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This report presents the results of a series of simulation studies of calcium metabolic changes which have been recorded during human exposure to bed rest and space flight. Space-flight and bed-rest data demonstrate losses of total body calcium during exposure to hypogravic environments. These losses are evidenced by higher than normal rates of urine calcium excretion and by negative calcium balances. In addition, intestinal absorption rates and bone mineral content are assumed to decrease.

The bed-rest and space-flight simulations were executed on a mathematical model of the calcium metabolic system. The purpose of the simulations is to theoretically test hypotheses and predict system responses which are occurring during given experimental stresses, in this case, hypogravity. This occurs through the comparison of simulation and experimental data and through the analysis of model structure and system responses. The model reliably simulates the responses of selected bed-rest and space-flight parameters. When experimental data are available, the simulated skeletal responses and regulatory factors involved in the responses agree with space-flight data collected on rodents. In addition, areas within the model that need improvement are identified.

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Space-Flight Simulations of Calcium Metabolism Using A
Mathematical Model of Calcium Regulation

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# 1.0 INTRODUCTION

The Skylab program, in 1973, provided the Life Sciences Division at the Johnson Space Center with the first opportunity to investigate human physiological adaptive responses to the weightless environment. During the Mercury, Gemini, and Apollo programs, only a limited number of physiological measurements, during restricted time periods (pre- and postflight), could be collected on the astronaut crews. However, the data collected during these early flights did suggest that physiological changes were occuring inflight (1,2). The Skylab program provided the opportunity to investigate pre-, in-, and postflight alterations in human neurophysiology, biochemistry, hematology, cytology, musculoskeletal function, cardiovascular function, and metabolic function (3).

This paper will focus on data analyses addressing the calcium metabolic and skeletal changes recorded in the Skylab crews during space flight. Because the opportunities for conducting life sciences experiments in space are few and the subject population sizes are small, these space-flight data analyses will be supplemented with data collected during a series of bed rest studies conducted at the United States Public Health Hospital in San Francisco (4), and with data generated through a theoretical analytical tool, a computerized mathematical model of calcium metabolism.

Bed-rest studies provide a ground-based technique for simulating many of the physiological changes that are observed during space flight. A brief review of these physiological changes is as follows. A consistent loss of whole-body calcium has been observed in humans during space flight (5) and bed rest (4) studies. This loss is demonstrated by rapid (within one to two weeks) increases in urine calcium excretion rates and decreases in whole-body calcium balances. The suspected source of calcium deprivation is the skeletal system since 98 percent of total body calcium is contained in the hard tissues of the human body (6). Bed rest studies provide the opportunity to investigate further, in a hospital laboratory setting, and with a higher statistical subject population, these calcium metabolic changes.

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The mathematical model of calcium metabolism provides a theoretical tool for testing hypotheses and predicting system responses to a given experimental stress, in this case, exposure to zero-gravity. Specifically, the purpose of the model is to define regulatory and interactive calcium metabolic events that may be occuring within the normal, healthy physiological system during periods of an applied experimental stress. In this report, a series of simulation studies of bed rest and space flight are recorded. The objectives of these simulation studies are to validate the calcium model's output with experimental data, to test with the model some of the current hypotheses related to bed rest, and to predict with the model the nature of gross skeletal changes during human exposure to hypogravic environments.

## 2.0   PROCEDURES

### 2.1   EXPERIMENTAL DATA

Space-flight data collected during the Skylab missions have been obtained from the published reports of Rambaut and Johnston (5), Leach and Rambaut (7), and Leach, Rambaut, and DiFerrante (8). Bed rest data were obtained from studies conducted over a ten-year period at the U.S. Public Health Hospital in San Francisco. These data were provided by Dr. V. Schneider (4). A summary of the space-flight and bed-rest results are presented in Figure 1. For most of the metabolic variables, the sets of bed-rest and space-flight data are qualitatively similar. However, quantitative differences do exist; for example, the space-flight metabolic responses are generally more rapid and greater in magnitude than those of bed rest.

### 2.2   THE CALCIUM MODEL

The calcium metabolic model was developed by Jaros, Coleman, and Guyton (9) and is implemented on a Digital Equipment Corporation VAX 11/780 series computer. All of the elements of the model are contained in seven subsystem models that mathematically describe four calcium compartments and three hormonal regulators (10). The central compartment, which describes the calcium concentration of the extracellular fluid, is regulated by passive exchange rates between the renal, intestinal, and skeletal compartments. The renal compartment eliminates calcium from the central compartment, the intestinal compartment adds calcium to the central compartment, and the bone compartment stores calcium in an internal reservoir and acts as a long and short-term buffer to the central compartment. The three hormonal regulators, parathyroid hormone, calcitonin, and metabolites of Vitamin D, actively stimulate or inhibit the passive calcium fluxes between compartments through negative feedback control. A schematic of the seven subsystems and their relationships is presented in Figure 2.

The three regulatory subsystems of the Jaros, Coleman, and Guyton (9) model have been replaced with subsystem models developed by Brand (10,11,12). These new subsystems have not changed the function of the original subsystems; i.e.,

