CR-171892

AN INTEGRATED ANALYSIS OF THE PHYSIOLOGICAL EFFECTS OF SPACE FLIGHT

Executive Summary

Prepared for

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1985

This work was supported by the following NASA contracts:

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

ACKNOWLEDGEMENT

This document is the executive summary of a publication, "An Integrated Analysis of the Physiological Effects of Space Flight," which was originally intended to become a NASA Reference Publication. Unfortunately, this book has not yet been published, although the manuscript is nearly complete with some of the sections already typeset. The book contains a description of the approach and accomplishments of an eight-year effort (1972-1980) to perform the only multi-disciplinary effort that NASA funded for integration of Skylab data. The analytical studies themselves involved a large number of dedicated people who were part of a GE/MATSCO unit which is presently called the Biomedical Research, Analysis & Planning (BRAP) group. In addition, the task of writing this NASA RP-in-preparation was itself an arduous task involving several editors and a publication team including technical writers who were often the authors of the original study. This foreword is intended to acknowledge those GE/MATSCO personnel who contributed to this total effort and their names are listed below in alphabetical order. A special acknowledgement is due to Dr. John A. Rummel (NASA) who conceived and managed the physiological systems analysis project and provided the vision to take this aspect of NASA's biomedical research into the next century.

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AN INTEGRATED ANALYSIS OF THE PHYSIOLOGICAL EFFECTS

OF SPACE FLIGHT

Joel I. Leonard, Ph.D.

The most complete set of observations on man's adaptation to weightlessness that the U.S. has collected to date was obtained during the Skylab program. The primary goal of the Skylab medical experiments was to define the changes which took place in the human body and, thus, to achieve an understanding of the physiological responses which occur during extended exposure to the space-flight environment. Achieving a unified theory of adaptation to weightlessness has been difficult because of the requirement to integrate a voluminous quantity of data obtained by many scientist from various disciplines. This task is further confounded by the need to consider supplementary results from a diverse spectrum of ground-based studies which mimic the hypogravic environment of space flight. Interpretation of all this data requires the unraveling of a complex network of feedback regulators developed, based on an interdisciplinary systems analysis approach, to address this task. The systems analysis approach is particularly applicable in this situation because of the requirments to analyze and assimilate vast quantities of information, to understand the behavior of complex homeostatic systems, and to test scientific hypotheses explicitly and in as unambiguous a manner as possible.

Of the various analytical techniques developed to satisfy these requirements, the primary tool used was a set of mathematical models capable of simulating a number of physiological systems. Physiological function of the human body is often viewed as consisting of an aggregate of subsystems, each one of which is complicated, and these subsystems are integrated so that the organism as a whole maintains homeostasis. Each subsystem may be viewed as a type of control system operating with negative feedback to restore stability following a stress disturbance. These control features are often amenable to mathematical description, and the use of a computer permits such models to be used in dynamic simulation. The benefits of using mathematical models are well known among physiologists who employ them in their research studies. Among other benefits, such models provide a systematic approach for: (a) assembling existing knowledge about a system; (b) identifying important parameters and determining the overall system sensitivity to the variation in these parameters; (c) predicting the values of quantities that may be difficult or impossible to measure directly; (d) developing and testing hypotheses rapidly, quantitatively, and relatively inexpensively; and (e) identifying specific elements that must be further quantified and suggesting the type of experiments that are needed to obtain missing information.

Although mathematical modeling is now well established in the life sciences, this is the first time that a large array of models has been applied in a uniform manner to solve problems in space flight physiology. Since the time between major space missions is so great and the number of astronaut-subjects is relatively small, the decision was made to use mathematical simulation as an alternative way of looking at physiological systems and maximizing the yield from previous space flight experiments. This use of mathematical models was expected to be complementary to the ongoing NASA program of employing ground-based experimental simulations of zero g to provide additional insight into man's response to weightlessness.

Systems Analysis Techniques and Approach

An important objective of the systems analysis program, at the outset, was to develop the mathematical and statistical techniques required to support an extensive integrative effort related to man's response to weightlessness. It was apparent that data from all the major flight experiments of Skylab would need to be available in a single data base, coupled with the appropriate analysis software. Toward this end, a medical data analysis system was created which consisted of an automated data base, a computerized biostatistical and data analysis system, and a set of simulation models of physiological systems (see fig. 1). Data from a wide variety of investigative areas were collected, including cardiopulmonary function, body fluids, biochemistry, nutrition and energy metabolism, musculoskeletal function, body composition, and hematology (see table 1). An indication of the data utilized during the course of these studies is given by the selected parameters shown in fig. 2. The total quantity of data contained in the data base is quite large, in spite of the small number of astronaut subjects; information for approximately 900 man-days of space-flight study is provided by 80,000 measurement values representing over 900 independent parameters. Algorithms were provided to perform routine statistical tests, multivariate analysis, non-linear regression analysis, and autocorrelation analysis. Special purpose programs were prepared for rank correlations, factor analysis, and the integration of the metabolic balance data using conservative models for mass, water, and energy.

Five basic models were employed in this project: a pulsatile cardiovascular model (fig. 3); a respiratory model (fig. 4); a thermoregulatory model (fig. 5); a circulatory, fluid, and electrolyte balance model (fig. 6); and an erythropoiesis regulatory model (fig. 7). A major objective that was achieved earlier in the program was the integration of these subsystem models into a common framework termed the "whole-body algorithm" (fig. 8). In addition, a model of calcium regulation is currently under development (fig. 9). The basic compatibility of the subsystem models seems evident from the diagrams in figures 3 to 9, since they are all represented by an active controlling system which regulates a relatively passive controlled system, and taken together, these units function as a negative feedback control system. The feedback variables for these models include many of the actual sensors present in the body including temperature sensors, chemoreceptors, baroreceptors, oxygen sensors, and osmoreceptors. A majority of these models resulted from research directly associated with this project.

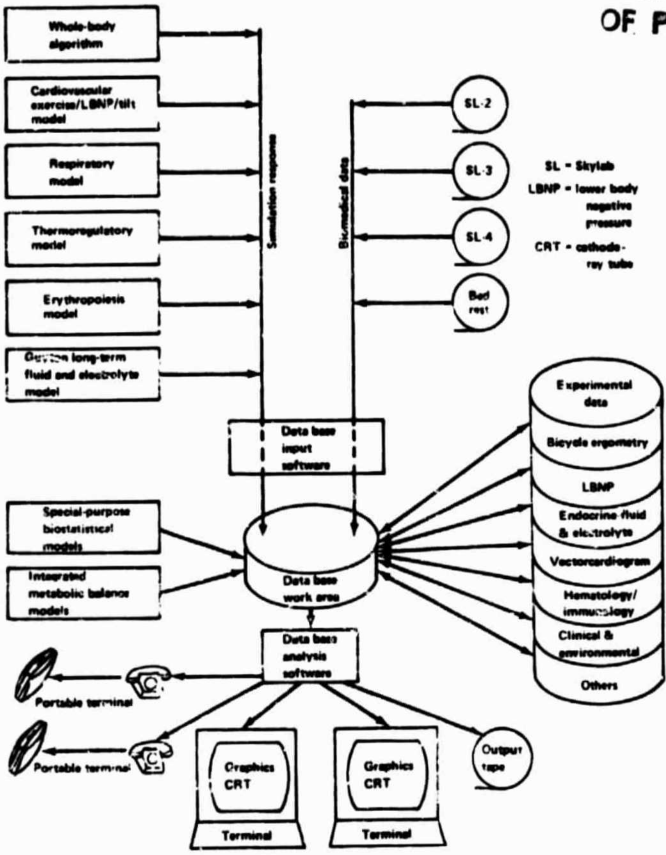


Figure 1. Skylab Integrated Medical Data Analysis System

TABLE 1

BIOMEDICAL EXPERIMENTS OF SKYLAB IN DATA BASE

Cardiovascular System

- o Lower body negative pressure
- o Submaximal exercise response
- o Resting flows, pressures, heart rate

Musculoskeletal Function

- o Bone densitometry
- o Calcium balance
- o Strength tests
- o Anthropometric measurements
- o Lean body mass measurements

Pulmonary Function

- o Respiratory function during rest and exercise
- o Mechanical and metabolic efficiences during exercise

Body Fluids and Composition

- o Body fluid volumes
- o Composition of plasma, urine, and feces
- o Hormones related to fluid-electrolyte balance and to stress

Nutrition and Biochemical Metabolism

- o Metabolic balances of water, nutrients and electrolytes
- o Energy balance
- o Body mass measurements

Hematology

- o Red cell mass
- o Blood volume
- o Hemoglobin
- o Indices of erythropoiesis

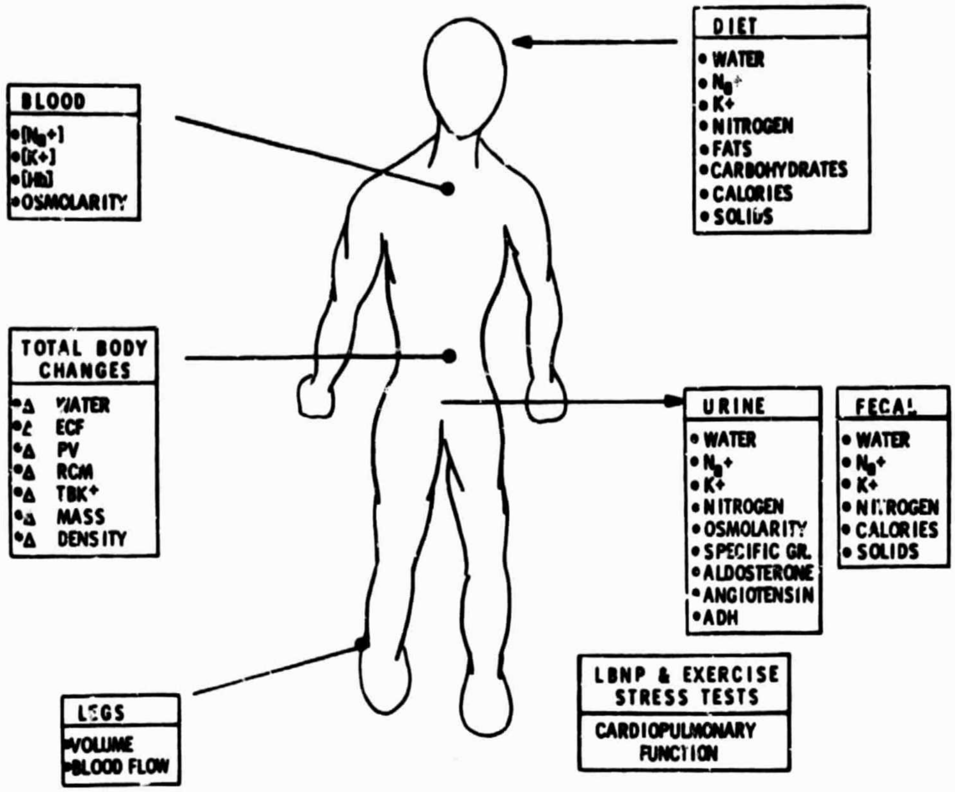
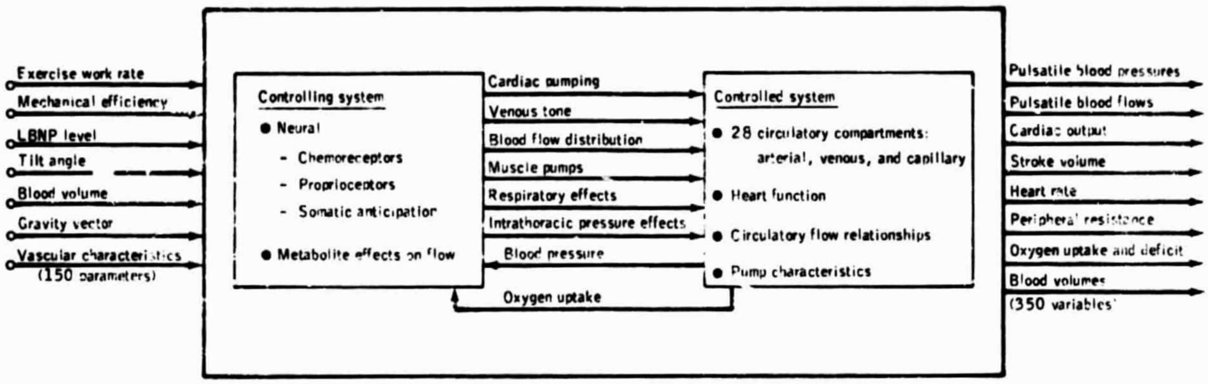


Figure 2. Selected Data Utilized in Systems Analysis Study

TABLE 2

STRESSES RELATED TO SPACE FLIGHT THAT WERE STUDIED USING SIMULATION MODELS

- HYPOGRAVIC STRESS
  - Supine Bed Rest
  - Head-down Bed Rest
  - Water Immersion
  - Space Flight
- ORTHOSTATIC STRESS
  - LBNP
  - Tilt Table
  - Postural Change
- METABOLIC STRESS
  - Exercise
  - Diet Restriction
- ENVIRONMENTAL DISTURBANCES
  - Hypoxia
  - Hypercapnia
  - Temperature
  - Ambient Pressure
- FLUID SHIFTS
  - Hemorrhage
  - Infusion
  - Water and Salt Loading
  - Dehydration



Model of Cardiovascular Regulation

A model of the human cardiovascular system and its controls was developed to simulate bicycle ergometry exercise. Subsequent modifications to this short-term model were made to enhance the design for simulation of lower body negative pressure, tilt, and tilt bicycle ergometry. This model includes gravity effects, muscle pumping, venous tone, venous valves, respiratory frequency, and intrathoracic pressure effects. Complex cardiovascular control hypotheses are modeled for the control of the heart period, peripheral flow resistances, venous tone, and other controlled variables. Metabolic control mechanisms are modeled by mathematical representations of oxygen uptake, oxygen deficit, and accumulating metabolites to simulate a transient metabolic state. The cardiovascular circulatory system is divided into 28 compartments to describe pulsatile blood flows, pressures, and volumes. Command inputs to the model are assumed to be from chemoreceptors, neurogenic inputs from muscular activity, and neurogenic anticipation. Other inputs needed are the exercise workload, work rate, blood volume, and angle and magnitude of the gravity vector. Typical outputs which can be selected are oxygen uptake, oxygen deficit, total metabolites, heart rate, various blood flows, systolic pressure, mean pressure, diastolic pressure, stroke volume, venous pressures, and arterial pressures. This model occupied a central position in the short-term segment of the whole-body algorithm and was used to simulate the provocative stress tests used in the space flight program.

