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SUBJECT
Description, Validation, and Modification of the Guyton Model for Space-Flight Applications

The mathematical model that has been a cornerstone for the systems analysis of space-flight physiological studies is the Guyton model describing circulatory, fluid and electrolyte regulation. This document describes the model and the modifications that were made to permit simulation and analysis of the stress of weightlessness. This material was originally prepared for a NASA Reference Publication.

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DESCRIPTION, VALIDATION, AND MODIFICATION OF THE GUYTON MODEL FOR SPACE-FLIGHT APPLICATIONS

PART A. GUYTON MODEL OF CIRCULATORY, FLUID AND ELECTROLYTE CONTROL

PART B. MODIFICATION OF THE GUYTON MODEL FOR CIRCULATORY, FLUID AND ELECTROLYTE CONTROL

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PART A.

GUYTON MODEL OF CIRCULATORY, FLUID AND ELECTROLYTE CONTROL
Physiologists have long recognized the intimate relationship between circulatory function and fluid-balance function. Early in the manned-space-flight program, the biomedical investigators of NASA identified the need to monitor these systems for their involvement in the fluid redistri-

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dynamic feedback control pathways regulating the volume and composition of the extracellular fluid compart-

6. Contain a circulatory system with sufficient
detail to realistically simulate blood pressures,
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7. Contain an autonomic system with efferents
sensitive to blood pressure, plasma osmolarity, and
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(antidiuretic hormone (ADH), angiotensin, and
aldosterone), and body water, the latter by thirst

8. Contain a representation of adaptation effects
(both active and passive) in the heart, vessels, and
pressure receptors for controlling long-term blood
pressure disturbances

As this list of objectives suggests, the complete
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Physiologists have long recognized the intimate relationship between circulatory function and fluid-balance function. Early in the manned-space-flight program, the biomedical investigators of NASA identified the need to monitor these systems for their involvement in the fluid redistribution in zero g and the orthostatic intolerance usually accompanying recovery. With the extension of flight duration from weeks to months, the need to examine the long-term adaptive responses of both the circulatory and fluid-balance systems with simulation models was proposed (ref. III-83).

The following objectives were established for a model of body fluid regulation. The desired model should

1. Be capable of predicting the volume and electrolyte composition of the major fluid compartments, including plasma, interstitial, and intracellular fluid compartments

2. Contain the appropriate capillary and membrane interfaces between these compartments and the capability to simulate exchange of fluids and electrolytes under the influence of hydrostatic, oncotic, osmotic, and active transport forces

3. Contain representation of at least two of the major body cations: sodium (extracellular ion) and potassium (intracellular ion)

4. Contain a representation of the kidney with sufficient detail to predict realistic urine excretion of salts and water under such conditions as fluid/salt loading and restricted fluid intake

5. Contain neural, hormonal, and hemodynamic feedback control pathways regulating the volume and composition of the extracellular fluid compartment

6. Contain a circulatory system with sufficient detail to realistically simulate blood pressures, flows, and volumes in arteries and veins during acute and long-term disturbances such as hemorrhage and infusions

7. Contain an autonomic system with efferents sensitive to blood pressure, plasma osmolarity, and tissue oxygenation and with afferents for controlling blood flow and pressures, hormonal secretion (antidiuretic hormone (ADH), angiotensin, and aldosterone), and body water, the latter by thirst and renal mechanisms

8. Contain a representation of adaptation effects (both active and passive) in the heart, vessels, and pressure receptors for controlling long-term blood pressure disturbances

As this list of objectives suggests, the complete specification of a fluid-electrolyte regulatory system requires the inclusion of several fluid compartments which are controlled by the kidney's acting in conjunction with the endocrine and circulatory systems. An important part of the model selection phase of this project was directed toward identifying models that contained these sub-systems or, alternatively, searching for fluid-electrolyte models that could be used to complement existing circulatory models (refs. III-84 and
With regard to the latter approach, most of the mathematical models with the required fidelity to simulate responses to circulatory disturbances were relatively short-term models and did not have the elements necessary to account for changes in fluid balance. On the other hand, the models of fluid-electrolyte regulation had representations of cardiovascular function that were highly simplistic or absent altogether.