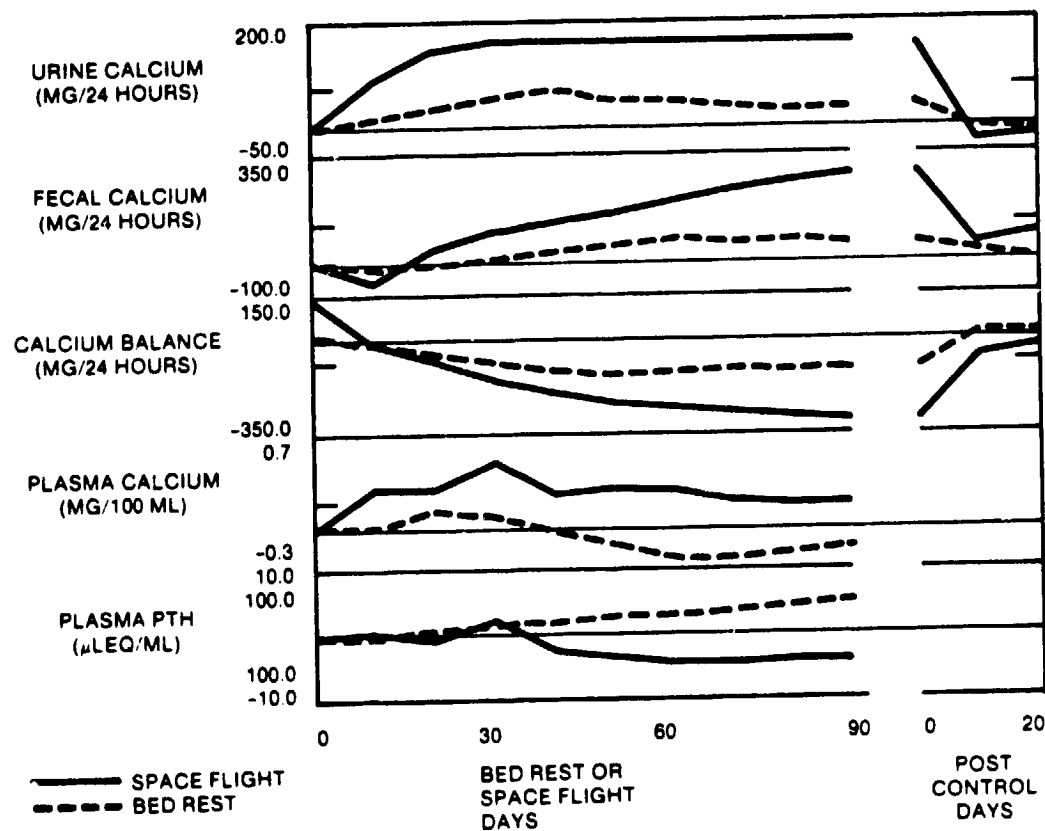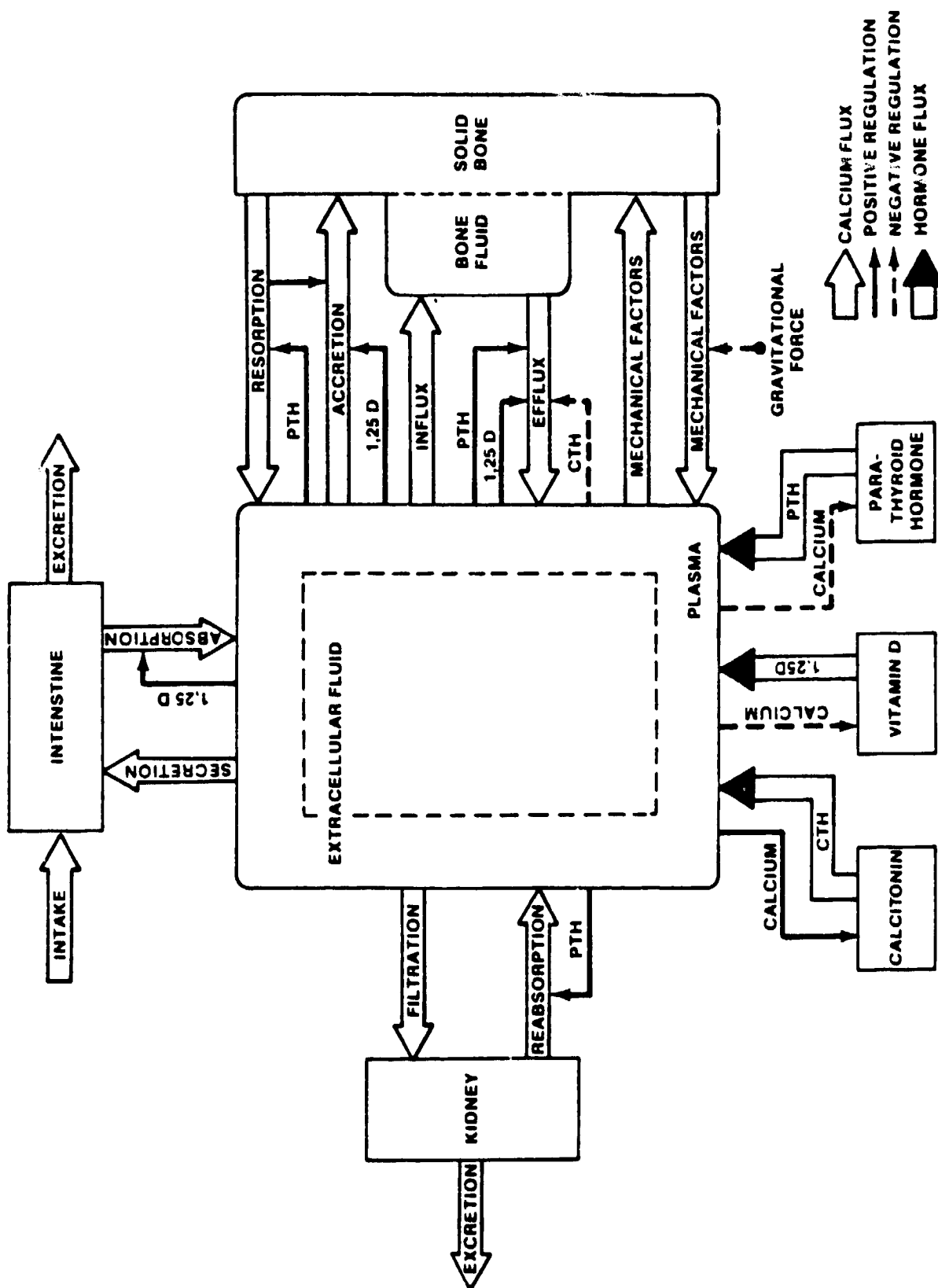3

(Mean Delta from the Ambulatory Control)



Figure 1.- Selected parameters from the bed rest and space flight data.

# FIGURE 2: MAJOR COMPARTMENTS AND FLUXES OF THE CALCIUM MODEL



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calculating hormonal plasma concentrations, but they have provided more detail within each particular hormonal system. This feature is particularly useful when examining the Vitamin D metabolic subsystem. For example, changes in the production rate of 1,25-dihydroxyvitamin D (1,25-(OH)2 D) can be traced through the Vitamin D metabolic path (Vitamin D to 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D) and/or by its regulatory agents, plasma calcium and phosphorus (or parathyroid hormone) concentrations.

As much as possible, the model has been developed with the idea of representing, mathematically, distinct physiological activities. Unfortunately, this has not always been possible. The skeletal subsystem of the calcium model contains the terms resorption, accretion, efflux, and influx. In the actual physiological system these terms identify specific cellular or biochemical activities, but in the model they represent net changes in the solid bone and bone fluid compartments that are assumed to be related to specific cellular and biochemical activity rates. For example, the term resorption represents a general degradation, or loss of calcium out of the solid bone that is assumed to be caused primarily by cellular osteoclastic activity. Accretion represents the buildup, or increase of calcium into the solid bone mineral by osteoblastic activity. Influx and efflux represent general gains and losses, respectively, from the bone fluid.

## 2.3    MODEL SIMULATIONS

The main function of the model is to provide a theoretical foundation for analyzing and developing hypotheses of human calcium metabolic responses to an experimental stress. Although this can be done in a variety of ways, the most useful approach in this study has been, first, to establish model credibility through validation testing, and second, to analyze the model responses through hypothesis testing.

In this report, the purpose of validation testing is to assess the degree of correspondence between model output and actual experimental data by comparing the qualitative and quantitative trends of common variables. The major objective of this type of "curve fitting" analysis is to demonstrate the ability of the model to reliably simulate overt responses of the calcium

metabolic system to given experimental stresses and thereby establish a sense of credibility in the model. Another objective is to test the premises with which the simulations are initialized (see section 2.4). The simulation studies cannot substantiate the initializing assumptions but they can provide theoretical support for their plausibility. The results of the validation tests during the zero-gravity simulations are presented in section 3.0.

The purpose of hypothesis testing is to assess pathways that are involved in a particular set of metabolic responses. Contrary to the validation studies, the model output from these simulations rarely are "curve fit" to experimental data; instead, the model outputs are qualitatively evaluated for plausibility. The output of each variable typically is defined in terms of direction and approximate magnitude of change from baseline, factors responsible for the change, and reciprocal effects generated by the change. The results of these tests are presented in section 4.0.

A significant asset of the modeling approach is that the usefulness of the model does not rely upon the correctness of simulation results. Although good correlation of simulation and experimental results is desirable, important objectives are also met when agreement is poor (13). Inconsistent results entice a researcher to critically examine both the model, which reflects the researcher's simplified perception of the system, and the experimental analyses. These inconsistencies generally lead to refinements in the model, suggestions of additional data analyses, and designations of new experiments.

## 2.4   SIMULATION INITIALIZATIONS

The calcium metabolic balances, calculated from the space-flight and bed-rest data, suggest that calcium is lost from tne whole body during exposure to weightless environments (Fig. 1). When the calcium output is greater than the calcium input, the excess calcium being excreted must be obtained from an internal source. The largest internal pool of calcium in the human body is the bone, as it contains about 98 percent of the total body calcium (6). The soft tissues contain the remaining 2 percent of total body calcium which is distributed between three major subcompartments:  muscle, skin, and extracellular fluid. In this analysis, calcium sources from the muscle and

skin are assumed to be negligible during exposure to hypogravic environments. Consequently, the above scenario insinuates that calcium is removed from the bone and excreted from the body.