Figure 3

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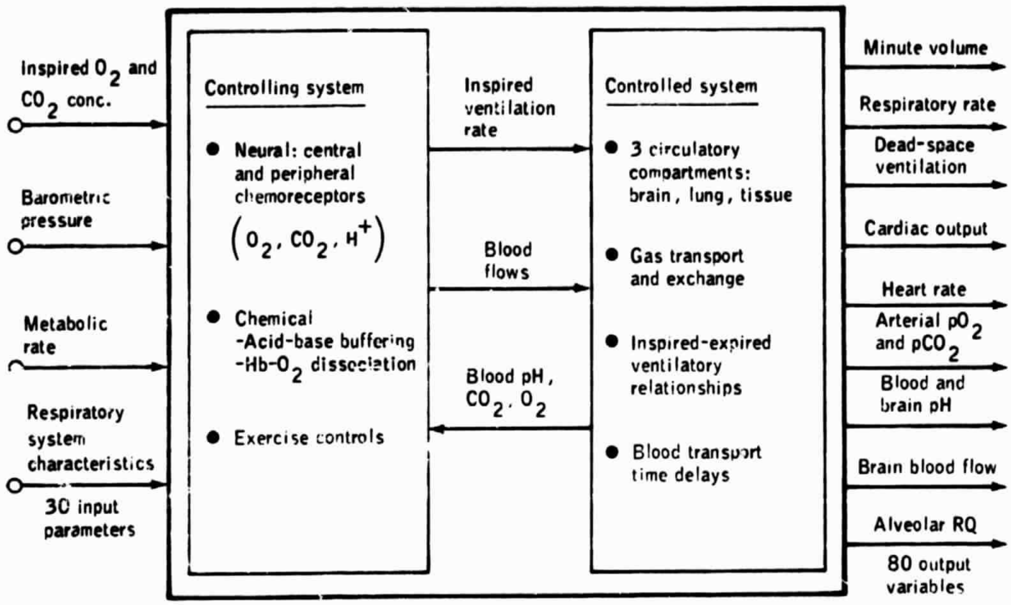
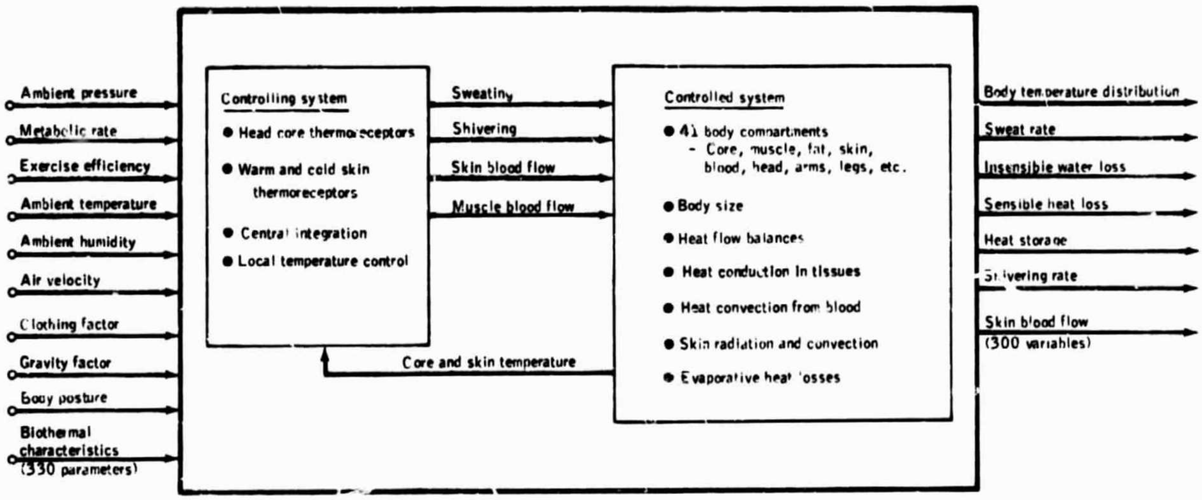


Model of Respiratory Regulation

The respiratory system model of Grodins was selected for use in the development of the whole-body algorithm. The controlled system is divided into three compartments (lung, brain, and tissue). The blood passes through the lungs and after a transport delay that is dependent on vascular volume and blood flow rate, the arterial blood arrives at the brain or the tissue compartment. In this model, CO_2 and O_2 exchange rates are governed by metabolism. Venous blood exiting the brain combines with venous blood from the tissue after a time delay, forming mixed venous blood. After another delay this mixed venous blood enters the lungs to complete the cycle of gas transport and exchange. The real system is composed of receptor elements which monitor chemical concentrations, afferent nerves which transmit this information to the central nervous system, neural centers, and motor nerves to the respiratory muscles which drive the thorax lung pump. In the model of this system, this process is represented by using chemical concentrations at receptor sites as inputs to the system, and ventilation as the output. Typical short-term stresses for which this model is suited include hypoxia, hypercapnia and acid-base disturbances. Modification of the original respiratory model provided the capability to simulate exercise.

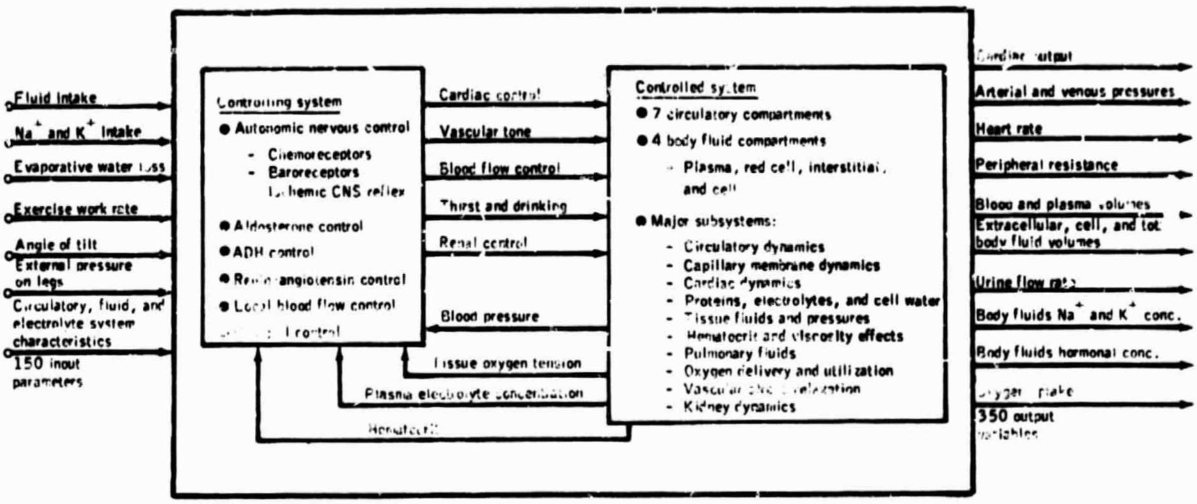
Figure 4



Model of Thermal Regulation

A dynamic model of physiological regulation of body temperature in man has been developed by Stolwijk and modified by NASA for various applications to the space-flight program. The controlled system is the mathematical representation of the thermal characteristics of the various geometric compartments of the body. These compartments (or nodes) represent the head, trunk, arms, hands, legs, and feet and are further divided into concentric layers designated as blood core, muscle, fat and skin. Each node has appropriate metabolic heat production and convective heat exchange with adjacent compartments. The skin exchanges heat with the environment via radiation, convection, and evaporation. The thermoregulatory model receives temperature signals from all tissue compartments and, after integration and processing, the control system sends commands to all appropriate compartments changing metabolic heat production, blood flow, distribution, or the rate of sweat secretion. The thermoregulatory model is well suited to examine short-term stresses such as the effects of external temperature variation (environmental change) and the effects of changing metabolic heat production (exercise level change). This model formed an important link in the whole-body algorithm, especially for the simulation of exercise. It was also employed to predict evaporative water losses in the hypobaric, reduced convective flow environment of Skylab.

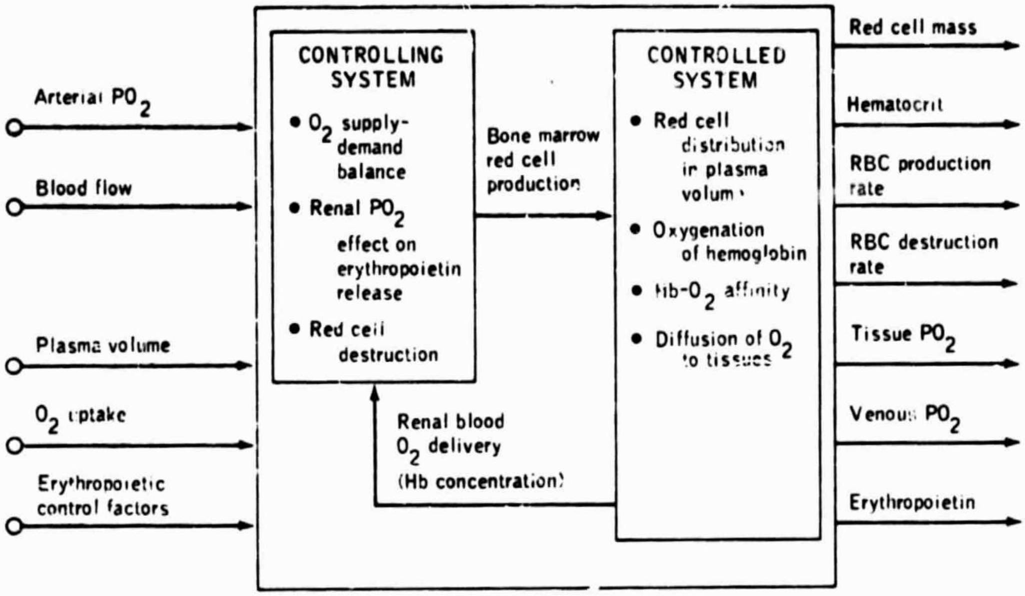
Figure 5



Model of Circulatory, Fluid and Electrolyte Regulation

The long-term model of circulatory, fluid, and electrolyte control, which was originally developed by Guyton, has been modified to include several new representations of certain regulatory functions. This model consists of 354 blocks, each representing one or more mathematical functions that describe an important physiological facet of circulatory regulation including autonomic, metabolic, renal, hormonal and fluid transport function. The circuit of blood flow in the Guyton model is divided into five volume segments: system arteries, system veins, right atrium, pulmonary arteries, and pulmonary veins-left atrium. Exchange of fluids (water and proteins) and electrolytes (sodium and potassium) is permitted to occur between the plasma, interstitium and intracellular fluid compartments via diffusion, active transport, transcapillary exchange, and lymph flow. Heart function is represented in a high degree of detail including representations for ventricular muscle strength, hypertrophy of the heart, deterioration of the heart, and sympathetic stimulation. Most of the above characteristics of the model can be viewed as the controlled system, while the controlling system consists of three major components - local control, hormonal control, and autonomic control. The inclusion of such elements as hormonal control, autoregulation, baroreceptor adaptation, erythropoiesis control, protein formation and destruction, venous stress relaxation and cardiac conditioning factors clearly indicate that the Guyton model was developed to be useful as a long-term model. Many varied experiments have been simulated with this model including infusions of water, electrolytes, and plasma, congestive heart failure, loss of kidney function, nephrotic proteinuria, and angiotensin infusions. The addition of gravity-dependent stress and the inclusion of leg compartments extended the capability of this system to include simulation of bed rest and weightlessness.