The renal system is perhaps one of the most complex body systems amenable to a mathematical modeling approach. When the model identification search was initiated, few models were available that contained an adequate representation of the fluid-electrolyte regulating capability of the renal system. Some of the most detailed models of the kidney were presented as complex mathematical formulations unaccompanied by numerical solutions and they, therefore, remained conceptual in nature (refs. III-86 to III-88). The model of DeHaven and Shapiro (refs. III-89 and III-90) contained excellent representations of the relationships between more than 100 chemical species in several fluid compartments but was devoid of dynamic regulation as well as direct representations of the circulatory, neural, and endocrine systems. Other models considered a number of important conceptual ideas but had characteristics that limited their applicability (refs. III-91 and III-92). Other models of fluid and electrolyte balance include those of Cameron (ref. III-93), Tostes and Oatley (ref. III-94), and Badke (ref. III-95); these were unavailable for consideration in this project and are mentioned here merely for completeness.

The most comprehensive model of fluid and electrolyte control available, and one which satisfied the requirements of the project, was that developed by Guyton (refs. III-8 and III-96 to III-98). This model has been particularly useful in the NASA physiological simulation project, and it formed the cornerstone of the whole-body algorithm. At the time of its formulation, it was perhaps the most complex physiological mathematical model in existence. There have since been few such comprehensive attempts to subject long-term, whole-body biochemical and circulatory function to the rigors of systems analysis and mathematical modeling which are not directly related to the fundamental work of Guyton.

Description of the Guyton model—The systems analysis of overall circulatory regulation as developed by Guyton involves a large number of the physiological subsystems. The current model, illustrated in figure III-32, is based on cumulative knowledge of the circulation and on experimental data. A model as complex and encompassing as this one is difficult to summarize in one or two diagrams; detailed flow charts and model explanations are available (refs. III-8, III-84, III-98, and III-99).

The relevant physiological systems have been divided into 18 major subsystems, each describing some important physiological aspect of circulatory, fluid, and electrolyte control (fig. III-33). The circuit of blood flow in the original model is divided into five volume compartments: arterial volume, venous volume, right atrial volume, pulmonary venous volume, and combined left atrial and pulmonary venous volume (fig. III-34). Cardiac output is calculated from function curves, whereas other flow rates are calculated from simple pressure-resistance relationships. Arterial-venous flow is determined by summing flow through three parallel circuits (muscle, renal, and other).

The circulation is not closed but “leaks” through the capillaries, “excretes” through the kidneys, and “drinks” directly into the blood. Fluid intake is controlled by plasma osmolarity and tissue oxygen tension. Fluid excretion is based on glomerular filtration and the action of ADH. The blood, composed of plasma (with dissolved proteins and electrolytes) and red blood cells, serves as a filtrable fluid. Other fluid-volume compartments include the interstitial compartment (composed of a gel volume and free fluid volume), the intracellular volume, and pulmonary fluid volume. The relationships between these compartments are illustrated in figure III-35. The capillary filtration rate is determined from a whole-body version of Starling’s relationship, which states that net filtration pressure is equal to capillary pressure plus tissue colloid osmotic pressure, minus interstitial fluid pressure, and minus plasma colloid osmotic pressure. Lymph flow rate is calculated from free interstitial fluid pressure, total tissue pressure, and lymphatic pumping. Flow into the pulmonary reservoir is obtained by subtracting pulmonary lymph return from pulmonary capillary filtration. Protein (colloid) is produced and lost by the body and is distributed between the interstitial space and the
plasma. The representation of the interstitial fluid compartment reflects the years of study by Guyton and co-workers which revealed the importance of the gel-free fluid matrix and subatmospheric pressures of this compartment in controlling edema and transcapillary filtration. Fluid flows into the cells are assumed to occur by osmotic imbalance between extracellular and intracellular fluids.

Two electrolytes are considered in the model. Sodium is distributed evenly in the extracellular fluid, and potassium is stored primarily in the intracellular fluid with allowance for active transport from the extracellular to the intracellular compartments. Dietary intake of both these electrolytes is considered as well as renal excretion, the latter being controlled in large part by a renin-angiotensin-aldosterone mechanism. The pathways that regulate fluid and electrolyte balance are described in more detail in Section V.

The model uses basic cardiac function curves modified by the effects of autonomic stimulation, arterial pressure afterload, and cardiac hypertrophy or degeneration of the pumping ability of the heart. The unstressed volumes of each capacitive region are controlled by the level of autonomic stimulation, the level of angiotensin in the blood, and the pressure in the veins (through stress relaxation). The flow resistances are controlled by a combination of local effects and hormonal effects. The oxygen transport features of the circulation are present, and hematocrit and red cell control are considered. The autonomic system included is basically regulated by mean blood pressure and tissue oxygen tension and includes the effects of the baroreceptors, chemoreceptors, and ischemia of the central nervous system. Total autonomic output is expressed as a positive effect for sympathetic output and a negative effect for parasympathetic output.