For model simulation purposes, the initializing factors that drive the calcium out of the bone must be assessed. To aid in this analysis, visualize the bone compartment as a large calcium pool and the extracellular fluid compartment as a small calcium pool (Fig. 3). Homeostasis of the extracellular fluid calcium concentration is tightly maintained by intestinal calcium absorption and urine calcium excretion rates, symbolized in Figure 3 by inflow and outflow faucets to the external environment, and by an internal buffer reservoir, the large pool. In the actual metabolic system, calcium can also be lost from the body through sweat and intestinal secretion rates. In this analysis, however, these rates are assumed to be constant.

In the normal, healthy adult, the skeletal system is fully developed and the homeostatic rate of calcium flow between it and the extracellular fluid is zero (Figure 3A). Homeostasis of the extracellular fluid is disturbed when one or more of the input or output flow rates is altered. For example, if the urine calcium excretion rate increases, as it does in Figure 1, the extracellular fluid compartment loses calcium. To compensate, calcium flows from the bone compartment to the extracellular fluid compartment (Figure 3B) and restores the extracellular fluid calcium concentration. The skeletal "fix" is only a temporary "fix" though until the rate of input (intestinal absorption) increases and homeostasis is restored. If the intestine does not respond to the demand for increased calcium input, then the bone continues to compensate for the calcium losses (Figure 3C) by drawing upon normally inaccessible calcium reserves (such as the hydroxyapatite of solid bone), and the system becomes negatively balanced.

In the analogy just presented, and diagramatically shown in Figures 3A, B, and C, the kidney initiates calcium loss from the extracellular fluid, the intestinal calcium input remains steady, and the bone responds by compensating for the loss. Unfortunately, the experimental bed-rest data do not appear to support this scenario (4); the kidney does not appear to initiate the hypogravic calcium metabolic changes. The urinary excretion

A. Homeostasis:
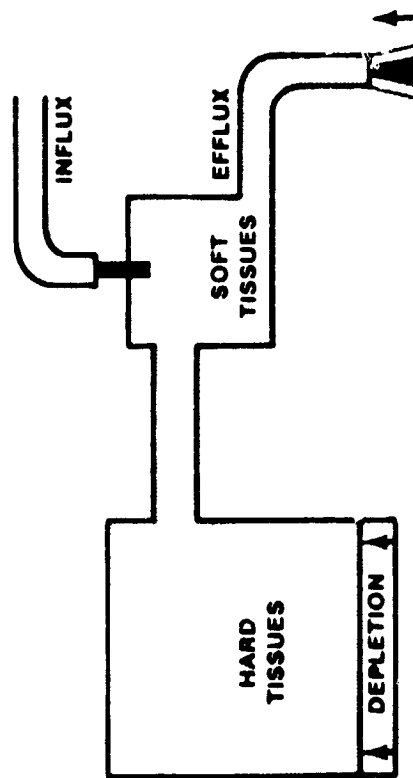Rate of Influx = Rate of Efflux
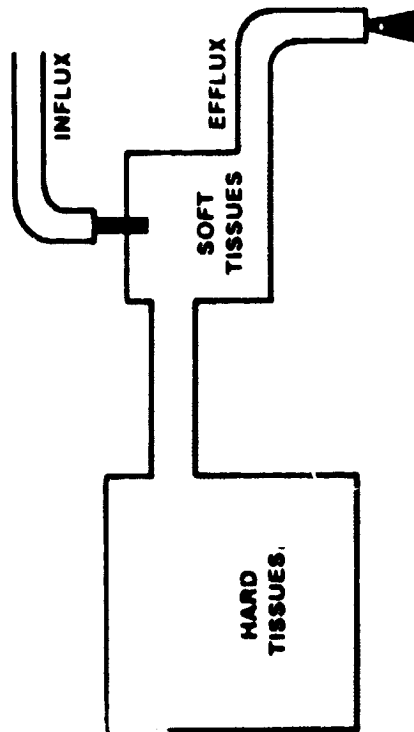
B. Imbalance:
Increase in Rate of Efflux, lowers levels of small pool but is compensated by passive redistribution from large pool
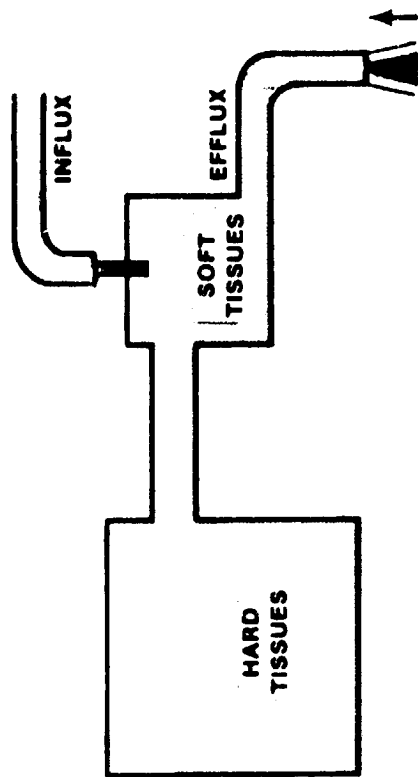
C. Continuation of B
Results in depletion of large pool while maintaining supply to small pool



Figure 3. Hypothesis development of gross calcium metabolic responses to hypogravic conditions using a two-compartment model.

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rates of creatinine, a product of catabolism, do not appear to be affected by the zero-gravity stress, and a diuresis and/or natriuresis which may concurrently force higher rates of renal calcium excretion, have not been detected. In addition, the urine calcium excretion rates probably are not receiving hormonal stimulation because changes in plasma hormonal concentrations, during bed rest or space flight, appear to occur late in the experimental period. Instead, the data suggest that the kidneys appear to respond passively to excesses in extracellular fluid calcium concentration. The kidney is compensating for higher than normal rates of plasma calcium input.

The intestinal and hormonal (in particular 1,25-(OH)2 D) data further support the idea that the calcium metabolic system is attempting to remove, rather tnan restore, calcium from the extracellular fluid. In the model of Figure 3B, homeostasis is restored by increasing the rate of inflow, decreasing the rate of outflow, or both. In the bed-rest data, the intestinal absorption rate decreases late (five to six weeks) in the experimental period. Considering the constant dietary intake rates during the bed rest studies and the reduced levels of plasma 1,25-(OH)2 D, the system appears to be shutting off, rather than turning on, its extraneous source of calcium input. Referring to Figure 3, the only other input source of calcium is the internal buffer system.

Bone is known to be highly sensitive to changes in its customary amount of intermittent loading and deformation. Although unsupported by experimental research, this premise is the basis of most clinical orthopaedic practice (14) and is implicated, from an intuitive point of view, in the skeletal changes observed during bed rest and space flight.

Bone is a unique tissue because it appears to be a durable, firm, inanimate, ceramic material. Historically, it has been characterized in terms of strength, toughness, elasticity, and chemical integrity so that clinical guidelines of stress-strain relationships, fracture thresholds, and bending traits could be developed. Yet, in the living vertebrate, the tissue is metabolically active and adaptive. The structural design of each bone is genetically predetermined, but the actual mass, texture, and shape is molded

by mechanical, functional demands. The mechanisms and sites responsible for sensing changes in mechanical function and translating them into structural modifications are not clear, but proposals include cellular mediation, biochemical mediation, and electrical signalling as well as changes in skeletal blood flow and calcium solubility rates (14).

In the weightless environment, tremendous mechanical alterations can occur to the supporting structures of organisms. The first and most obvious is the immediate reduction in the amount of habitual intermittent loading and deformation of weight-bearing bones. This tremendous loss of function is assumed to initiate a remodelling of tissue mass in weight-bearing areas, generating an overall decrease of skeletal mineral content and an increase in skeletal calcium efflux. Upon entry into an hypogravic environment, the skeletal system is assumed to dump, in some undefined manner, calcium into the extracellular fluid (4,5). The extracellular fluid will, in turn, force calcium through the kidneys at a higher rate. The calcium metabolic system then attempts to restore homeostasis to the extracellular fluid with a series of compensatory and hormonal feedback responses. These series of responses are examined in the calcium model.