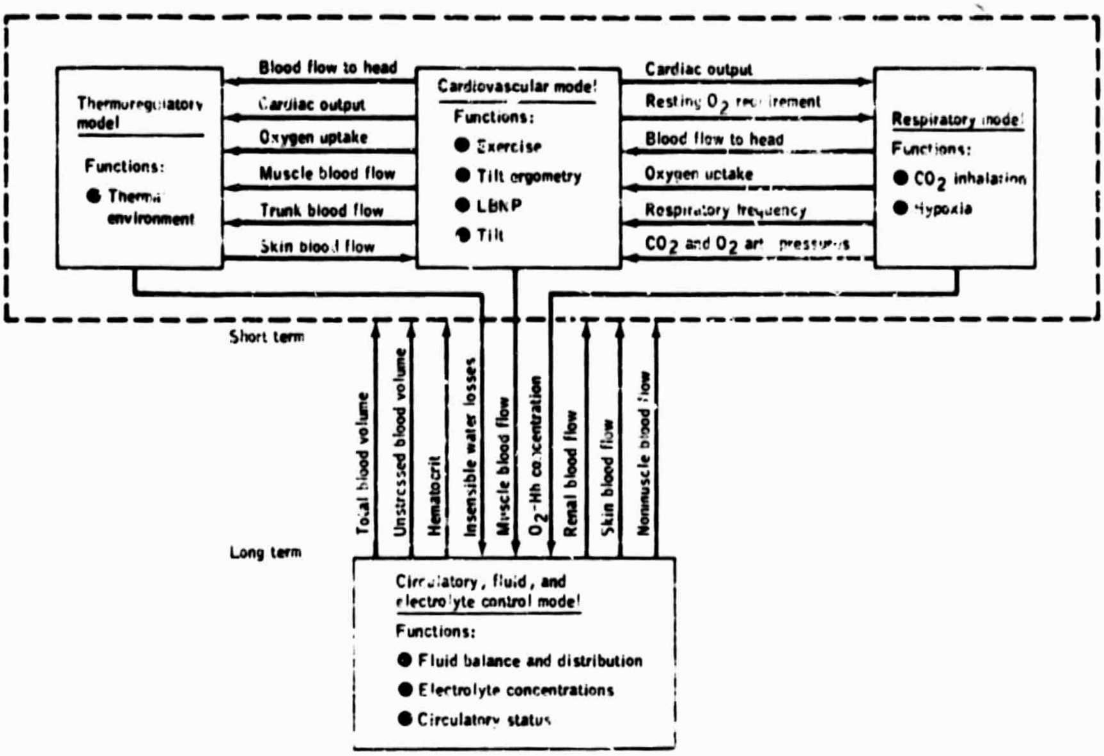
Figure 6



Model of Erythropoiesis Regulation

A model representing the control of erythropoiesis was originally developed to replace the red cell control algorithm in the Guyton model, but it has become an important investigative tool in a stand-alone mode as well. Elements in the feedback regulation loop include oxygenation of hemoglobin, oxygen supply by blood transport to a renal site, change in tissue pO_2 based on the balance between oxygen supply and oxygen demand, and secretion of erythropoietin from tissues sensitive to pO_2 levels. Production of red cells is based on the levels of circulating erythropoietin. Hemoglobin concentration in blood is computed from the addition of new cells to existing cells and plasma while accounting for cell destruction. The model is designed to investigate the relative influence of the controlling factors of erythropoiesis on total red cell mass. A wide variety of simulations have been performed with this model including altitude hypoxia, red cell infusions, dehydration, bed rest and spaceflight, as well as certain clinical abnormalities.

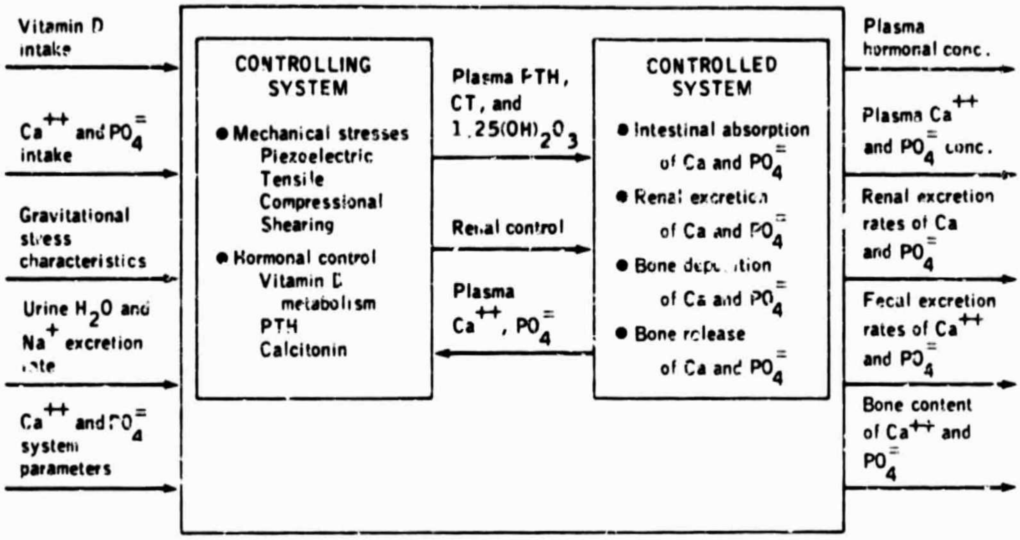
Figure 7



Whole-Body Algorithm

The design of the whole-body algorithm provides for the simulation of both long and short-term stresses. The long-term simulation is accomplished by a circulatory, fluid, and electrolyte subsystem model which then initializes a set of three short-term models representing the cardiovascular, respiratory, and thermoregulatory systems. These three short-term models, which are designed to simulate the responses to acute environmental changes and short-term experimental stresses, operate in parallel fashion interchanging information as often as every half second of simulation time. Modifications were required to interface these subsystem models and to permit them to simulate the stresses and experimental conditions of interest. One advantage of combining subsystem models is that each model considers various time lags, fast and slow controllers, and integration step sizes appropriate for their respective simulations. The primary function of this complex model is to permit evaluation of physiological interactions between subsystems. It also provides a capability for realistically simulating space-flight missions in which long-term adaptation occurs concomitantly with shorter term environmental or experimental stresses. For example, a typical Skylab protocol can be simulated by performing stress tests such as lower body negative pressure or exercise at various intervals over a prolonged inflight period during which time adaptation to the zero-g environment is achieved. In addition, the whole-body algorithm provides a central repository for collecting hypotheses for physiological changes due to weightlessness.

Figure 8



Model of Calcium Regulation

This model of calcium metabolism is still under development. The design specifications define the calcium fluxes between the intestinal tract, kidney, bone, and plasma as the controlled system. These elements are controlled by the plasma concentrations of parathyroid hormone, calcitonin, and the active metabolites of vitamin D, as well as by changes in mechanical stresses due to changes in the gravitational load. Other controlling elements include the urinary excretion rates of sodium and water. The feedback loops influencing the controlling system are directed via the plasma concentrations of calcium and phosphate. Thus, the model is designed to investigate the relative influence of the factors controlling calcium and bone metabolism.

Figure 9

These models can be characterized as being deterministic,and non-linear, and use finite difference formulations. All models operate in an interactive time-sharing mode the automated capability to display responses graphically, and to compare experimental data and model responses simultaneously. Most models were modified to include gravity dependent effects and to permit simulation of a human response to the stresses related to the space flight program. Some of the experimental and clinical conditions for which the models were validated include hypogravic stresses, orthostatic stresses, metabolic stresses, environmental disturbances, and fluid shifts (see table 2). Multiple stresses and sequential degrees of stress can be simulated just as in a real experimental protocol. Many hypotheses can be tested merely by adjusting the value of one or more of the fixed system parameters.

The combination of the data base analysis system with the group of simulation models formed the basis of the hypothesis testing approach that was used for integrating the Skylab findings (see fig. 10). The basic analysis system permitted large arrays of space-flight data to be scanned rapidly, graphical visualization of correlations between variables, and of testing hypotheses statistically. This preliminary evaluation of space-flight data led naturally to qualitative examination of the mechanism involved in producing the observed responses. This procedure drew heavily upon the theory of physiological feedback regulating systems and often suggested hypotheses capable of being tested by using the predictive capabilities of the simulation models. The elements of the medical data analysis system (fig. 1) were designed to interact in either sequential or parallel fashion, so that, for example, results from a data analysis could be employed as input forcing functions to a simulation model and the model's predicted responses could then be compared to additional data from the data base. While good agreement between model and data was desirable at times, it was not always essential. The heuristic value of modeling is such that even more important objectives are often realized when this agreement is poor, including suggestions for additional data analysis, refinements of the mathematical models, changes in the hypothesis being considered, and suggestions for the design of new experiments to be performed either in space or on Earth. This is an iterative process, as suggested by fig. 10, and is the heart of the systems analysis approach.

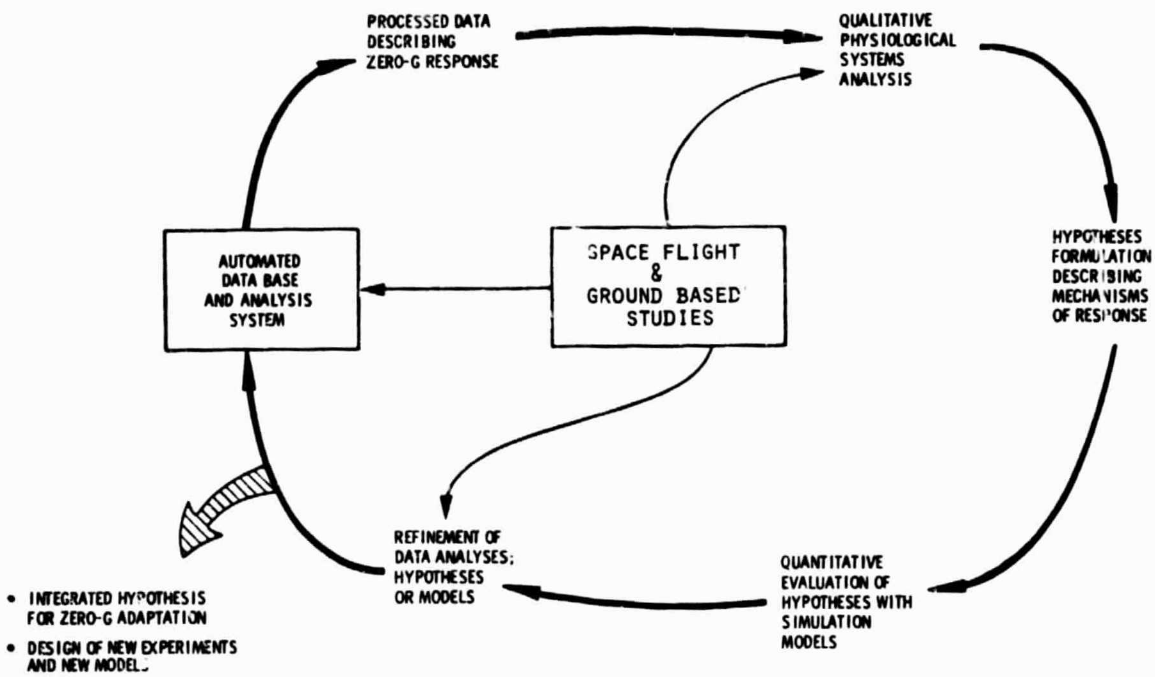


Figure 10. Systems Analysis Approach for Evaluation of Space-flight Data

Statistical and modeling techniques naturally complemented each other for integrating and correlating results from many different investigative areas. Predicting the consequences of hypotheses on unmeasured variables from many subsystems is within the ability of models, such as the whole-body algorithm, but is impossible if the testing of hypotheses is done by statistical methods. As the simulation study progressed, it was possible to incorporate more and more diverse kinds of experimental results and hypotheses into a single model. While each hypothesis alone would not support a generalized theory, all of them taken together should converge toward a coherent picture of zero-g adaptation.

Integrated Hypotheses for the Response to Weightlessness

This study addressed most of the physiological systems that have been extensively examined during previous space flights, particularly during the Skylab program. These investigative areas will be grouped, for purposes of summation, into four categories: (a) fluid, electrolyte, and renal function; (b) cardiovascular function; (c) hematology; and, (d) musculoskeletal function and body composition. The major systems analysis accomplishments for each area have been summarized in table 3. The results from these studies have led to an interpretation of the space-flight findings which are reviewed briefly below. Undertaken only recently was an analysis of the musculoskeletal system, with particular emphasis on calcium regulation. Therefore, the progress summarized for the last category is more limited. Also, while the indirect effects of space motion sickness on diet were considered in some detail, the vestibular system (which is believed to be the origin of this disturbance) was not addressed directly, because of resource limitations.

The interpretation of the space flight-data was guided by the need to answer certain questions which can be considered fundamental to a new area of environmental physiology such as weightlessness. These can be briefly stated as follows: (a) can the space-flight findings be explained in terms of disturbances and responses of well known homeostatic systems or are there pathological components and non-regulatory characteristics involved?, (b) are there only a few common elements in the space flight response (i.e., gravity unloading, fluid shifts, lack of orientation, deconditioning), the identification of which would explain most of the observed findings?, (c) is there a typical "zero-g response" and if so, what are its most characteristic features? Also, is it permissible to treat the nine Skylab crewmen as a composite group in order to delineate this response, or were there significant differences between the three missions (other than duration) that are important to consider?, and (d) in what ways are certain ground-based experimental maneuvers (i.e., water immersion, bed rest, head-down tilt) suitable analogs of weightlessness, and in what significant ways do they differ from the space-flight environment?

As a starting point in the analysis of each investigative area, an in-depth review was performed to reveal those "critical" areas in the observed responses fruitful for systems analysis investigation. These areas of unusual or unexplained events were systematically addressed by the hypothesis testing procedures outlined previously. A selected group of the most important of these 'critical' areas are listed in table 4. Most of these observations will be touched on in the following discussion.