Comparison of the blood flow circuit in the Guyton model (fig. III-34) to that of the Croston model shows a great difference in the number of volume regimens. These differences reflect a higher fidelity response for short-term stresses in the latter model. However, the Croston model as well as the other models described earlier have used a basic closed circulatory flow system with no leaks. This kind of approach can be justified when the simulated challenge is acute. When longer duration simulations are required, a large number of other regulatory mechanisms must be included to describe overall circulatory control, even in a crude manner. The lack of detail in Guyton's circulatory subsystem can be contrasted with the complexity of the connections between the cardiovascular system and the interstitial-cell complex. The inclusion of such elements as cardiac hypertrophy, cardiac deterioration, baroreceptor adaptation, hormonal pathways, regeneration of red blood cells and plasma proteins, delayed autoregulation of resistance vessels, and stress relaxation of veins clearly indicates that the Guyton model was developed to be useful as a long-term model. This feature has made it very attractive as a companion.
FIGURE III-33.—Composition of Guyton model of the circulatory, fluid, and electrolyte system. Each block represents a subsystem which consists of a family of function blocks indicated by the numerical figure in parentheses. Modified from reference III-4.

FIGURE III-34.—Blood volumes and flows in the original Guyton model.
to a short-term pulsatile model for the whole-body algorithm application.

The evolution of the Guyton model from a basic circulatory system to a much more complex grouping of subsystems revealed that a model of the cardiovascular system must include elements from most of the entire body if it is to be used in the study of intermediate to long-term phenomena. The Guyton model clearly illustrates the importance of considering the interaction between various subsystems in predicting fluid volumes and electrolyte levels. The real system and the model itself are extremely stable, so much so, in fact, that the function of any single control mechanism can be in error by as much as 50 percent without significantly affecting the overall output of the system. One of the most important features of this model is that it is large enough to obtain this stability level, similar to that in the real system, despite the fact that each subsystem is modeled in a gross sense...
with many minute details omitted. Because of this
stability, the model is adequate for predicting the
outcome of many long-term experiments.

The system of equations representing this
closed-loop model contains more than 370 math-
eatical relationships and is a large, stiff system
with response times ranging from 0.5 second to 40
days. Numerical integration over extended periods
would be extremely time consuming unless special
techniques were employed. The basic method of in-
tegration is a variant of the simple Euler method
made possible by the fact that, for many simula-
tions, all short-term subsystems can be separated
from the rest of the model and integrated many
times using small time steps without disturbing the
remainder of the system. When these rapidly acting
subsystems have developed near steady-state
values, the remainder of the system is numerically
integrated, using a relatively large time step, and
the whole process is repeated. This procedure is
only possible when slow, nonvascular changes are
taking place. With rapid overall transitions, as in
exercise, a small integration step must often be
used for the entire system, greatly slowing the
model simulation.

Guyton model limitations and modifications—The
original Guyton model was built to simulate a large
number of diverse situations, but there were some
specific stresses for which the model response was
inadequate. Since the model did not include sep-
ate vascular compartments representing the legs,
the model was incapable of responding to either
gravitational or postural changes. Analysis of
Skylab data has shown that the rapid shifts of fluid
from the lower to the upper body as well as a more
gradual dehydration of leg tissues play a very im-
portant role in the physiological adaptation to zero
g (refs. III-100 and III-101). The data from bed-rest
studies, taken as a ground-based experimental
analog to zero g, have also shown similar important
changes involving the legs (ref. III-102).

There have been a few studies in which the grav-
itational effects of posture on the body fluid com-
partments have been modeled. However, no
studies have been done to account for long-term
simulation of gravity disturbances such as bed rest
or weightlessness. Models of the circulatory system
that contain short-term gravity effects have met
with various degrees of success. The models of
short-term circulatory gravity effects include those
of Snyder (ref. III-15), Croston et al. (ref. III-10),
and Green and Miller (ref. III-103). Several studies
by Luetscher and co-workers (refs. III-104 to
III-106) resulted in models that included the effects
of intravascular-interstitial fluid shifts on circulato-
ry and renal responses to postural change and,
thereby, allowed for slightly longer term simula-
tions. These latter models, however, were not
designed to account for even longer term effects
such as lymph return, extravascular protein circula-
tion, and hormonal effects. Nevertheless, the ideas
embedded in these models were useful in altering
the Guyton model.