To initiate th  simulation in the calcium model, skeletal efflux is stimulated by reducing the value of an abstract gravitational term. The calcium efflux from the bone disturbs the homeostasis of the system and generates a series of metabolic responses that are compared to available experimental data. One liter of extracellular fluid volume is also removed to simulate the rapid, day one loss of extracellular fluid observed during space flight.

## 3.0   RESULTS OF THE VALIDATIONS TESTS

### 3.1   VALIDATION OF THE BED-REST SIMULATIONS

Many of the bed-rest simulation data presented in Figure 4 qualitatively and
quantitatively agree with the experimental bed-rest data of Figure 1.  In both
the model and the actual physiological system, rapid renal calcium filtration
tends to compensate for the skeletal unloading of calcium into the plasma,
resulting in the maintenance of fairly stable plasma calcium levels
(simulation data: +4 percent variation: experimental data: +/- 2 percent
variation) in spite of the input load.  The intestinal absorption rate does
not change significantly for the first 5 weeks of bed rest, but after 5 weeks,
it decreases below the ambulatory baseline value.  Summating these results
demonstrates that the body is continually eliminating whole body calcium
stores which leads rapidly into a negative calcium balance.

### 3.1.1   Urine Excretion

The maximum urine calcium excretion rates of the simulated and experimental
data are equivalent, about 45 percent above the ambulatory norm.  The
experimental data increase, over a three week period, to the maximal rate and
then decrease for the duration of the study to about 10 percent above the
ambulatory mean.  The simulated excretion rate increases immediately, rising
to 41 percent after the zero-gravity initialization.  It remains between this
value and the maximum level for the duration of the simulation.  The
difference between the trends of the two sets of data is due to an artificial
stimulation of the simulated urine calcium excretion rate which is initialized
with, and maintained throughout the zero-gravity stress.

This artificial stimulation in the urine calcium output provides an excellent
example of how poor agreement between simulation and experimental data
generate important analyses of the actual and simulated calcium metabolic
system.  When the zero-gravity simulations were first executed on the model,
the plasma calcium concentration increased high enough to stimulate responses
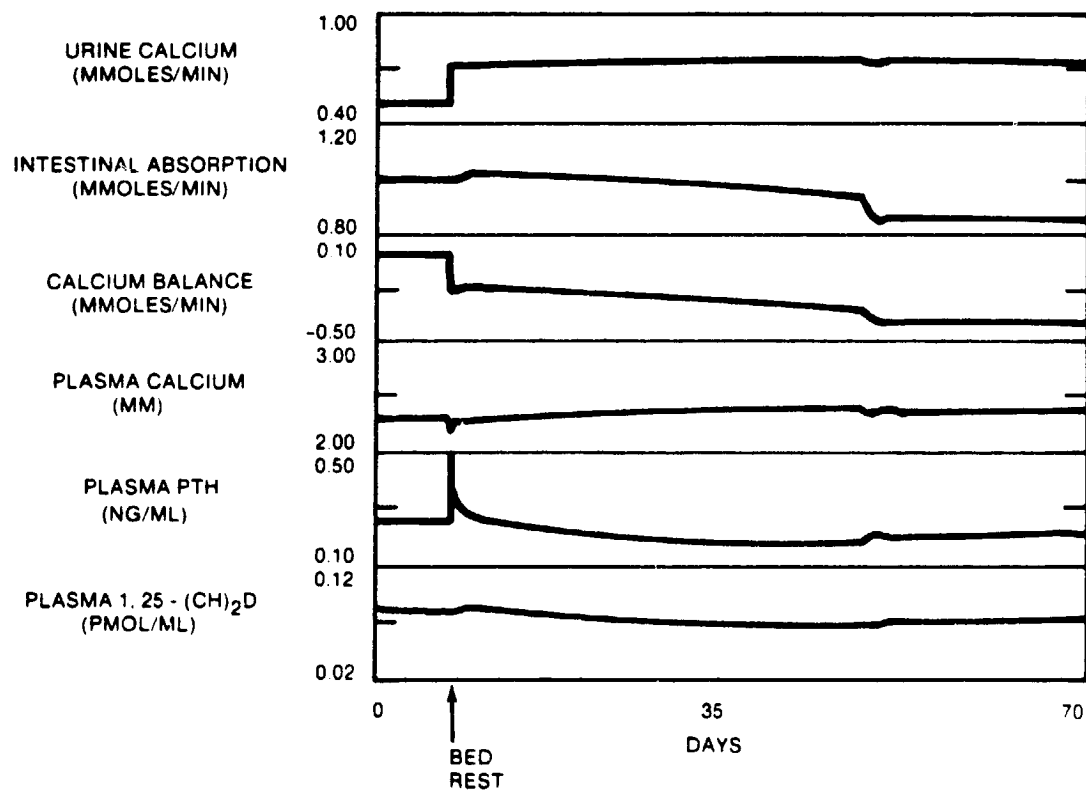which were exaggerated in many other system variables.  The model's structure

**Figure 4.- Selected variables from the bed-rest simulation.**

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and simulation output were analyzed. The results suggested that the high plasma calcium levels were due to insufficient renal compensation for changes in skeletal calcium efflux.

In the model, the relationship of the kidney to the calcium metabolic system (during a hypogravic stress) was further defined by artificially manipulating the urine excretion rate and analyzing the model output. The kidney was found to be the first and most influential metabolic response for the maintenance of short-term plasma calcium homeostasis. A suitable urine calcium excretion rate for the bed-rest simulation was established (forced), and this forced urine excretion rate, which is comparable to the actual excretion rate, has become an integral part of the bed-rest initialization package. It will remain so until the renal subsystem model is modified to simulate the handling of calcium more realistically.

Ideally, an extension of the renal simulation analyses, presented above, is to test the renal hypothesis in an experimental setting and confirm or redefine the simulation results. It must be remembered that a model is only a simplified representation of the system under investigation; as such, the simulations must continually be tested for validity and reliability with experimental data. Unfortunately, the modeling work conducted by this group is not supported by concurrent experimental research. Consequently, the major contributions of the simulation analyses are to predict relationships, and their relative significance, within the calcium metabolic system. The theoretical importance of the kidney to the calcium metabolic system during bed rest is an example of such a contribution.

## 3.1.2 Intestinal Absorption and Vitamin D

The simulated intestinal calcium absorption rate (Figure 4) decreases after four weeks of bed rest to a minimum rate that is 13 percent below the ambulatory norm. This value is midway between the experimental intestinal absorption rates calculated from the calcium isotope data (18 percent loss) and the fecal data (10 percent loss). In the model, the intestinal absorption rate is regulated by the plasma level of 1,25-dihydroxyvitamin D (1,25-$(OH)_2$ D). This vitamin is 12 percent (simulation data) and 23 percent (experimental

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data) below baseline by the third week of the bed-rest period. In the model, the 1,25-(OH)2 D production rate is inhibited by the 4 percent increase in the plasma calcium level. The responsible hormonal regulator in the experimental bed-rest data has not been identified.

### 3.1.3 Plasma Parathyroid Hormone

The plasma parathyroid hormone (PTH) results obtained during simulated and experimental bed-rest studies are difficult to interpret. In the model, the 4 percent increase in the plasma calcium concentration suppresses the plasma PTH concentration by 30 percent after 5 weeks of simulated bed rest (Figure 4). After 5 weeks of experimental bed rest, the plasma PTH concentration increases over 300 percent; however, the experimental data are subject to dispute. The PTH data were collected in only one of the bed-rest studies conducted at the U.S. Public Health Hospital in San Francisco. The PTH results are consistent for the three subjects within that one study, but the reliability of the data is questionable. A 300 percent increase in the plasma PTH concentration is extremely high, particularly since most of the other system responses are small.