TABLE 3

ACCOMPLISHMENTS OF SYSTEMS ANALYSIS STUDY

A. ACCOMPLISHMENTS: FLUID-ELECTROLYTE REGULATION

- Modification of the Guyton model (circulatory, fluid and electrolyte regulation) to include gravity-dependent elements, leg compartments, and improvements in the erythropoietic, renal, autonomic and renin-angiotensin subsystems.

- Validation of the modified Guyton model for fluid-loading, hemorrhage, and postural-change studies.

- Simulation analysis of the fluid-electrolyte response to hypogravic studies including water immersion, head-down tilt, bed rest, and space flight.

- Analysis of evaporative water loss in the hypobaric, reduced convective flow environment of Skylab using metabolic balance analysis and the modified Stolwijk thermoregulatory model.

- Metabolic balance analysis of water, sodium, potassium, calcium, nitrogen, and magnesium including Skylab nine-man composite summaries of dietary intake, renal excretion, and sweat losses.

- Composite time profiles of the nine-man Skylab mean responses for plasma and urinary electrolytes, hormones, and total body changes in water, sodium, and potassium.

- Analysis of fluid-electrolyte regulatory feedback mechanisms involved in acute and long-term responses to weightlessness.

- Interpretation of all Skylab data related to disturbances in body fluid volumes and their composition.

- Major support of bed rest and Spacelab flight experiment proposals.

TABLE 3 (CONTINUED)

B. ACCOMPLISHMENTS: CARDIOVASCULAR REGULATION

- o Development of a new pulsatile cardiovascular system model.
- o Validation of cardiovascular model for exercise, tilt, lower body negative pressure (LBNP) in one g.
- o Modification of the pulsatile model to include elements responsive to hypoxia and hypercapnia.
- o Modification of the respiratory model of Grodins to include the capability to respond to exercise.
- o Simulations of the exercise response using the combined thermoregulatory, respiratory, and cardiovascular subsystem models of the whole-body algorithm.
- o Simulation analysis of space-flight LBNP and postflight exercise (supine and sitting) using pulsatile model.
- o Simulation of disturbances in the circulatory system during short-term water immersion and head-down tilt and long-term bed rest and space flight using the modified Guyton model and whole-body algorithm.
- o Composite time profiles of the nine-man Skylab mean responses to LBNP.
- o Sensitivity analyses for effects of blood loss and venous compliance changes on tilt and LBNP responses.
- o Analysis to examine possible changes in inflight baroreceptor sensitivity.
- o Analysis of mechanical and metabolic efficiencies and other performance indices during bicycle ergometry flight experiments.
- o Modification of the pulsatile cardiovascular model to include physical training (conditioning) effects and evaluation of these hypotheses against Skylab exercise data.
- o Formulation and evaluation of hypotheses to account for decreased orthostatic tolerance and decreased aerobic capacity during inflight and postflight phases.
- o Support of flight experiment proposal for advanced cardiopulmonary studies.
- o Design of improved autonomic subsystem to include sympathetic/parasympathetic and high pressure/low pressure pressoreceptor effects as well as an experimental proposal to validate this system.

TABLE 3 (CONTINUED)

C. ACCOMPLISHMENTS: HEMATOLOGY

- o Development of new models for control of erythropoiesis in the human and the mouse.
- o Simulation analysis of hematological responses to altitude hypoxia and descent, red cell infusions, bed rest, water-restricted dehydration, and space flight.
- o Interactive support of a research program which examined suppressed erythropoiesis in dehydrated mice.
- o Analysis of all space flight and ground-based studies related to loss of red cell mass during hypogravity.
- o Formulation and tentative evaluation of candidate hypotheses to explain the "anemia" of space flight with particular emphasis on explaining the differences in red cell loss among crewmen.
- o Simulations of clinical syndromes (anemias, polycythemias, and Hb abnormalities) and partial development of a teaching model of erythropoiesis regulation.

D. ACCOMPLISHMENTS: MUSCULOSKELETAL SYSTEM AND BODY COMPOSITION

- o Metabolic mass, water and energy balance analyses including a new method for estimating cumulative total body changes (water, fat, protein, electrolytes) as a function of flight duration.
- o Analysis of body composition changes (lean body mass and fat) based on body water, body potassium, nitrogen-potassium balance, and body density data.
- o Analysis of inflight requirements for exercise and diet.
- o Interpretation of components of body weight loss based on fluid and energy regulation and gravity unloading.
- o Design and partial development of a new model for calcium regulation.
- o Support of a flight experiment proposal for advanced calcium regulation studies.

TABLE 4

SELECTED OBSERVATIONS FROM SKYLAB EXPERIMENTS ADDRESSED BY SYSTEMS ANALYSIS

Fluid-Electrolyte System

- o Rapid loss of water early in flight.
- o Much larger increase in leg fluid volume compared to bed rest.
- o Absence of measurable diuresis following headward fluid shifts.
- o Unusual combination of hormonal changes compared to bed rest and water immersion.
- o Presence of a hyponatremic plasma maintained throughout flight.
- o Increased water and sodium excretion throughout mission without continuous body losses.
- o Differences in ADH response between missions.
- o Decreased evaporative water loss in presence of hypobaric atmosphere.
- o Disproportionate losses of potassium and cell water

Cardiovascular System

- o Acute cardiovascular disturbances expected from headward fluid shifts were not observed.
- o Decreased orthostatic tolerance as measured by lower body negative pressure tests.
- o Maintained aerobic capacity during flight in spite of decreased blood volume and decreased orthostatic tolerance.
- o Decreased aerobic capacity immediately following flight.
- o Differences in aerobic capacity among the three crews.

Erythropoietic System

- o Inflight loss of red cell mass.
- o Delay in postflight recovery of red cell mass on shortest mission.
- o Significant differences in rates of red cell loss among the three crews.

Musculoskeletal System

- o Progressive loss of calcium from body.
- o Urinary calcium stabilizes at elevated level while fecal calcium increases progressively with flight duration.
- o Changes in PTH during space flight not similar to changes in bed rest
- o Rates of nitrogen losses appear to decrease as a function of flight duration and increasing levels of exercise.

Body Composition

- o Rates of water, muscle, and fat losses appear to be disproportionate to ratio in body tissues.
- o Body mass losses decrease with flight duration.
- o Water losses appear independent of flight duration.
- o Large differences in body composition changes between the three Skylab missions.
- o Energy requirments in zero-g and one-g appear similar

Fluid-Electrolyte Response to Weightlessness

There is unequivocal evidence that hypogravic stresses such as bed rest, water immersion, and space flight 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 fig. 11. As a result of central volume expansion, a complex set of reactions occurs: (a) stimulation of all cardiopulmonary pressoreceptors and decreased sympathetic activity; (b) increased blood pressures and secondary decreases in peripheral resistance, promoting enhanced renal blood flow; (c) altered secretion of the fluid-electrolyte regulating hormones including ADH, the renin-angiotensin-aldosterone triad, catecholamines, and possibly a natriuretic agent, as well as renal prostaglandins; (d) enhanced renal excretion of fluid and electrolytes as a result of the alterations in sympathetic activity, hormone secretion, and blood pressures and flows; (e) increased transcapillary filtration of plasma into the interstitium; and, (f) a decrease in thirst following reduction in angiotensin levels and augmented by space motion sickness anorexia. The net result of these processes is the loss of extracellular fluid and electrolytes, which has been observed frequently during and following weightless space flight.

This description evolved from examining such ground-based studies as water immersion and blood volume expansion. A simulation of immersion demonstrating many of these events is shown in fig. 12. Most, if not all of the rapidly acting mechanisms described above (which serve to correct the original blood volume disturbance) would most likely be observed only during the first hours of a hypogravic stress. However, on the basis of 24-hour metabolic balances, urine flow in the Skylab crew was not increased and the entire loss of body fluids could be accounted for by deficit fluid intake (possibly as a result of space motion sickness). Computer simulation analysis of the acute stress period indicated that a reduction in fluid intake always diminished, but did not abolish, the diuresis response and the period immediately following this diuresis was accompanied by a reduction of renal excretion below control. Thus, it is postulated that a diuresis was not observed because void-by-void urine samples could not be obtained and because an early diuresis would be masked in a 24-hour pooled sample in the presence of diminished intake. The short-term renal response to space flight in well hydrated subjects is not yet known.

Whatever the mechanism, most of these early losses were probably derived from observed decrements in leg volume involving a contraction of the plasma, interstitial, and possibly intracellular fluid spaces of the lower limbs. By the end of the first two days in space the reduction in body water and body sodium was largely complete (see fig. 13). Also during the early stages of flight, significant quantities of potassium escape from intracellular compartments. This may be deduced from elevated renal excretion of potassium, increases in plasma potassium, increased levels of cortisol and aldosterone which are involved in releasing and controlling potassium, and potassium balance studies on which the data of fig. 13 is based.

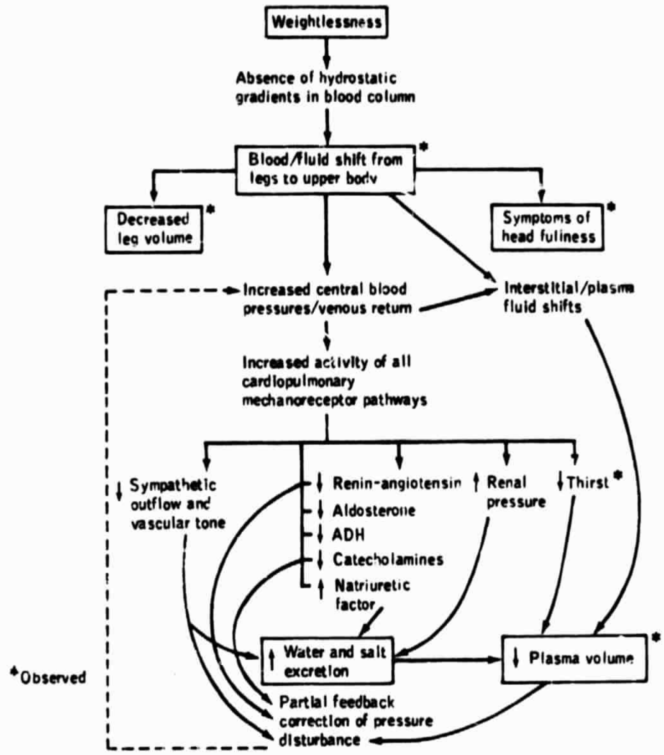


Figure 11. Hypothesis of Fluid-Electrolyte Regulation Following Acute Stress of Weightlessness

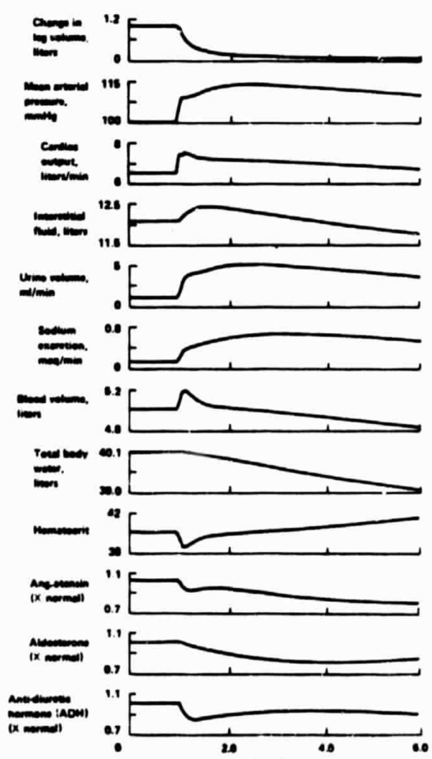


Figure 12. Simulation of Acute Effects of Water Immersion in Normally Hydrated Subjects