The circulatory subsystem of the Guyton model
contained only two lumped systemic blood com-
partments representing the arteries and veins.
Modifications made to the model included increas-
ing the number of compartments of the circulatory
system so that lower body (i.e., legs) and upper
body blood and tissue fluid compartments could be
identified separately and adding gravity effects on
blood flow and baroreceptor elements to permit the
new circulatory system to respond to a variable
gravity vector. These modifications are illustrated
in figure III-36.

Cardiac output was divided into three pathways,
as previously described. However, flow through the
legs was taken to be the same as the muscle flow of
the original model. In addition, a filterable capillary
bed was added to this pathway. Details of these
modifications are discussed in appendix C. These
changes added the basic capabilities to simulate
such stresses as postural change (tilt, including
head-up and head-down), LBNP, bed rest, and
weightlessness.

Other modifications to the Guyton model, in-
troduced during the course of this project, included
alterations in the renin-angiotensin system, the
baroreceptor system, the stress relaxation of the
vasculature, the autoregulation of muscle blood
flow, and the red blood cell control system. Most of
these changes were not made because of limitations
of the model for space-flight applications; they
were made because other ground-based physiologi-
cal studies revealed that their inclusion would be
more appropriate. Details of these modifications,
including the changes for gravity dependency, are
available in two study reports (refs. III-99 and
III-107) as well as in appendix C.

One weakness in the Guyton model, for some
special circumstances, is the lack of a description
of hydrogen-ion regulation (i.e., acid-base balance).
Hydrogen-ion levels are controlled by the renal
system, the buffering system of the body, and the
FIGURE III-36.—Circulatory and fluid compartments in modified Guyton model. Leg blood and interstitial compartments have been added. Gravity influences carotid baroreceptors and blood flow in legs.
respiratory system, all acting together. In fact, the hydrogen-ion control system is one of the main links between the circulatory, renal, and respiratory systems. A preliminary analysis which lays the foundation for a model of this valuable subsystem was performed during this project (ref. III-99), and other researchers have studied this subsystem in some detail (ref. III-108).

In the latter stages of this project, it has become apparent that new techniques are required to simulate the weightlessness of space flight and its ground-based experimental analogs such as water immersion and head-down bed rest. These stresses were never contemplated in the design of the original Guyton model. Some of the required features which have been identified include collapsible leg veins, fluid reservoirs above the heart (i.e., jugular vein system and head tissues), and orthostatic mechanisms. The latter elements would allow the model to assume an upright reference position in addition to its present supine reference. These modifications are discussed in Section VI.

Validation of the basic Guyton model—The formulation of the Guyton model was based on a wide variety of experimental data, and the model has been tested extensively. Some of the experiments that have been performed with this model are simulation of the development of hypertension in a salt-loaded, renal deficient patient and simulation of congestive heart failure, nephrosis, circulatory changes during severe muscle exercise, and unilateral heart failure of the right or left side. Other simulations performed were of the effects of the removal of the sympathetic nervous system on circulatory function, infusions of various types, and the effects of extreme reduction of renal function on circulatory function. The model performed adequately in almost every case. These initial validation studies are discussed in reports issued by Guyton and co-workers (refs. III-8, III-96, III-98, and III-109).

The capability of the Guyton model to predict the appropriate response to fluid-volume shifts in the space-flight environment was established more easily and convincingly by suitable validation studies based on ground-based experiments. (See table III-2.) The basic model itself was based on detailed organ level studies and required almost 20 years to develop. However, Guyton and his co-workers were more interested in developing a model for hypertension research and did not report model responses for the stresses directly relevant to space flight. Since the weightless state is associated with initial expansion of the central blood volume and subsequent partial depletion of plasma and body fluids, the model was validated for such common one-g stresses as infusions and dehydration for which much data are available.

Several of these studies are illustrated in figures III-37 to III-39. The first two figures illustrate the responses to fluid-electrolyte infusions and the third demonstrates the response to dehydration and subsequent rehydration. In all cases, a variety of infusions was performed, including those of hypertonic, isotonic, and hypotonic fluid. The model is capable of distinguishing between variations in the tonicity of the infusion.