Since the direction and magnitude of the plasma PTH response to bed rest is undefined, the model was used to test the impact of a PTH increase, decrease, or no change on the calcium metabolic system. The decrease is simulated in Figure 4, but to simulate an increase or absence of change in plasma PTH, an additional PTH regulator that was capable of overriding calcium control was incorporated into the PTH subsystem model. The bed-rest simulations with the artificial manipulation of PTH secretion rates were executed on the model and the results of three simulations (bed rest plus a PTH increase, decrease, or no change) were compared.

Selected variable responses to the PTH manipulations during the bed-rest simulations are reported in Table 1. The results suggest that in hypogravic environments, plasma PTH concentrations exert little influence on overt calcium metabolic responses. A plus or minus 30 percent change from normal in the plasma PTH concentration only slightly affects the urine calcium excretion rate and plasma calcium concentration. The effect on the intestinal

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Table 1:  Results of Selected Variable Responses During Bed-Rest Simulations
With Changes in Plasma PTH Concentration (percent change from baseline).

| Plasma PTH | Urine excretion | Plasma calcium | Intestinal absorption | Plasma 1,25-(OH)2 D |
|---|---|---|---|---|
| -30 | 45 | 4 | -13 | -12 |
| 0 | 47 | 5 | -16 | -17 |
| +30 | 49 | 6 | -20 | -22 |

absorption rate is more pronounced. This is because of the sensitivity of the renal production rate of 1,25-(OH)2 D to plasma calcium concentrations.

## 3.2   VALIDATION OF THE SPACE-FLIGHT SIMULATIONS

Initialization of the space-flight simulation is similar to that of the bed-rest simulation. One liter of extracellular fluid is removed from the system and the value of the gravitational factor, which artificially stimulates the skeletal calcium efflux rate, is reduced by the same magnitude as in the bed-rest simulation. In fact, the only difference between the bed-rest and space-flight initializations is the rate with which calcium is artificially forced into the urine. The 45 percent increase in the urine calcium excretion rate for the bed-rest simulation is elevated to 80 percent in the space-flight simulation.

The initialization procedures, listed above, generate simulation results which usually agree in direction, but not in magnitude, with the experimental space-flight results or proposed hypotheses (Figure 5, Table 2). For example, the plasma calcium concentration increases to a maximum value of one percent in the simulation and to seven percent in the experimental data. Based upon the space-flight fecal calcium excretion and dietary calcium ingestion rates, Rambaut and Johnson (5) have hypothesized long-term decreases in the intestinal absorption rate of calcium and the production of 1,25-(OH)2 D. The model agrees with these hypotheses by predicting a long-term decrease of four percent in the intestinal absorption rate and five percent in the renal 1,25-(OH)2 D production rate. The only obvious discrepancy between simulation and experimental results occurs in the plasma concentration of PTH which decreases by seven percent in the simulation, but increases by 47 percent in the space-flight data.

The changes in variable output recorded during the space-flight simulations are smaller than the bed-rest experimental data and simulation output. This is contrary to the results illustrated in Figure 1 where the calcium metabolic changes measured during space flight are greater than those recorded during

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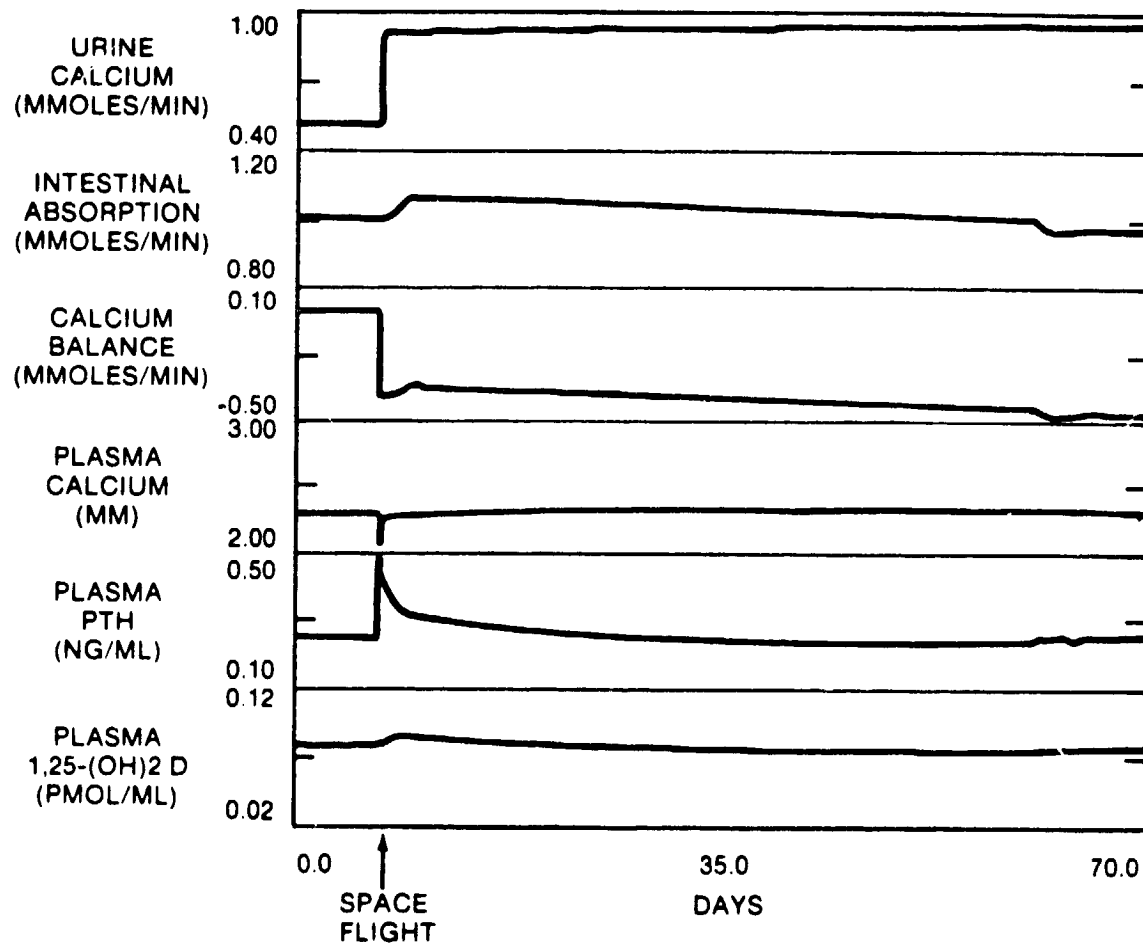
**Figure 5.- Validation of the space flight simulation.**

Table 2:  Comparison of Bed-Rest and Space-Flight Simulation and
Experimental Results (percent change from baseline).

|  | Urine Excretion | Intestinal Absorption | Plasma Calcium | Plasma PTH | Plasma 1,25(OH)2D |
|---|---|---|---|---|---|
| **Simulations** |  |  |  |  |  |
| Bed Rest | 45 | - 13 | 4 | - 30 | - 12 |
| Space Flight | 80 | - 4 | 1 | - 7 | - 5 |
| **Experiments** |  |  |  |  |  |
| Bed Rest | 45 | - 18 | +/-2 | -317 | - 23 |
| Space Flight | 80 | -(H) | 7 | 47 | -(H) |

-(H)  Represents a decrease of undefined magnitude which has been hypothesized
from the experimental data (5).

bed rest. The cause of the small space-flight simulation results can be traced to the initialization procedures and to the intrinsic structure of the model.