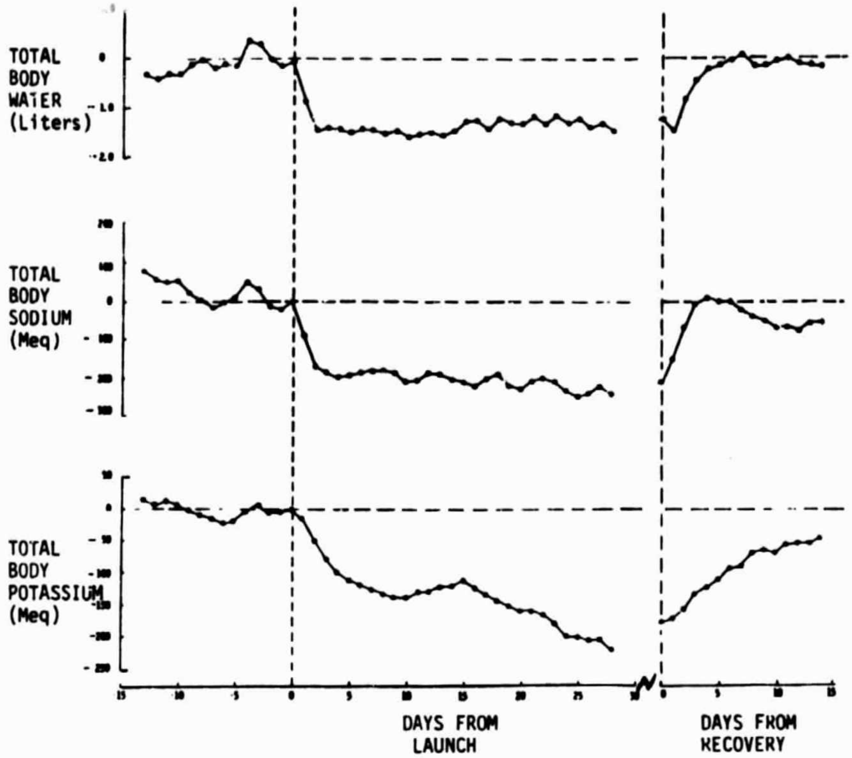


Figure 13. Changes in Body Fluids and Electrolytes of Skylab Crew

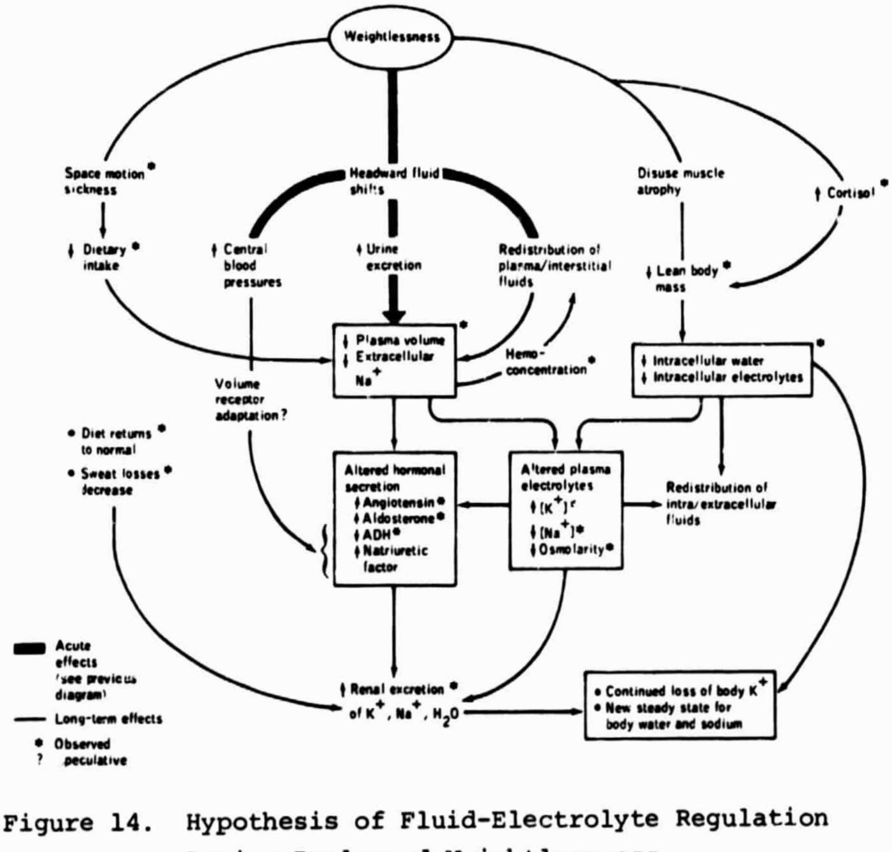


Figure 14. Hypothesis of Fluid-Electrolyte Regulation During Prolonged Weightlessness

The more prolonged adaptive phase was characterized by a new steady-state with respect to water and sodium and a slightly negative balance of potassium (fig. 13 and 14). The modest increase of water and sodium excretion throughout this adaptive phase did not necessarily reflect continued body loss inasmuch as excretion could have been offset by a decreased sweat component. Both a steady-state metabolic balance analysis and model simulation analysis supported this concept. The continued loss of body potassium is expected from the atrophy of lean body tissue, a consequence of gravity unloading and muscle disuse.

The importance of autonomic, hemodynamic, and hormonal regulators of circulatory and renal function during the chronic phase was ascertained by model simulation. These pathways were influenced by fluid shifts between body compartments, altered metabolic balance, potassium loss from the cells, and plasma electrolyte concentrations. On the basis of model anlaysis it appears that plasma volume is depressed about one-half liter throughout the flight. This prediciton is supported by postflight measurements. The failure of the plasma volume to return to normal in zero g is presumptive evidence of the presence of blood volume controllers responding to the tendency of fluids to pool headward. During the adaptive phase of flight, angiotensin and aldosterone presumably reversed direction from the suppression hypothesized in the acute stress stage. Increased release of these substances can account for the elevated renal potassium rates of excretion. It was necessary to introduce a natriuretic factor in the model (responding to central blood volume expansion) to obtain realistic simulations of enhanced sodium excretion in the face of elevated aldosterone, and also to generate the hyponatremic plasma that was observed. The average behavior of ADH for all Skylab subjects (increased during the first 10 days and suppressed thereafter) exhibits the expected inverse correlation with urine output. Not so easy to understand is the elevation of plasma angiotensin I. Since renin-angiotensin is usually released in response to hypovolemia, it is not clear why angiotensin is elevated in zero g (and also in some bed-rest studies) at a time when there is a tendency for central blood volume expansion. A mild reduction in plasma osmolarity and sodium concentration occurs early in flight and continues through the longest mission. The mechanisms which maintain this condition are not clear. However, the combination of mild hypo-osmolarity and hyperkalemia helps account, at least in part, for the increases in angiotensin and aldosterone and decreased ADH.

Hematological Response To Weightlessness

The most important hematological finding is a reduction in the circulating red cell mass during the flight interval. The working hypothesis prior to Skylab was that the pure oxygen gaseous atmospheres in the space capsule represented a toxic stimulus and resulted in early death of significant numbers (up to 20 percent loss) of red cells. For the Skylab crew who existed in a supposedly normoxic environment, this hypothesis was no longer tenable to explain their average loss of 10 percent of total red cell mass. In the absence of a consistent finding of increased red cell destruction, it was assumed that this loss was likely a result of suppressed erythropoietic activity. However, no conclusive proof of this is available and no one mechanism has been identified which is consistent with all the data.

The regulation of erythropoiesis during weightless space flight was studied using a theoretical model (fig. 7). Several approaches were used, including: (a) parameter sensitivity analyses which helped identify the factors most likely to have a sensitive influence on erythropoiesis; (b) dynamic simulation of experimental studies such as altitude hypoxia and recovery from altitude hypoxia, red cell infusions, dehydration, and bed rest, all of which helped reveal behavior of the real system; and, (c) collaboration with investigators, performing human and animal studies, to test in the biological system those hypotheses suggested by the computer model.

The most important finding from these theoretical and experimental studies was that moderate increases in hematocrit, up to the 12 percent measured on Skylab, if unopposed by other factors involving oxygen delivery to tissues, can proportionately increase oxygen tension at a renal sensing site and exert a sensitive suppressant effect on erythropoietin and red cell production (fig. 15). The erythropoietic regulatory system may be viewed, when operating in this fashion, as a hemoglobinometer; i.e., red cell production decreases so as to eventually relieve the hyperoxic condition. The final predicted result is a nearly complete restoration of hematocrit accompanied by a diminished red cell mass. Although not yet confirmed experimentally during hypogravic maneuvers, the model suggests that red cell mass will eventually stabilize as hematocrits normalize. This process can, therefore, be explained in terms of normal feedback regulation of the erythropoietic system in the face of sustained decreases in plasma volume.

However, hemoconcentration effects, by themselves, could not explain the dissimilarity between red cell mass loss on the different Skylab missions. Two theories were examined to explain the findings that the Skylab crews who returned to earth after longer periods of weightlessness exhibited smaller losses of red cell mass. The time course of red cell loss in space flight is not yet known, but based on a composite of postflight measurement of all crewmembers, it was postulated by others that red cells disappear by some as yet unknown mechanism during the first month and then begin to replenish during the second and third months. Acceptance of this hypothesis as a generalized theory of erythropoietic regulation in weightlessness is confounded by the fact that decreasing losses of red cell mass in Skylab were associated not only with longer flight duration, but also with increasing levels of diet and exercise. On the basis of animal studies, it was hypothesized that dietary restriction can reduce, and increasing exercise can enhance, erythropoiesis. Diet and exercise also appeared to have demonstrable effects on maintenance of body tissue and cardiovascular condition of the Skylab crew, and their further involvement in the oxygen transport-erythropoietic system was postulated in this study. An alternate and more plausible theory was, therefore, proposed, which suggests there were two components to the suppression of red cell production: one related to energy balance and one related to water balance. Differences among the crewmen's red cell losses were thereby considered to be a result of different levels of dietary intake and exercise, superimposed on a common loss due to hemoconcentration (see fig.15). According to this concept, the kinetics of red cell disappearance would not include regenerative behavior, but would be more similar to the continuous, linear losses observed in bed rest. Statistical correlations between diet levels and red cell losses, as well as model analysis, tended to support this theory. Thus, it is not necessary to invoke the occurance of red cell regeneration to explain the Skylab data. Other

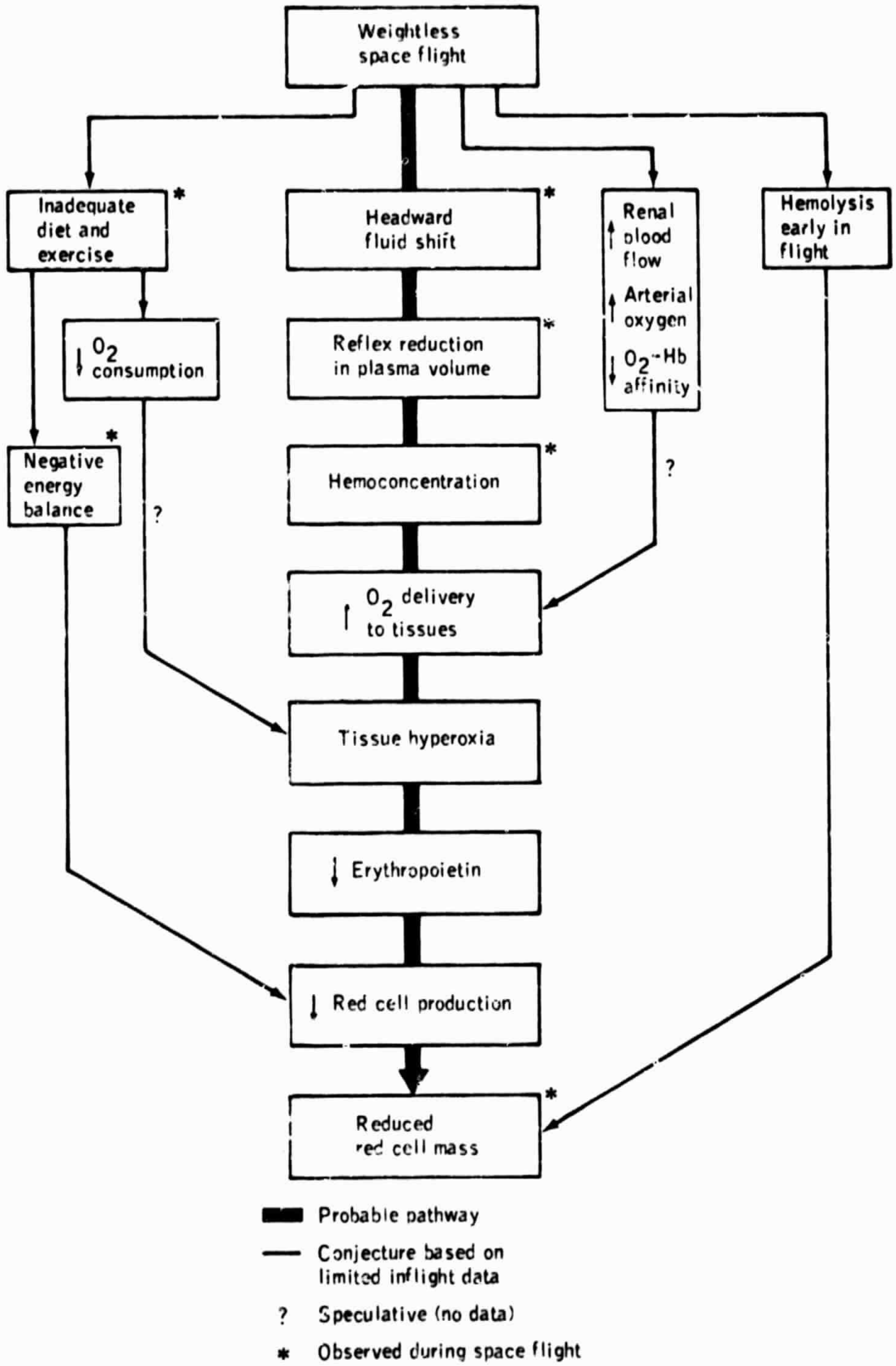


Figure 15. Hypothesis of Erythropoiesis Regulation During Prolonged Space Flight

factors (also shown in fig. 15) which may have enhanced oxygen delivery and produced the same effects as hemoconcentration cannot be ruled out at this time (i.e., shifts in renal blood flow, oxygen-hemoglobin affinity, and arterial pO_2), but direct data are only available to support the hemoconcentration effect. Also, the simulation analysis indicated that a major role of inflight cell destruction was considered unlikely, although it was impossible to rule out some small degree of acute red cell destruction early in flight which may have contributed to the reduced red cell loss. Indeed, Skylab measurements indicated that some hemolysis may have occurred on the shortest flight.

