX computer system dedicated to

the use of the Medical Sciences Division. The contractor shall write these programs and any future programs in American National Standards Institute (ANSI) standard FORTRAN IV, and shall include sufficient internal documentation to allow a user to determine the function of each of the program elements easily and quickly.

6.1.2 The contractor shall develop special purpose numerical algorithms for fast and efficient solution of the equations arising from the modelling approach, as required in Sections 2.0 - 5.0.

6.1.3 The contractor shall develop special purpose statistical analysis approaches to the hypothesis testing problems faced in space flight biomedical research, as required in Sections 2.0 - 5.0.

6.1.4 The contractor shall develop and maintain a system for assuring that the configuration of all software systems is known and documented.

7.0 REPORTS

7.1 The contractor shall provide the results of his studies in a series of ongoing reports, issued in a timely fashion as each major step in model development is completed. These reports should contain a description of the work, including analyses, and should be fully referenced. If no major landmarks have been reached in any particular model after each year, a report should be issued detailing what work has been done on that model during the past year.

7.2 The contractor shall publish, to the maximum extent feasible, all of his results in the open (referred) literature. Publications will be done only after approval from Technical Monitor.

7.3 The contractor shall submit quarterly progress reports in letter format listing achievements during the past quarter, goals for the cooming quarter, and any unexpected difficulties encountered. See Article XIV for instructions.