In the first series of simulations (fig. III-37), 1 liter of water, 150 milliequivalents sodium, and 1 liter of isotonic saline (1 liter water plus 150 milliequivalents sodium), respectively, were infused. These infusions were made directly into the circulation, so that the response was more rapid and more dramatic than if they had been administered orally. The three infusions all produce appropriate osmotic shifts between extracellular/intracellular spaces and renal excretions of salt and water, as well as proper hormonal responses. Similar responses would be expected for the human subject (refs. III-112 and III-113). For water infusion, the diuresis is completed within the first few hours. For isotonic saline, the diuresis is maintained at a lower level but continues beyond several hours. In the case of water or sodium infusion, large variations in cell fluid volume are observed, whereas in the case of isotonic saline, the cell fluid volume is essentially unaffected. Antidiuretic hormone was also appropriately responding to osmotic concentrations of extracellular fluid (ref. III-114), decreasing rapidly in the case of the water infusion, increasing threefold in the case of pure sodium, and barely changing in the case of isotonic saline. Aldosterone in the model is regulated by angiotensin, extracellular potassium, and extracellular sodium. It reacted appropriately to the primary stress of these experiments by showing a change in extracellular sodium concentration in the first two cases and a fall in angiotensin (not shown) in the last case, due to increased renal arterial pressure. Experiments such as these illustrate the importance of electrolyte considerations in water-balance studies, a concept quite familiar to most clinicians.

A more detailed study of an isotonic saline infusion, particularly as it affects plasma-interstitial
FIGURE III-37.—Simulated infusion responses using circulatory, fluid, and electrolyte model. These studies demonstrate capabilities of model to distinguish between the toxicity of fluids in acute water and salt loading. Arrows demarcate infusion period. (a) Infusion: 1000 milliliters water (hypotonic). (b) Infusion: 150 milliequivalents sodium (hypertonic). (c) Infusion: 1000 milliliters saline (isotonic).

fluid exchange, is shown in figure III-38. The simulation consisted of a 2-liter transfusion over a 30-minute period into a nephrectomized subject. Capillary filtration increases markedly as the transfusion begins and lymph return increases more slowly, resulting in a net outward flow of fluid from the plasma. Since net flow into the interstitial space is less than the transfusion rate, fluid accumulates in the plasma, and plasma volume increases considerably. When the transfusion is stopped, capillary filtration falls to equal lymph flow, and the interstitial fluid continues to expand at the expense of plasma volume until transcapillary flow is reduced and equals lymph flow. At the end of the transfusion, 37 percent of the added fluid remained in the plasma, but within 30 minutes, only 24 percent of the transfusion volume remained. If the transfusion had been large
enough, the interstitial fluid compartment would have entered the region of low compliance and almost all additional fluid beyond a certain point would have entered the interstitial space. The results of this simulation compare quite favorably with recent experiments (ref. III-115) and demonstrate the suitability of this model for studying situations involving fluid shifts and circulatory function.

Model validation was also extended to include such similar stresses as hemorrhage, salt depletion, and salt loading—for both short-term and long-term changes. Rehydration through use of various fluids has different effects on plasma-volume recovery. In these studies, shown in figure III.39, and others not shown, interstitial fluid does not always act like the fluid reservoir that some investigators have claimed (ref. III-116). Following simulated hemorrhage, for example, the interstitial space provides only 20 percent of the acute plasma refilling response. This has also been noted experimentally by others (ref. III-117). After dehydration

**FIGURE III.38.**—Simulation of isotonic saline infusion showing capillary filtration responses in nephrectomized subject (from ref. III-110).

**FIGURE III.39.**—Plasma volume response to thermal dehydration and subsequent rehydration with fluids of different tonicity: Guyton model response compared to data. (a) Experimental data (ref. III-111). (b) Computer simulation.
without rehydration, there is very little tendency for acute refilling of blood either in the model or in the real system. Also, after infusion, the interstitial compartment first expands but, within 24 hours, returns to normal. This has relevance to the Skylab experience, in which infiltra losses from all fluid compartments were observed to change except for the interstitial space.

Simulations that are even more relevant to the zero-g model validation are the water-immersion studies discussed in Section VI. Where appropriate, the model was modified slightly in accordance with more recent experimental evidence.

Validation of leg compartments and gravity function—Although the validation studies cited are related to the fluid shifts associated with weightlessness, they do not directly evaluate the capabilities of the model concerned with leg recompartmentation and gravity dependency. The modified Guyton model was validated for the following four conditions. (Results of these studies are presented in other portions of this publication.)

1. Supine mode at rest—The Guyton model is initialized in a so-called “supine position.” That is, the values of such quantities as heart rate, blood pressure, and cardiac output agree with measurements from human subjects in the resting horizontal (supine) position. Steady-state values for the gravity-dependent model in the supine, unstressed mode should have agreed with those of the original unmodified model, and they did. This test does not really represent a validation study; however, it was important to ensure that the modifications did not change the basic output variables of the model such as cardiac output, mean arterial pressure, fluid volumes, concentrations, and renal function. In addition, for the sake of consistency, values of flows, pressures, and volumes of the new lower body compartment should compare favorably with the pulsatile cardiovascular model (Croston model) and with available data on human subjects who are supine for relatively short periods. Documentation of this study is given in reference III-107.