Recommendations were proposed for future flights based on this analysis. For example, it is crucial to obtain direct inflight measurements of erythropoietin and bone marrow activity. If reduced erythropoietin levels cannot be demonstrated during space flight, then the hemoconcentration theory may have to be abandoned. Also, the importance of diet and exercise on erythropoiesis needs to be studied more carefully in humans with and without accompanying hypogravity. Finally, the differences between postflight and post-bed-rest kinetics of red cell recovery were not entirely resolved in thisstudy, and it would be desirable to examine bone marrow activity upon recovery of hypogravic maneuvers.

Cardiovascular Response to Weightlessness

The most dramatic changes in the resting cardiovascular system probably occurred early in flight, well before the first measurements could be performed. As simulated by the modified Guyton model and demonstrated by one-g experimental analogs of weightlessness, the primary event of the headward fluid shifts leads to central blood volume expansion, increased venous and arterial pressures, increased stroke volume, and elevated cardiac output. Secondary reactions following stimulation of central mechanoreceptors are immediately activated, and include a decrease in heart rate and decreased peripheral resistance. These reflexes, together with enhanced transcapillary filtration and excess renal excretion, tend to correct both the central blood volume and associated pressures. Although the Guyton model predicts a complete normalization of central blood volume, whether or not this occurs is still a matter of controversy. Engorgement of neck veins and facial tissues and feelings of head fullness, which continue throughout the flight, are symptomatic of the continued tendency of fluids to pool in the upper body in zero g. Also, a residual excess volume in the vicinity of the low pressure cardiopulmonary receptors can account for the longer term increase in resting heart rates (e.g., Bainbridge reflex) noted in the majority of the Skylab crew (and in bed rest). One of the long-term effects of space flight may therefore be that, as arterial pressure normalizes, the low pressure volume receptors increase their influence while the high pressure receptors decrease their influence, at least at the level of the heart. Other long-term effects were identified during simulations of weightlessness which assist the circulation to adapt to a reduced blood volume, an emptying of leg veins, and fluid pooling in the upper body. These poorly defined mechanisms include volume receptor adaptation, devascularization, stress relaxation, baroreceptor resetting, and autoregulation of blood flow.

Cardiovascular function was evaluated during the Skylab missions by an orthostatic stress test (lower body negative pressure, LBNP), and by an exercise stress test (bicycle ergometry). The most prominent findings from these tests were a decrease in orthostatic tolerance during and following flight and a post-flight decrease in aerobic capacity. Hypotheses to explain these findings were formulated and tested in the pulsatile cardiovascular model (see fig. 3 and 16). It was convenient and useful that the same model for the cardiovascular system be used to analyze both LBNP and exercise, each of which present different challenges to the cardiovascular system with significantly different responses.

A. Analysis of Orthostatic Testing

The observed decrease in orthostatic tolerance is not unexpected in the light of significant loss of blood volume (-600 ml). Upon application of LBNP or standing in one g, the increase in leg pooling coupled with a reduced blood volume significantly lowers central blood volume and venous return to the heart. The model simulations quite accurately predicted the increased heart rates and decreased pulse pressures characteristic of the Skylab crews' intolerance to orthostasis. The inflight heart rate response to maximal LBNP (-50 mmHg) was shown to be nearly equivalent to a 15 percent hemorrhage. However, blood volume loss alone was not sufficient to explain all of the observed findings. For example, an increase in leg volume pooling during LBNP (compared to the degree of pre-flight pooling) was noted during space flight. The most promising explanation of this phenomenon, as suggested by simulation analysis, was the partial collapse of leg veins in association with a reduced leg blood volume during the pre-LBNP control period. Small increments of LBNP would be expected to draw significant quantities of blood into the empty leg veins, more so in zero g than in one g.

The response to orthostasis was observed to stabilize and even improve in some subjects during the latter part of the mission. One of the more promising hypotheses to explain these findings was a long term downward adjustment of vascular capacity in the legs (in response to the reduced leg fluid volume) which could be manifested physiologically by retoning, devascularization, or reverse stress relaxation. Changes in plasma electrolyte concentrations (increased potassium and calcium, decreased sodium) may also be involved in altering vascular tone. Little is known concerning autonomic influences on venous tone during long term adaptation to hypogravity.

B. Analysis of Exercise Response

Tolerance to exercise was essentially maintained during the flight period. It was only after return to Earth that aerobic capacity was found to be diminished. This is similar to results reported for bed rest. Analyses performed with the whole-body algorithm permitted the circulatory adaptation of long-term bed rest to initialize the short-term LBNP and exercise model so that pre- and post-bed rest stress tests could be simulated. Results from these studies suggested that decrements in blood volume in association with some reduction in unstressed volume in the legs could quantitatively account for most of the observed changes in post-bed rest exercise (and LBNP) and post-flight exercise in the crews of the two shortest Skylab missions. However, there was a notable qualitative difference between the degraded post-flight exercise responses of the crews of the two shortest flights and

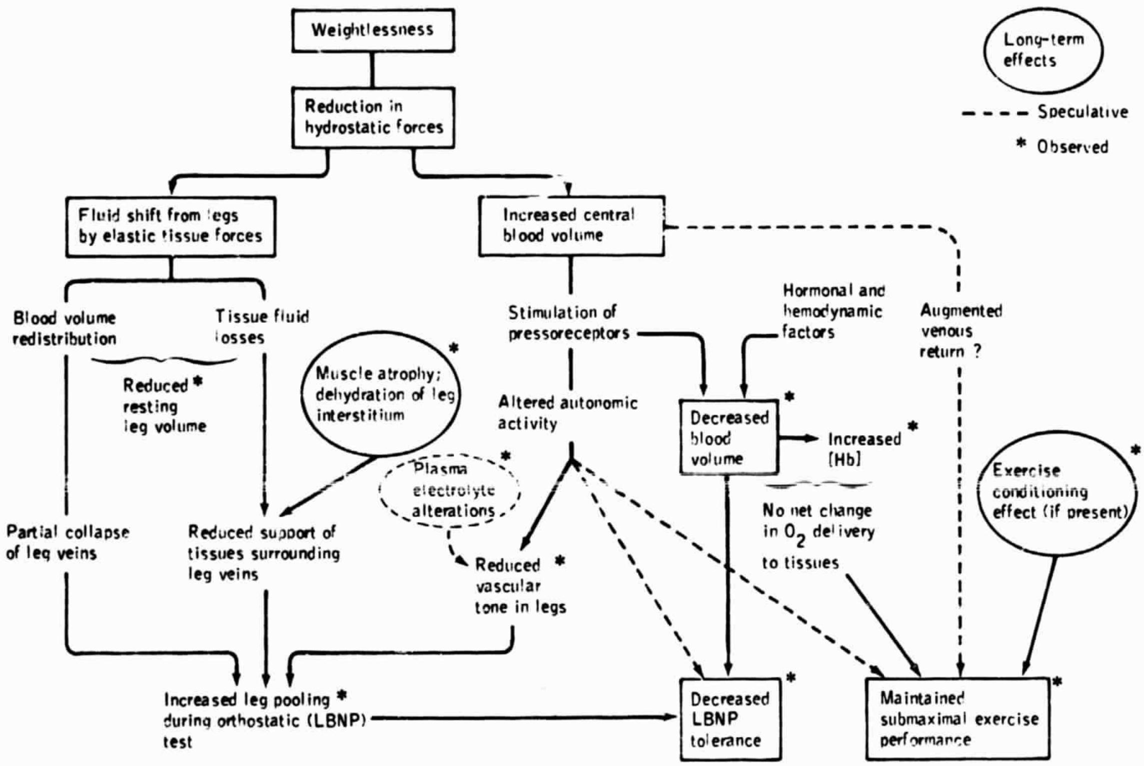


Figure 16. Hypotheses to Account for Inflight Responses of Orthostatic and Exercise Stress Tests

the crew of the longest flight that was tentatively ascribed to an inflight exercise training effect. (The level of personal daily exercise increased on each longer flight). A systems analysis task was therefore devoted to developing the most feasible explanation of the interaction of zero-g adaptive changes (deconditioning) and exercise training (conditioning). In this regard, the cardiovascular exercise model was modified and validated to represent the simulation of a highly trained subject's response to bicycle exercise in one g. This model was used in the "trained" and "untrained" mode to simulate the postflight bicycle ergometry experiments in both sitting and supine positions. The results led to the conclusion that a training effect was quantitatively consistent with the exercise response for the crew that trained the hardest.

The absence of any notable decrease in inflight exercise capacity for all crewmembers indicates that the contracted blood volume is an appropriate adaptation to zero gravity. Nevertheless, the nature of this adaptation is not clear. The current analysis suggested that normal oxygen delivery was maintained in the face of diminished blood volume by the hemoconcentration of weightlessness, and by the tendency of fluid to pool in the upper circulation, thereby augmenting venous return to the heart. Conversely, the hemodilution observed upon recovery (in addition to reduced blood volume) would be expected to contribute to the postflight degradation in exercise performance.

Musculoskeletal Responses to Weightlessness

The Skylab findings support the concept of a generalized atrophic response of the musculoskeletal system in toto during extended exposure to hypogravity. Losses in bone and muscle mass were among the more significant physiological changes observed in the astronaut subjects (fig. 17).

A. Muscle Atrophy

The losses in muscular tissue were particularly well documented. One of the systems analysis tasks demonstrated that lean body mass was reduced by approximately 1.5 kg (N=9) over the inflight period. This was revealed by several independent methods which showed losses in body water, potassium, nitrogen, and volume. More direct evidence of muscle and collogen breakdown was provided by the measured increase in renal excretion of urinary 3-methylhistidine, hydroxylycine, and hydroxyproline. Also, excesses of intracellular electrolytes and amino acids appeared in the plasma and urine. Further analysis of space-flight data indicated a significant degree of local muscle loss in the legs and perhaps in the skeletal muscle groups that normally control anti-gravity or posture. The data supporting these contentions come from space-flight studies showing a gradual loss of leg volume, decreased leg strength, a reduction in duration of the Achilles reflex, and, in animals, diminished mass and response of red fiber groups.

It is well known that atrophy of skeletal muscle occurs in response to disuse, inadequate functional load, and insufficient food intake. Space flight may be associated with more than one of these conditions. The absence of gravity results in diminished use of the lower limbs for postural support and locomotion, reduced body weight loading on weight-bearing tissues, and perhaps interference with proprioceptor reflexes which can influence muscle metabolism and function. Dietary insufficiency, noted in some of the crewmen,

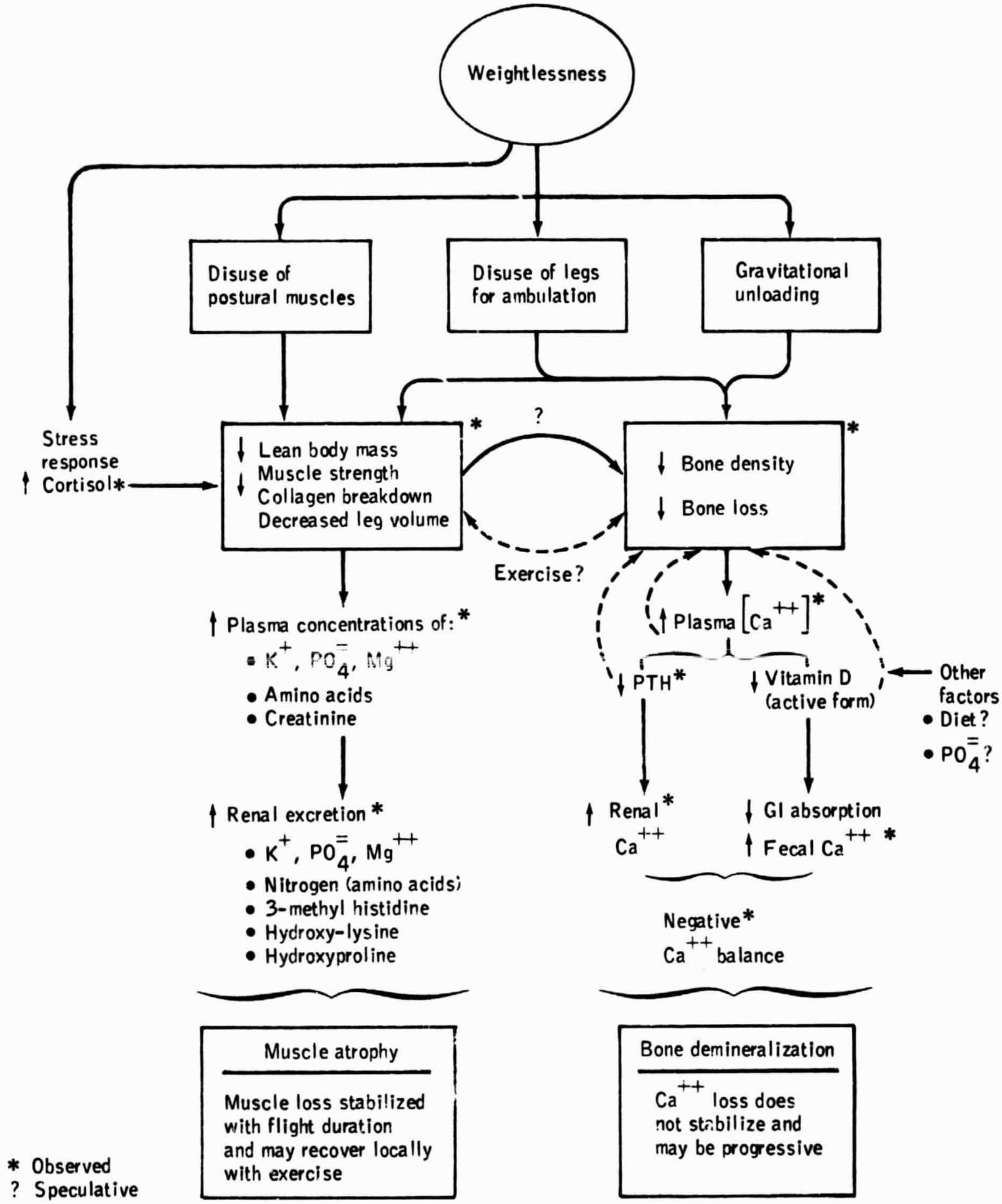


Figure 17. Hypotheses of Musculoskeletal Changes During Prolonged Space Flight

was most likely not of major significance in accounting for muscle losses, since nitrogen balances were similar for all crewmen, including those with adequate diet. The muscle disuse atrophy hypothesis receives support from the finding that the more intensive exercise performed by the crew of the longest flight (mainly exercise of the leg muscles) was associated with the smallest decreases in leg volume and strength. Little is known, however, about the changes occuring in other muscle groups, particular those used for postural support in the upper body. The kinetics of whole body protein losses, based on nitrogen and potassium balances, appeared to be similar in all crews for the first month (regardless of exercise performed) and, thereafter, the losses seemed to stabilize. The lack of suitable controls makes it difficult to assess whether the stabilization of muscle loss is due to exercise or to some other long-term adaptive influence. If postural muscles are primarily targeted for zero-g loss, appropriate locally applied exercise might reverse this trend.