Hypothetically, the reduction in the gravitational force to weight-bearing bones is similar during bed rest and space flight. This assumption suffices for the initialization of the model simulation, but probably is not true in the actual physiological system. The identical rates of skeletal calcium efflux during bed rest and space flight stimulate identical rates of calcium gain into the plasma. However, the diverse rates of renal calcium excretion for the bed-rest and space-flight initializations result in variant rates of plasma calcium loss. Within the structure of calcium model, the higher rate of urine calcium excretion for the space-flight initialization compensates more for the plasma calcium gain due to the skeletal efflux rate than does the urine excretion rate for the bed-rest initialization. Since the concentration of calcium in the plasma is the main regulator in most of the subsystem models of the calcium model, the simulation results are proportional to the changes in the plasma calcium concentrations.

Given these conditions, the model predicts that calcium metabolism is only slightly affected by space flight and is more dramatically affected by bed rest. These predictions are clearly contrary to experimental results (Table 2). In the actual physiological system, the change in the plasma calcium concentration is greater during space flight than during bed rest. This suggests that the rate of skeletal calcium efflux is greater and is less compensated by the urine calcium excretion rate during space flight than during bed rest. From these analyses, three main questions emerge. First, is the rate of skeletal calcium efflux greater during space flight than during bed rest? Second, what is the nature of the skeletal loss? Finally, is the skeleton the major source of calcium being eliminated from the body or do soft tissue calcium pools contribute?

## 4.0   HYPOTHESIS TESTING

### 4.1   GRAVITY VECTORS DURING BED REST AND SPACE FLIGHT

The skeletal system is a large, significant component of the calcium metabolic
system and is thought to play an important role in the zero-g metabolic
changes.  Assumptions of human bone degradation have been based on negative
calcium balances (which are indirect indicators of whole bone body mineral
loss), urine hydroxyproline excretion rates (which are indirect indicators of
collagen breakdown), and changes in bone mineral density (which, when measured
by photon absorptiometric techniques, are only detectable after the third
month in space, (5)).  In both the bed-rest and space-flight studies, urine
hydroxyproline excretion rates are above the baseline averages throughout the
experimental period, suggesting higher rates of osteoclastic resorption
(5,8).  Alternative sources of hydroxyproline may be collagen degradation in
ligaments and tendons (and even the skin as muscle atrophy develops), and the
diet.  Rodent histological and tracer studies demonstrate decrements in the
bone accretion rates, but no change in the bone osteoclastic resorption rates
(15,16).  Similar bone studies have not been conducted in man.

The quantitative differences between the data obtained from the space-flight
and bed-rest studies are assumed to be related to distinct physiological
alterations that occur during exposure to the two environments.  The most
significant environmental factor that exerts an influence on the physiological
changes is the gravity vector and its relationship to body orientation.  In
the space-flight studies experimental data collected in subjects in the
absence of a gravity vector are compared to control data, collected in
ambulatory subjects in one-gravity.  The bed-rest studies always are conducted
in a one-gravity environment.  In these studies, experimental data collected
in subjects in the supine position are compared to control data collected in
subjects in the ambulatory position.  Consequently, bed-rest studies
investigate the influence of the gravitational force when the gravity vector
is parallel or perpendicular to the polar axis (lengthwise or y-axis) of the
body (Figure F).  The purpose of changing the body orientation in relationship
to the gravity vector is to attempt to eliminate the effect of the gravity
vector on physiology and, thereby, simulate the space-flight environment.  In
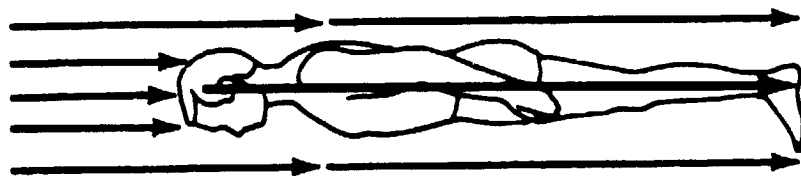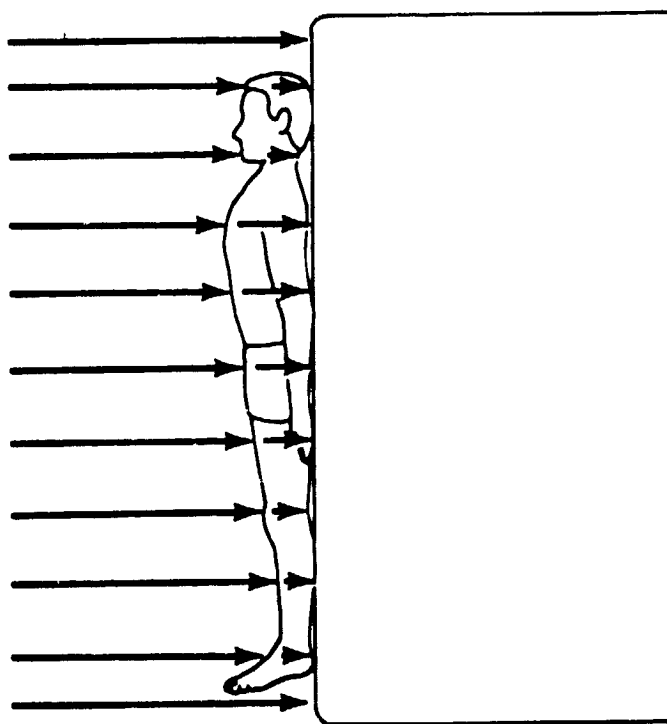
ZERO-G.*

1-G ANALOG OF ZERO-G.
(BED-REST)

1-G CONTROL
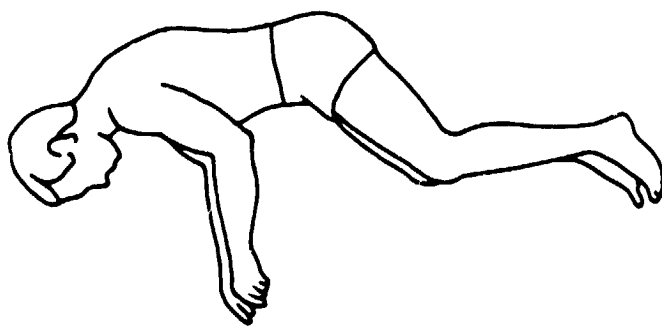
*Thornton, W.E., Hoffler, G.W., and Rummel, J.A.: Anthropometric changes and Fluid Shifts. Biomedical Results from Skylab. (eds. R.S. Johnston and L.F. Dietlein). NASA SP-377, 330-338, Washington, D.C., 1977

Figure 6.- Comparison of gravitational stress upon the human body under one-G (ambulation), zero-G analog (one-G supine), and zero-G conditions.

actuality, this effort is only partially successful. The change in orientation reduces the effect of the gravity, but does not eliminate it.

Gross descriptions of the differences in mechanical force applied to the skeletal system, in each of the three body positions, are given below. These differences are described in terms of externally-applied compression from gravity, and internally-applied torsion, tension, compression, and shear from muscle-bone interactions. The relationship of internally applied forces to bone degradation and integrity are poorly understood. They may be involved in skeletal changes as muscle groups gain and lose functional dominance in the new environment and as anti-gravity muscles undergo disuse atrophy. Hypothetically, their influences can be diminished when the musculature is maintained through appropriate exercise regimes. The primary mechanical force considered in this report is externally applied compression from gravity.

In a one-gravity environment, the gravitational vector on an individual in the vertical orientation concentrates the force of body weight to the feet. The vertebra, femur, humerus, tarsals, metatarsals, and phalanges are structured to bear the weight of the body and to absorb the energy generated by the shock of impact when the body is in motion (17). When the individual is in the horizontal position, the gravity vector is distributed along the entire length of the body. The amount of weight supported at any given point of body-surface contact is proportional to the vertical mass above that point. This redistribution of gravitational force transposes the normal, weight-bearing and shock absorbing structures within the bone to other surfaces and structures. This results in a concomitant redistribution of hydroxyapatite, or bone mineral. In space, the skeletal system is completely relieved of gravitational forces, and therefore, of body weight loads and impact forces. Consequently, the difference between the bed-rest and space-flight calcium metabolic responses may be due to a redistribution of hydroxyapatite during bed rest that otherwise might be eliminated during space flight.