2. Supine mode under stress—The restructured model responded to various supine stresses in a manner essentially similar to that of the original model. The stresses were those already discussed in the section describing the validation of the basic Guyton model. In addition, the capability to perform LBNP simulations was demonstrated. Simulation results for this stress were compared with results of the pulsatile cardiovascular model that were previously validated for LBNP. The Guyton model did not exhibit the same degree of accuracy as the Croston model for some cardiovascular indices during LBNP; however, the capability to account for capillary fluid shifts was more realistic (ref. III-107).

3. Standing mode at rest—Quiet standing results in different values of circulatory parameters (i.e., cardiac output, blood pressures, hematocrit) than those found in the supine position. Changing posture from supine to upright represents a stress to the individual and a suitable challenge to the model. Values of basic circulatory parameters in the standing mode should agree with data from human subjects performing quiet standing or tilt for relatively short periods of time. The model contains the capability to vary the angle of tilt with respect to gravity but does not include protective orthostatic mechanisms. These simulations of passive tilting and erect standing suggested new elements in the model to account for muscle pumps, venous valves, abdominal compression reflex, and venoconstriction, all of which are important in the real system to prevent orthostatic collapse (ref. III-107). The additional lower body compartment realistically simulated blood pooling, extravascular filtration, and peripheral vasoconstriction. Comparison of responses was made not only with human data but also with simulation responses from the models of other investigators. The “open” nature of Guyton’s circulatory system was expected to provide increased fidelity for simulations of tilt and LBNP. Extremely long-term effects of standing at rest without leg activity will result in continued pooling of blood in the legs, but these effects were not considered. The capability to simulate long-term stress was demonstrated only in the supine position.

4. Long-term bed rest—Long-term bed rest can be considered a special case of the supine mode. However, the Guyton model (already initialized in the supine position) required additional modification and hypotheses to simulate the headward shifts of fluids and the dehydration of leg tissues; both are characteristics of bed rest. Incorporation of the lower body segments into the Guyton model and the successful completion of the studies outlined previously has provided a solid foundation and the necessary level of detail with which to test theories of long-term adaptation, including weightlessness. The validation studies discussed
here (LBNP, postural change, and long-term bed rest) are described in Section VI.

The Guyton model represents an attempt to understand the interactions between acute and long-term adaptive control of the body fluids and the circulation. Because there is a notable scarcity of information regarding these complex processes in healthy subjects, long-term bed rest and space flight have been of particular importance in validating and modifying the original model of Guyton. This model is clearly relevant to space flight because some of the most notable physiological changes that occur can be traced to disturbances in fluid-electrolyte regulation. By accounting for long-term adaptive effects in the circulatory and autonomic systems, the model has been useful in predicting responses to stresses lasting up to several weeks or months.

**REFERENCES**


PART B.

MODIFICATION OF THE GUYTON MODEL FOR CIRCULATORY, FLUID AND ELECTROLYTE CONTROL
Modifications of the Guyton Model for Circulatory, Fluid, and Electrolyte Control

The original version of the model developed by Arthur Guyton and used extensively as a basis for much of this work was built as a general-purpose model of overall circulatory regulation and was used to simulate a wide variety of real situations, including congestive heart failure, various types of hypertension, fistula, and hypoproteinemia (refs. C-1 and C-2). Despite these successes, the model, as originally constructed, did not have the level of detail required to respond to the challenge of the microgravity environment, and changes were made in the original model to enable studying the responses to this challenge in more detail. These modifications are available in report form (refs. C-3 and C-4), but they are presented and summarized here for the convenience of the interested reader.

The original version of the Guyton model is presented in figure C-1. A legend of symbols, definitions, and units is included. In addition, Fortran language versions of both the original and the modified model are obtainable (refs. C-5 and C-6).

The following discussion summarizes the modifications that were concerned primarily with recompartmenting the circulatory subsystem to include leg volume and controller elements; adding gravity-dependent functions to the controlled and controller systems; and revising and updating the red blood cell block, the angiotensin block, and the baroreceptor block. These modifications have extended the capability of the original model so that the effects of gravity removal on fluid distribution may be simulated more realistically.

LEG CIRCULATORY COMPARTMENT

Two additional compartments have been added to the model of the circulatory system, one to represent the arteries in both legs and the other to represent the veins. (See fig. III-36.) Each compartment is characterized by a total blood volume, blood pressure, and compliance. (See table C-1.) The values for volumes and compliances of the leg compartments were derived from the model of the 28-compartment pulsatile cardiovascular subsystem of the whole-body algorithm. The blood volumes and compliances of the upper circulatory compartments were adjusted to keep the total volume and compliance of the arterial and venous vessels nearly identical to those in the original Guyton model.