B. Bone Demineralization

Evidence for inflight loss of bone mass comes primarily from observations of calcium metabolic balance and bone density. Inflight calcium balances were consistently negative on all flights, a result of excess urine excretion throughout the missions and a progressive increase in fecal calcium loss as a function of mission duration. Bone densitometric data indicated losses in the calcaneus (of the heel), but not in the radius and ulna (of the arm), suggesting that losses are not generalized throughout the body. A significant correlation between changes in calcaneus bone density and calcium balance for the nine crewmen was demonstrated. Additional evidence of demineralization is suggested by increases in urinary hydroxyproline and hydroxylycine which may indicate breakdowns of the collagen matrix in the bone. Analysis of all these data suggested that bone losses became progressively more severe on each longer mission, in contrast to the trend toward stabilized losses noted for muscle.

The initiation of bone loss is assumed to be due to reduction of mechanical forces induced by gravitational unloading, and/or reduced musculoskeletal interactions. These forces (piezoelectrical, compressional, tensile, and shearing forces) are known to be important in the normal maintainence and repair of bone. It appears logical that external forces, appropriately applied, might reverse the decalcification process. However, the search for suitable countermeasures has not met with notable success. The effect of exercise on bone demineralization remains unresolved.

Upon release from the bone into the extracellular pool, calcium and its concentration in plasma is under the control of a feedback system mediated by a hormonal system which influences renal excretion and gastrointestinal absorption as well as new bone formation. The observed elevation of urinary calcium may have been a result of increased plasma calcium concentration, decreased parathyroid hormone, and increased tubular sodium (see fig. 17). Progressive losses of fecal calcium have been tentatively attributed to a net decrease in dietary absorption of calcium from the gastro-intestinal tract. The active metabolite of vitamin D (1, 25 dihydroxycholecalciferol) is an important regulator of GI tract absorption, and a decrease in circulating levels of this substance could explain the fecal data. As suggested in fig. 17, a depression of parathyroid hormone and Vitamin D could have a negative feedback effect on demineralization and limit the losses of calcium from the bone. These preliminary hypotheses have been incorporated into proposals for future flight experiments which will examine several features of calcium regulation, including fluxes into and out of the bone and GI tract, hormonal regulation, and the effect of exercise as a countermeasure. To help support, define and evaluate these studies, a mathematical model of the physiology of calcium regulation is being developed (see fig. 9). Although the model is not yet complete, formulation of the model was instrumental in unifying space-flight and bed-rest data and in identifying critical areas in the regulatory system which might become altered in zero g.

Body Composition Changes

One of the more consistent findings in astronauts returning from space flight of any duration has been a loss in body weight. The dynamic behavior of this weight loss during flight was observed for the first time in the Skylab program, but ancilliary measurements of body composition were performed prior to and after the flights and, therefore, provided only estimates of gross overall change. Therefore, an analysis method was developed during the current systems analysis program to numerically determine the major components of body weight loss in terms of continuous time profiles for body water, body protein, body fat, body potassium, and body sodium. The basis of the approach was a group of metabolic models for water, mass, and energy balance, which, when combined with whole body measurements, allowed sequential accumulation of daily balance without incurring unreasonable error (fig. 18). Selected results of this study are illustrated in fig. 13 and 19. The general conclusion of this study was that little more than half of the weight loss observed during the Skylab mission can be attributed to loss in lean body mass, the remainder being derived from fat stores. As a working hypothesis, we have assumed the following: (a) acute water and sodium losses are obligatory as a result of normal physiological responses to headward shifts of fluid in zero g; (b) protein and intracellular mineral losses are primarily a result of disuse atrophy of postural muscles and may be obligatory in weightlessness (without appropriate exercise) although the losses appear to stabilize after about a month; (c) fat losses are more variable and are probably dependent on the usual one-g influences of diet and exercise; and (d) if present, the anorexia associated with space motion sickness will augment fat and protein losses by virtue of a caloric deficiency and will enhance water loss as a result of reduced fluid intake. These conclusions must be considered tentative because of the indirect method of estimation and because adequate experimental controls for assessing the role of diet and exercise in weightlessness were not available.

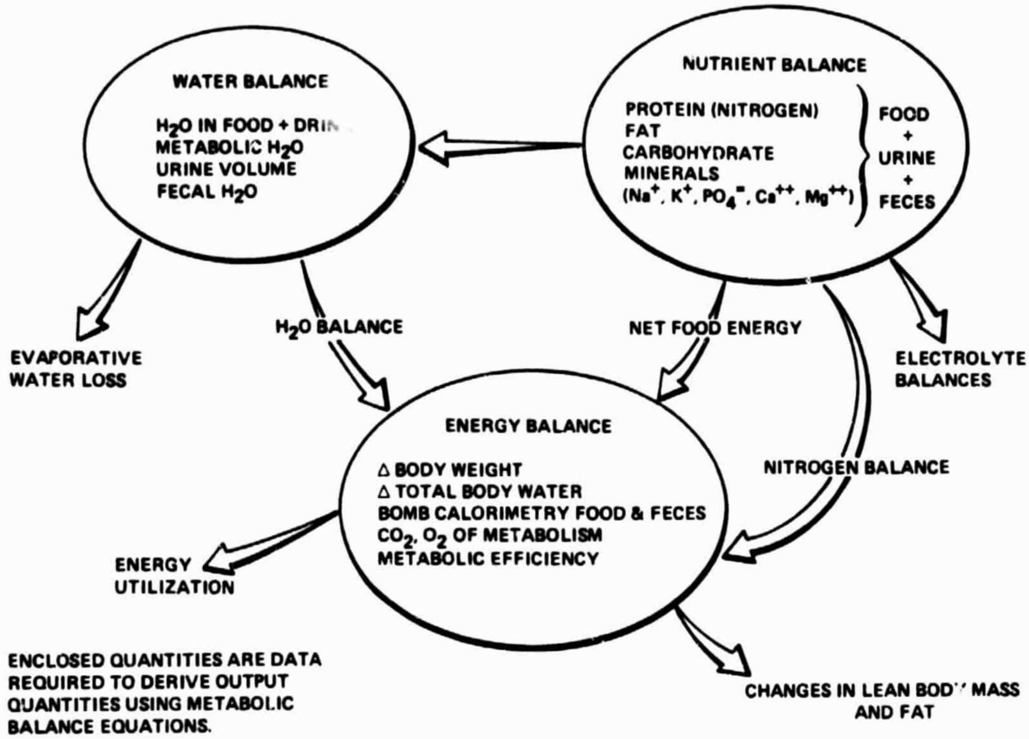


Figure 18. Integrated Metabolic Balance Analysis

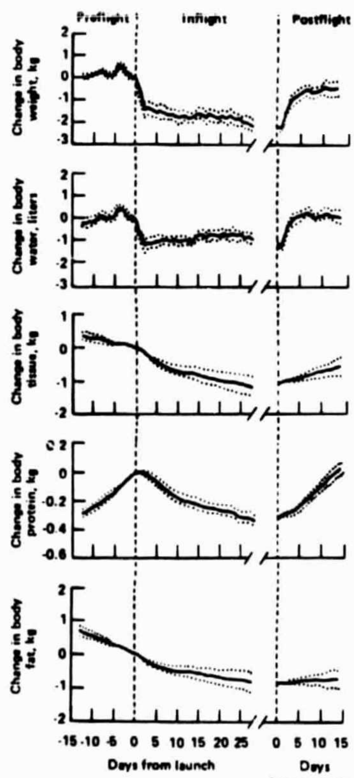


Figure 19. Body Composition Changes of the Skylab Crew

Integration of Subsystem Hypotheses

Figure 20 is offered as an integrated hypothesis of the adaptative response to weightlessness. It is obviously limited to the subsystems and specific hypotheses considered in the present analysis. Although a great amount of detail has been omitted for the sake of clarity, of interest here are the interactions between subsystems, and the generalizations that can be made about the behavior of the combined systems. The following broad picture has emerged.

Disturbances in the cardiovascular, fluid-electrolyte, erythropoietic, musculoskeletal, and metabolic systems, which are found during and after flights of varying duration, appear to be attributed to two major effects of weightlessness. These are, first, the absence of hydrostatic forces resulting in severe fluid shifts within the body, and second, the absence of deformation forces, resulting in degradation of normally load-bearing tissues. The first of these effects leads to a reduction in body fluids, most importantly, blood volume. The consequences of the second effect is a reduction in bone and muscle mass. In addition, a third factor, a long-term alteration of metabolic state, a reflection of changes in dietary intake and exercise, was found to play an important role in the responses of the Skylab crew. But it is doubtful at this time that these latter factors are beyond human intervention and correction on future missions. All of these events have both acute and long-term effects which lead to the notable and consistent findings of a loss in weight, change in body composition, decreased tolerance for orthostasis, and additionally, upon return to a one-g environment, a decreased aerobic capacity. Adaptation is said to occur when the body adjusts to these changes and reaches a new steady-state level (fig. 21). Figure 21 is an attempt to show the relative time course of adaptation for each major physiological system. The return to baseline reflects the establishment of a new homeostatic level appropriate to weightlessness.

Our studies have supported the concept that within the time span which man has so far been studied in space, these responses to weightlessness can be explained in terms of normal feedback regulatory processes. One classical example of these processes concern the blood volume controllers that reduce plasma volume when challenged by the cephalad shifts of peripheral fluid. Also, the reduction in red cell mass has been postulated to be partly a result of the homeostatic response to hemoconcentration and tissue hyperoxia. Another, of many examples, concerns the biochemical mechanisms which sensitively respond to small changes in electrolyte shifts resulting from cell demineralization, and, within limits, maintain the plasma composition at the expense of excess renal excretion.

Exposure to weightlessness invariably leads to loss of major body constituents at rates which, according to the present analysis, are disproportionate to their concentrations in the body. The most rapid losses are observed for extracellular fluids and salts, and are reflected by equally rapid decrements in leg volume. At the other extreme are a class of substances that disappear much more slowly. Calcium and, perhaps, red cells are representative of this category. Depending on the degree to which caloric

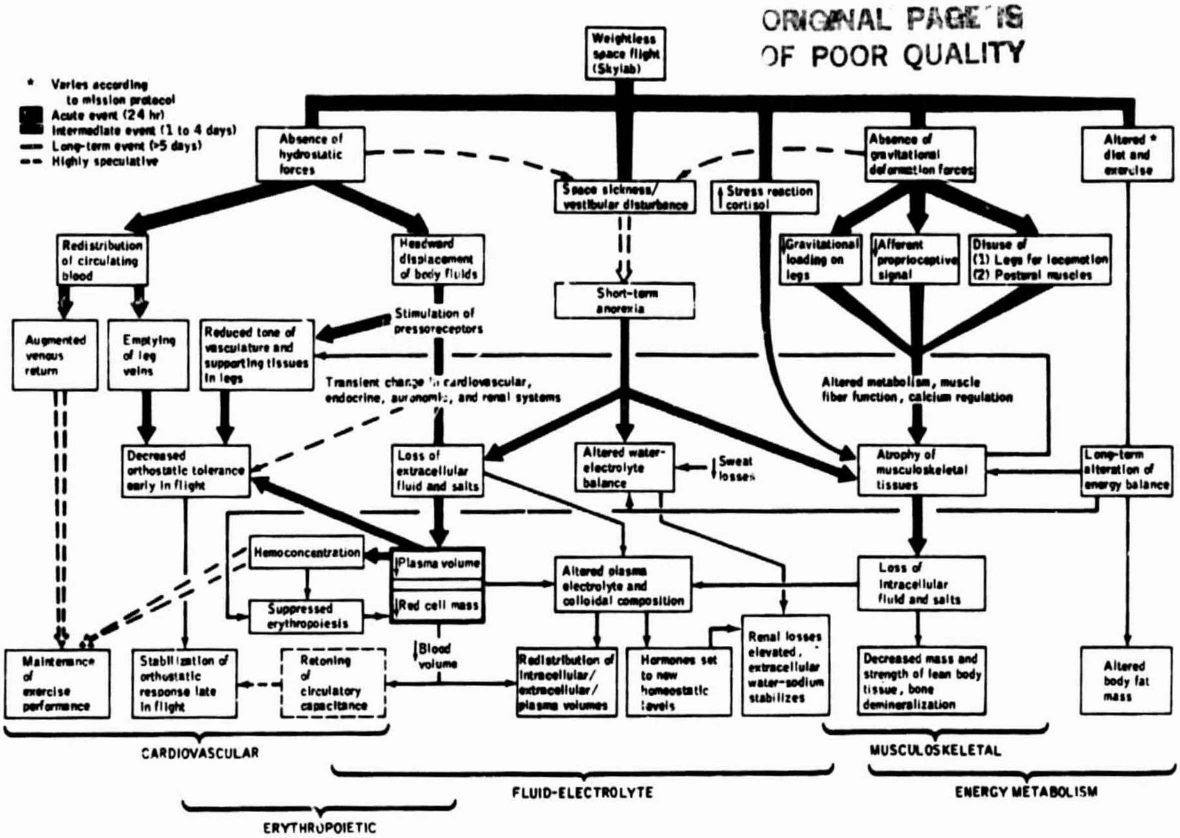


Figure 20. Integrated Hypothesis of Physiological Adaptation to Prolonged Space Flight