Although these mechanical properties of bone have been implicated in the calcium metabolic changes recorded during bed rest and space flight, limited experimental data and mathematical representation within the model prohibit

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further data analysis and hypothesis development. The only assumption which may be made is that mechanical alterations to the bone from reduced gravitational loads may result in a loss of calcium from the bone and, subsequently, from the body. The rate of skeletal loss appears to be greater during space flight than during bed rest, which could be assumed to be related to differences in mechanical factors applied to the bone within the two gravitational environments.

## 4.2   REGULATORY PROPERTIES OF BONE:  SIMULATION DATA

Hormonal regulatory properties of bone mineral content, as secondary skeletal responses, also may be implicated in the calcium metabolic changes recorded during bed rest and space flight. Secondary responses include regulatory properties which function to maintain plasma calcium homeostasis through hormonal feedback control of osteoblastic, osteoclastic, and osteocytic cellular activity rates. It is mainly these properties that are grossly represented in the skeletal subsystem of the calcium model. Because of the similarity between the bed-rest and space-flight calcium metabolic responses and because of the more accurate representation of the bed-rest data with the model simulation, only the bed-rest simulation data will be presented. The hypotheses discussed in this report are assumed to be applicable to space flight as well.

The results of changes in selected skeletal parameters are presented in Figure 7. In summary, the amount of calcium in the bone mineral decreases after about 20 days of bed rest. Although the rate of calcium resorption decreases slightly (by a maximum of 5 percent), and thereby reduces the rate of bone mineral removal, the rate of accretion, by which new collagen for new mineral formation is deposited, decreases by 20 percent. In addition, the rate of calcium efflux is inhibited by a maximum of 18 percent while the rate of influx is stimulated by six percent. This suggests that the bone fluid is buffering the amount of calcium being lost from the solid bone mineral and being dumped into the plasma. These skeletal results contribute significantly to the negative calcium balance presented in Figure 4.
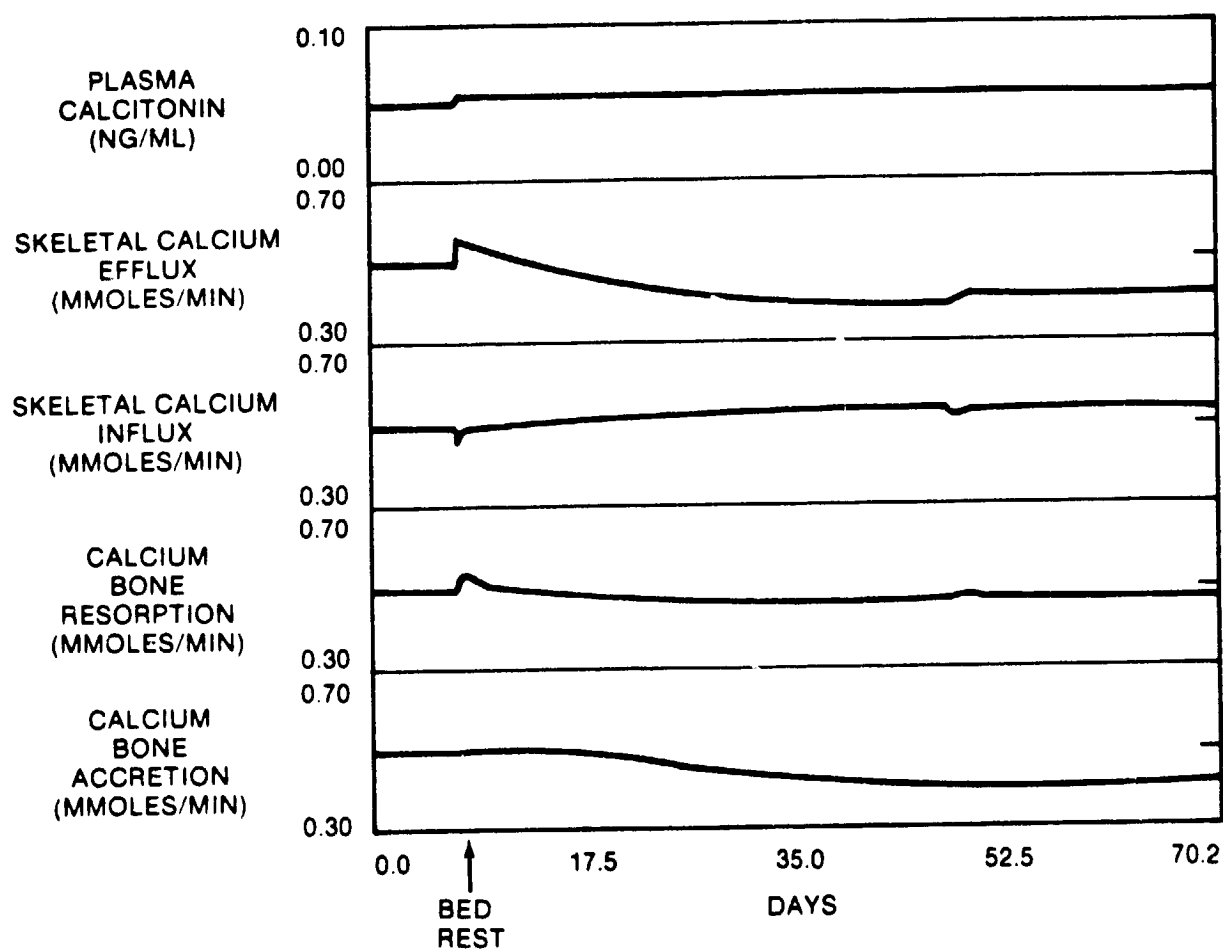
**Figure 7.- Selected variables from the bed-rest simulation (plasma PTH decrease).**

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Since the plasma concentration of PTH significantly influences the rate of change in several of the skeletal parameters, simulation results of the skeletal parameters during bed rest with 0 and 30 percent increases in plasma PTH concentrations also were examined (see section 3.1 for background information). The results of the three simulations are presented in Table 3 (see Table 1).

Manipulation of the plasma PTH concentrations significantly influences changes in the rate of bone resorption. Examination of the mathematical equations within the model reveal that the resorption rate is regulated directly, and solely, by the plasma concentration of PTH. Consequently, as PTH concentrations increase resorption rates increase and vice versa. Unfortunately, significant changes, from negative to positive, in the bone resorption rates only aggravate the negative calcium balances. Negative resorption rates represent decreased rates of calcium loss while positive resorption rates represent enhanced rates of calcium loss from the solid bone.

Changes in the rate of resorption regulate, in a direct one-to-one relationship, changes in the rate of bone mineral accretion. Consequently, when the rate of resorption decreases the rate of accretion decreases. Unexpected in the simulation, however, is the four-fold decrease in the rate of accretion and the disassociation of the accretion rate with the resorption rate as it increases above baseline. These results are due to an additional regulatory factor on the accretion rate, plasma concentrations of 1,25-(OH)2 D. The long-term decrements in the plasma concentrations of 1,25-(OH)2 D are greater than the changes in the resorption rates and thereby exert greater influence on, and generate long-term decrements in, the bone accretion rates.

The rate of calcium flow into the bone fluid (influx) is strictly a function of passive diffusion from the plasma into the bone fluid. The concentration gradient between the two pools of calcium are calculated and the difference is multiplied by a diffusion factor. Consequently, as the concentration of calcium in the plasma increases with each simulation (see Table 1) the rate of calcium influx increases.