BLOOD FLOW PATHWAYS AND METABOLIC RATES

The original Guyton model contained three blood flow pathways: renal, muscle, and the rest of the circulation. In the modified version, these three pathways remain intact; however, the muscle flow pathway represents the entire leg flow, and the nonmuscle, nonrenal pathway together with the renal flow represents total upper body flow. In this modified model, leg blood flow and muscle blood flow are identical. Muscle and nonmuscle, nonrenal flows were readjusted by changing their basic resistances so that cardiac output was similar to that of the unmodified version of the Guyton model and leg flow was similar to that of the leg blood flow of the short-term pulsatile cardiovascular model of the whole-body algorithm. Metabolic demand in terms of oxygen consumption was also readjusted in proportion to the new blood flow rates.

RESISTANCES OF THE LEG BLOOD VESSELS

The single resistance in the muscle blood flow pathway of the original version was replaced by two variables in series to allow capillary filtration to occur in the muscles. These represent a precapillary arteriolar resistance and a postcapillary venular resistance, the values of each being dependent on autonomic and angiotensin effects. In addition, the venular resistance responds to passive distention due to hydrostatic pressure, whereas the arteriolar resistance includes autoregulatory and viscosity effects. These formulations for the leg muscle
FIGURE C-1.—Systems analysis diagram for regulation of the circulation according to Guyton et al. Reprinted from reference C-1 with permission of the publisher. Units are the following: volume in liters; mass in grams; time in minutes; chemical units in milliequivalents; pressure in millimeters of mercury; and control factors in arbitrary units but in most instances expressed as the ratio to normal—for instance, a value of 1 represents normal. Normal values are given on the lines that represent the respective variables. The important dependent and independent variables in the analysis are listed in the key. Additional variables are present for purposes of calculation but generally have no physiological significance.
KEY

AAR—afferent arteriolar resistance
AHM—antidiuretic hormone multiplier, ratio of normal effect
AM—aldosterone multiplier, ratio of normal effect
AMC—aldosterone concentration
AMM—muscle vascular constriction caused by local tissue control, ratio to resting state
AMP—effect of arterial pressure on rate of aldosterone secretion
AMR—effect of sodium to potassium ratio on aldosterone secretion rate
AMT—time constant of aldosterone accumulation and destruction
ANC—angiotensin concentration
ANM—angiotensin multiplier effect on vascular resistance, ratio to normal
ANN—effect of sodium concentration on rate of angiotensin formation
ANP—effect of renal blood flow on angiotensin formation
ANT—time constant of angiotensin accumulation and destruction
ANU—nonrenal effect of angiotensin
AOM—autonomic effect on tissue oxygen utilization
APD—afferent arteriolar pressure drop
ARP—intensity of sympathetic effects on renal function
ARM—vasoconstrictor effect of all types of autoregulation
ARF—vasoconstrictor effect of rapid autoregulation
AR2—vasoconstrictor effects of intermediate autoregulation
AR3—vasoconstrictor effect of long-term autoregulation
AUB—effect of arterial pressure on rate of aldosterone secretion
AUC—effect of chemoreceptors on autonomic stimulation
AUN—autonomic stimulation of heart, ratio to normal
AUK—time constant of baroreceptor adaptation
AUL—sensitivity of sympathetic control of vascular capacitance
AUM—sensitivity of sympathetic vasoconstrictor effect on arteries
AUN—effect of CNS ischemic reflex on autoregulation
AUR—sensitivity control of autonomic control on heart function
AUY—sensitivity of sympathetic control of veins
AUX—overall sensitivity of autonomic control
AYE—sympathetic vasoconstrictor effect on veins
AZK—time constant of intermediate autoregulation
AJK—time constant of long-term autoregulation
AK—time constant for muscle local vascular response to metabolic activity
BFM—muscle blood flow
BFN—blood flow in nonmuscle, nonrenal tissues
CA—capacitance of systemic arteries
CCD—concentration gradient across cell membrane
CHY—concentration of hyaluronic acid in tissue fluids
CKE—extracellular potassium concentration