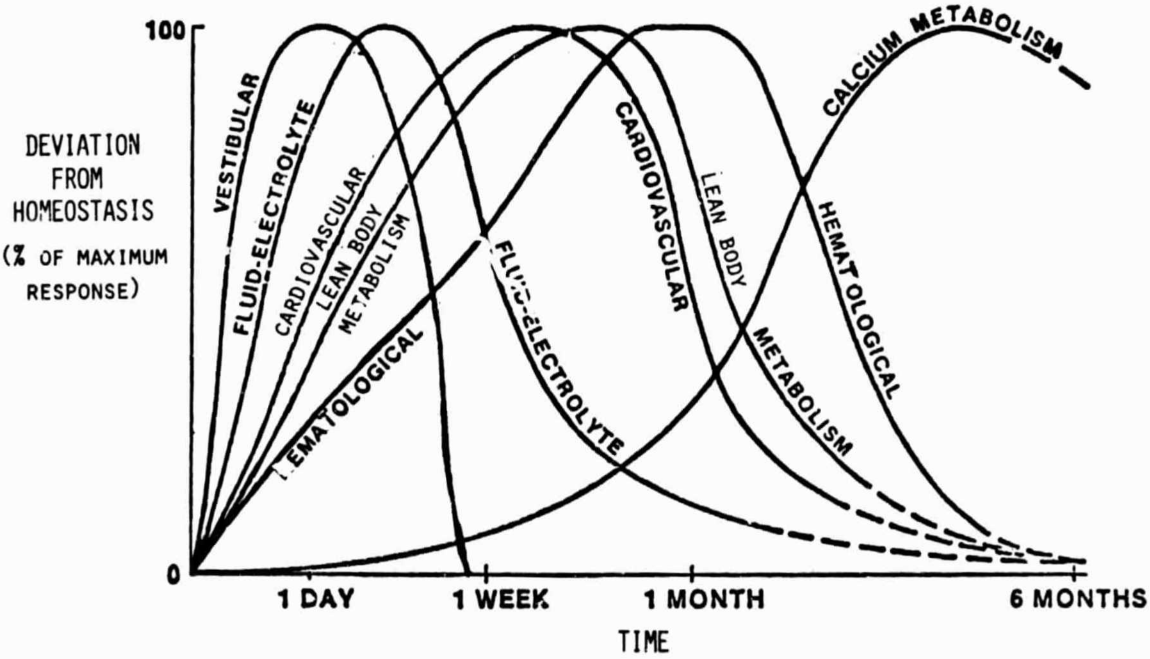


Figure 21. Approach Toward Homeostasis of Physiological Systems During Space Flight

intake matches energy requirements, fat stores can be included in this group as well. Muscle tissue appears to degrade at intermediate rates as exemplified by nitrogen and potassium losses. All these rates of disappearance from the body most likely depend on the nature of the disturbance, and on the effective time constant of the correcting homeostatic system.

These studies have confirmed the hypothesis previously suggested that the loss of blood volume is of central importance to the understanding of the zero-g responses of several major systems. While this loss is essentially an acute cicrulatory adaptation to volume overload, it was found to play a significant long-term role in the orthostatic intolerance and reduced exercise performance observed postflight. Also, the reduced plasma volume was found to have a potentially strong influence on the erythropoietic response. Finally, the long-term adaptation of the circulation may depend on the vascular elements responding to accommodate the hypovolemic condition. It should be noted however, that in none of these cases was the loss of blood volume alone sufficient to explain the entire response. Another event which had a wide spread effect was the negative energy balance noted for the crews of the two shortest missions and for all crews during the early flight period. In addition to the obvious effect on fat stores, an inadequate intake of fluid and food was found to be implicated in the lack of expected acute renal response, the loss of muscle tissue, the loss of water, and the differential loss of red cells among the crews.

A greater wealth of information than presented here can be found in the draft of the reference publication included with this proposal, and in the mathematical descriptions of the subsystem simulation models. When these descriptions are made part of the whole-body algorithm, then that algorithm will serve its main function as a central repository of a detailed integrated hypothesis of zero-g adaptation. This is not to imply that this study has provided a definitive theory of these events. Rather, what has been done is to examine available evidence to support or deny various scientific hypotheses, identify qualitative and quantitative interactions between various experimentally measured responses to space flight, and venture a tentative integrated physiological hypothesis for the adaptive processes.

Conclusions

The contribution of the simulation models was significant in constructing the hypotheses discussed above, although the limitations of space in this summary may not make this apparent. It is appropriate, therefore, to consider several illustrations of these benefits of the modeling process.

The normal functions of simulation models include the ability to evaluate hypotheses retrospectively, resulting in greater utilization of the acquired information, and perhaps leading to the most likely interpretation of the previously collected data. Using this procedure, the models predicted the dynamic changes of variables which may have been difficult or impossible to measure during space flight. Table 5 illustrates a selected number of parameters whose predicted responses were necessary for a complete interpretation of many events, but which were, unfortunately, not always available during flight.

TABLE 5

SELECTED QUANTITIES PREDICTED BY SIMULATION MODELS

PARAMETERS FOR WHICH INFLIGHT DATA EXISTS	PARAMETERS FOR WHICH INFLIGHT DATA DOES NOT EXIST
Total body water Leg volume Body potassium Extracellular sodium	Extracellular water Intracellular water Interstitial water Plasma volume
Plasma sodium Plasma potassium Plasma proteins Plasma hemoglobin	Red cell mass Red cell production rate Erythropoietin Tissue oxygenation
Angiotensin Aldosterone Antidiuretic hormone	Autonomic activity Volume receptor stimulation Natriuretic factor Capillary filtration
Urine volume Urine sodium Urine potassium Evaporative water loss	Cardiac output Peripheral resistance Venous pressure Local blood flows
Blood pressure Leg blood flow	Circulatory, renal, fluid, and hormonal changes on first inflight day
LBNP heart rate LBNP blood pressure LBNP leg volume	LBNP cardiac output LBNP venous pressures LBNP blood volume and flow distribution
Exercise heart rate Exercise oxygen uptake Exercise minute ventilation	Exercise cardiac output Exercise stroke volume Exercise blood gases

The utility of models, however, extended beyond these predictive capabilities. A benefit that was attributed to the modeling process related to the ways in which models shaped the data analysis effort. Quantitative modeling often required a new look at data which had already been analyzed by more traditional methods. The simulation approach requires certain patterns of data in very specific forms. Satisfying these model requirements led, in one instance, to the integrated metabolic balance analysis for describing body composition changes during space flight. In another situation, the study which led to an analysis of evaporative water loss in the Skylab crew was suggested originally by the need to validate the sweating mechanism in the thermoregulatory model for weightlessness. Another prime benefit of modeling, at this stage of its application to space physiology, was in forcing the analyst to think systematically, comprehensively, and quantitatively about the system of interest. The formation of the model, based on experimental evidence and known concepts, provided insights into the organization of the system elements and the multiple pathways connecting these elements. The complexity of models, reflecting the redundancy of the mechanisms in the body, helped resolve some paradoxical findings by suggesting the involvement of one or more competing pathways. Also, it was not always possible to explain the long-term adaptation phase of space flight in terms of regulatory feedback mechanisms more suited to corrective action of acute disturbances. This suggested a logical division of the space flight period into acute and chronic segments for purposes of systems analysis.

A comprehensive approach for relating the experimental findings from various ground-base studies to the space-flight observations was also facilitated by the integrative qualities of the models. These one-g studies employing hypogravic maneuvers often provided more abundant data than space-flight investigations, especially for the acute stress stage. Postural changes, water immersion, and head-down tilt studies have helped to characterize the short-term phase, while bed rest and space flight were useful in describing long-term processes (see fig. 22). All of these stresses have the common characteristic of a reduction in hydrostatic gradients and a rapid headward shift of fluid. The modified Guyton model, and the whole-body algorithm, both capable of simulating short- and long-term events, provided a framework upon which these diverse experimental results could be systematically examined. Within limits, the approach resulted in a better understanding of the complete temporal spectrum of hypogravic responses, and explained results which otherwise appeared to conflict.

During the present project, a qualitatively more advanced data evaluation was achieved than was previously available. Some of the key features of these accomplishments are summarized in table 6. The fundamental contribution of the systems analysis effort has been to organize many of the major biomedical findings from space flight and correlate these findings with the scientific concepts that describe the requisite organ systems. Out of this effort has come an array of methods, tools, and techniques that have proven essential for the handling, processing, and interpretation of experimental data in general and space flight data in particular. Another result is an improved understanding of the physiological events which occur during human adaptation to weightlessness. When this understanding is more complete it may be possible to predict individual responses to weightlessness and appropriately define indices of health during prolonged space flight and subsequent recovery. Finally, this study led to identification of critical

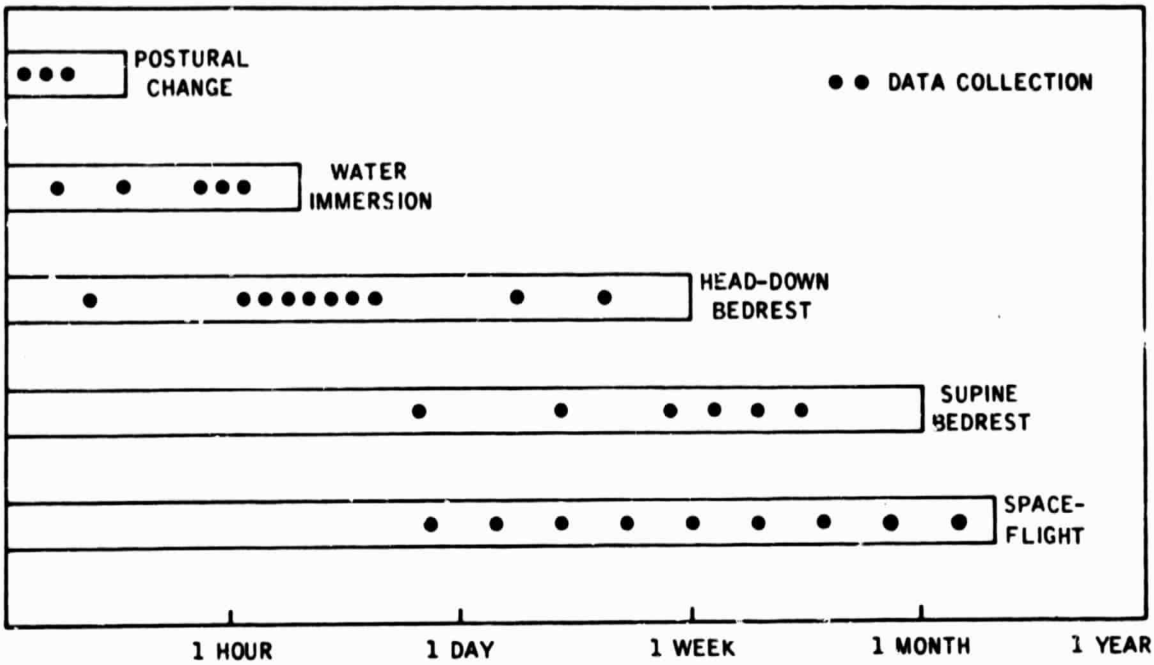


Figure 22. Relative Duration of Various Hypogravic Stresses Showing Typical Data Collection Periods

TABLE 6

SIGNIFICANT DATA ANALYSIS ACCOMPLISHMENTS

- A more definitive data analysis based on a composite picture of the nine crewmen from all flights.
- Estimates of quantities which could not be measured directly but could be derived from simple metabolic balance models or advanced simulation models.
- Integration of data across disciplinary lines.
- Quantitative evaluation of hypotheses by computer simulation and interpretation of data in terms of feedback control theory.
- Reevaluation and reinterpretation of previously published Skylab data in the light of more recent findings from ground-based studies and Soviet missions.

areas ripe for future study. Recommendations for new experimental approaches generated by the current program have already contributed to the design of ground-based and future Spacelab investigations. Full potential of the systems analysis method will be realized only by maintaining an iterative cycle between model development and experiments.