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Table 3: Results of Selected Skeletal Parameters During Bed-Rest Simulations With Changes in Plasma PTH Concentrations (Percent Change from Baseline).

| Plasma PTH | Bone Fluid Calcium Efflux | Bone Fluid Calcium Influx | Solid Bone Calcium Resorption | Solid Bone Calcium Accretion | Plasma 1,25-(OH)2 D |
|---|---|---|---|---|---|
| - 30 | - 18 | + 6 | - 5 | - 20 | - 12 |
| 0 | - 17 | + 7 | 0 | - 17 | - 17 |
| + 30 | - 15 | + 9 | + 7 | - 18 | - 22 |

Finally, the rate of calcium flowing out of the bone fluid is inhibited in the three simulations of Table 3. Three hormones regulate the rate of calcium efflux from the bone fluid, PTH, 1,25-(OH)2 D, and calcitonin. In these simulations, 1,25-(OH)2 D and PTH are the main regulators. When the plasma concentrations of the two hormones are depressed below normal the rate of bone fluid calcium efflux is inhibited. However, as the plasma PTH concentration increases above baseline values, the inhibitory control is reduced.

The concentration of calcitonin is uneffected by the bed-rest stress. This is due to the small variations in the simulated plasma calcium concentrations and the manner in which calcitonin secretion rates are stimulated in the model. The plasma calcium concentration must increase to a value that is 15 percent higher than the baseline concentration before the simulated calcitonin secretion rate will be stimulated. In both the space-flight and bed-rest simulation and experimental data, the plasma calcium concentration never rises more than seven percent above the baseline value. Consequently, the influence of calcitonin on the rgulation of bone fluid efflux rates is negligible.

In all three simulations, the data suggest that the skeletal system attempts to maintain bone integrity in the face of the slow, consistent, gravity-induced, mineral loss (initialization factor, see section 2.4) from the solid bone compartment. Bone mineral integrity is further impaired by a diminished ability to rebuild mineral mass despite the maintenance of calcium concentrations in the surrounding bone fluid. These factors results in whole-body negative calcium balances. Although the magnitude of the decrease in bone accretion may be exaggerated in the simulation it has been supported experimentally in studies conducted on rodents in the Cosmos space-flight program (15).

## 5.0 CONCLUSION

A diagram of the hypotheses developed from the validation tests of the zero-gravity simulations are presented in Figure 8. Briefly, a skeletal degradation occurs when an individual is in an hypogravic environment. This results in an increased rate of calcium input to the plasma. This excess calcium input is rapidly detected by the kidney and eliminated in the urine. However, the change in the plasma calcium level reduces the production rate of 1,25-(OH)2 D and eventually the rate of intestinal calcium absorption. Changes in the plasma levels of PTH and skeletal activity rates are undefined. All of these metabolic events result in a whole body loss of calcium, which is reflected as a negative calcium balance. The metabolic responses within the calcium system are slow, requiring weeks to maximally adapt, and the resulting steady state, particularly for the skeletal system, is as yet undefined (5).

The results of the bed-rest and space-flight simulations using the Jaros, Coleman, and Guyton calcium model (9) demonstrate that the model is capable of simulating calcium metabolic responses to hypogravic environments. Although the bed-rest simulation is better than that of space-flight, both simulations are expected to improve as the renal subsystem is modified to respond more appropriately to plasma calcium input stresses and as the skeletal subsystem is expanded and improved. Fortunately, Jaros, Guyton, and Coleman have published modifications and expansions of their skeletal subsystem so that it is more representative of the actual physiology and biochemistry of the bone (18). These modifications are being incorporated into the existing model to create an expanded version of the original model. The space flight simulations are also expected to improve as dietary intake and skeletal efflux rate changes are included in the initializations.
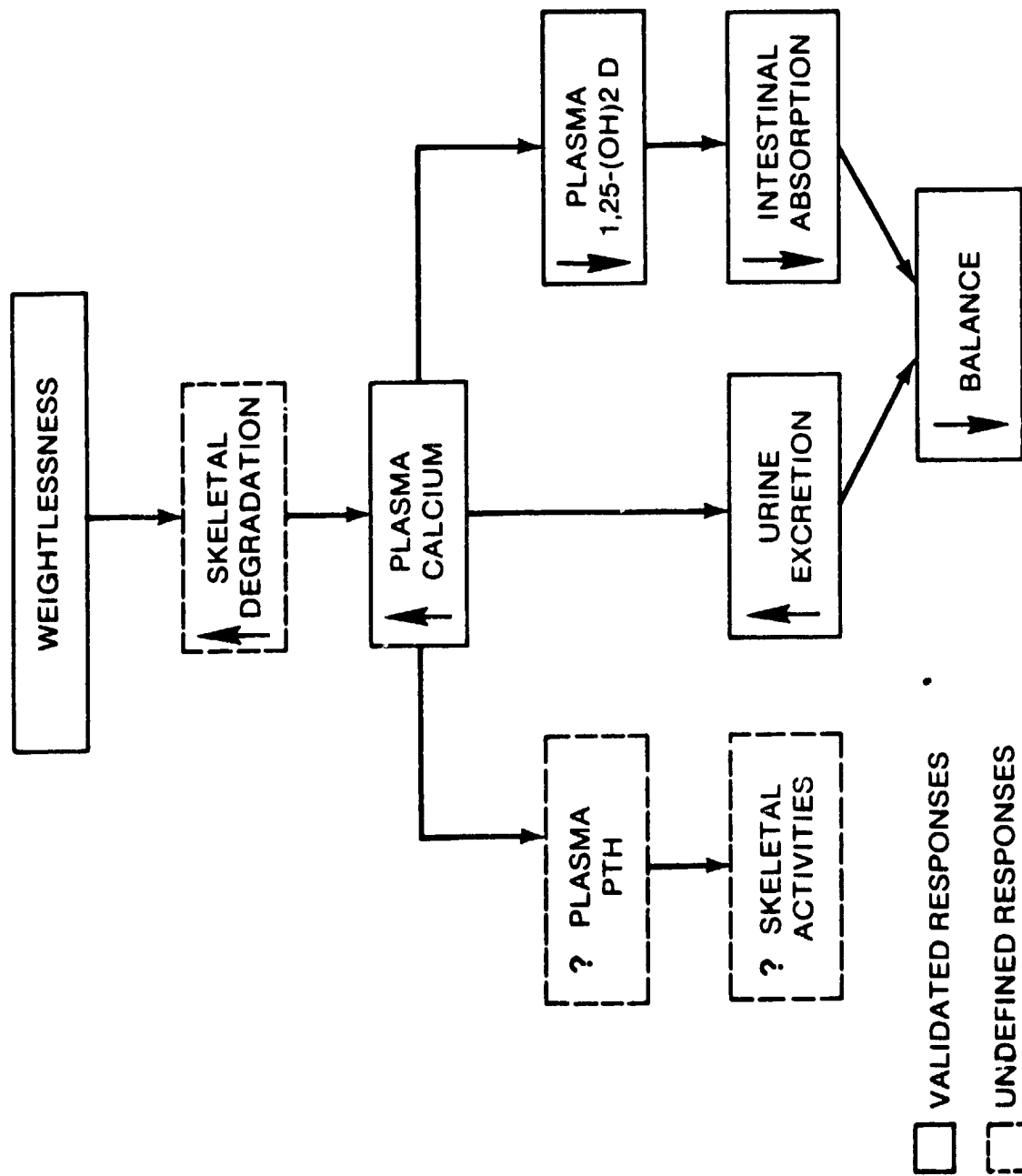
Figure 8· Physiological responses of the calcium metabolic system to the weightless environment.

WEIGHTLESSNESS

SKELETAL DEGRADATION

PLASMA CALCIUM

PLASMA 1,25-(OH)2 D

INTESTINAL ABSORPTION

URINE EXCRETION

BALANCE

? PLASMA PTH

? SKELETAL ACTIVITIES

VALIDATED RESPONSES

UNDEFINED RESPONSES

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