FIGURE C-1.—Continued.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVM</td>
<td>basic oxygen utilization in nonmuscle body tissues</td>
</tr>
<tr>
<td>PA</td>
<td>aortic pressure</td>
</tr>
<tr>
<td>PAM</td>
<td>effect of arterial pressure in distending arteries, ratio to normal</td>
</tr>
<tr>
<td>PC</td>
<td>capillary pressure</td>
</tr>
<tr>
<td>PCO</td>
<td>net pressure gradient across capillary membrane</td>
</tr>
<tr>
<td>PCP</td>
<td>pulmonary capillary pressure</td>
</tr>
<tr>
<td>PDO</td>
<td>difference between muscle venous oxygen $pO_2$ and normal venous oxygen $pO_2$</td>
</tr>
<tr>
<td>PFI</td>
<td>rate of transfer of fluid across pulmonary capillaries</td>
</tr>
<tr>
<td>PFL</td>
<td>renal filtration pressure</td>
</tr>
<tr>
<td>PCG</td>
<td>colloid osmotic pressure of tissue gel</td>
</tr>
<tr>
<td>PGH</td>
<td>absorbency effect of gel caused by recoil of gel reticulum</td>
</tr>
<tr>
<td>PGL</td>
<td>pressure gradient in lungs</td>
</tr>
<tr>
<td>PGP</td>
<td>colloid osmotic pressure of tissue gel caused by entrapped protein</td>
</tr>
<tr>
<td>PGR</td>
<td>colloid osmotic pressure of interstitial gel caused by Donnan equilibrium</td>
</tr>
<tr>
<td>PGI</td>
<td>pressure from veins to right atrium</td>
</tr>
<tr>
<td>PIF</td>
<td>interstitial fluid pressure</td>
</tr>
<tr>
<td>PL4</td>
<td>left atrial pressure</td>
</tr>
<tr>
<td>PLD</td>
<td>pressure gradient to cause lymphatic flow</td>
</tr>
<tr>
<td>PLP</td>
<td>pulmonary lymphatic flow</td>
</tr>
<tr>
<td>PMO</td>
<td>muscle cell $pO_2$</td>
</tr>
<tr>
<td>POD</td>
<td>nonmuscle venous $pO_2$ minus normal value</td>
</tr>
<tr>
<td>POX</td>
<td>sensitivity of rapid system of autoregulation</td>
</tr>
<tr>
<td>PON</td>
<td>sensitivity of intermediate autoregulation</td>
</tr>
<tr>
<td>POS</td>
<td>pulmonary interstitial fluid colloid osmotic pressure</td>
</tr>
<tr>
<td>P01</td>
<td>nonmuscle cell $pO_2$</td>
</tr>
<tr>
<td>PO21</td>
<td>sensitivity of red cell production</td>
</tr>
<tr>
<td>PO2</td>
<td>sensitivity of long-term autoregulation</td>
</tr>
<tr>
<td>PO2O</td>
<td>oxygen deficit factor causing red cell production</td>
</tr>
<tr>
<td>PPA</td>
<td>pulmonary arterial pressure</td>
</tr>
<tr>
<td>PPC</td>
<td>plasma colloidal osmotic pressure</td>
</tr>
<tr>
<td>PD0</td>
<td>rate of change of protein in pulmonary fluids</td>
</tr>
<tr>
<td>PPH</td>
<td>pulmonary interstitial fluid pressure</td>
</tr>
<tr>
<td>PPP</td>
<td>rate of pulmonary capillary protein loss</td>
</tr>
<tr>
<td>PPO</td>
<td>pulmonary lymph protein flow</td>
</tr>
<tr>
<td>PPR</td>
<td>total protein in pulmonary fluids</td>
</tr>
<tr>
<td>PRA</td>
<td>right atrial pressure</td>
</tr>
<tr>
<td>PMR</td>
<td>pressure caused by compression of interstitial fluid gel reticulum</td>
</tr>
<tr>
<td>PPS</td>
<td>total plasma protein</td>
</tr>
<tr>
<td>PTC</td>
<td>interstitial fluid colloid osmotic pressure</td>
</tr>
<tr>
<td>PTS</td>
<td>solid tissue pressure</td>
</tr>
<tr>
<td>PTT</td>
<td>total tissue pressure</td>
</tr>
<tr>
<td>PVC</td>
<td>venous pressure gradient</td>
</tr>
<tr>
<td>PVO</td>
<td>muscle venous $pO_2$</td>
</tr>
<tr>
<td>PVS</td>
<td>average venous pressure</td>
</tr>
<tr>
<td>QA0</td>
<td>blood flow in the systemic arterial system</td>
</tr>
<tr>
<td>QLN</td>
<td>basic left ventricular output</td>
</tr>
<tr>
<td>QLO</td>
<td>output of left ventricle</td>
</tr>
<tr>
<td>QOM</td>
<td>total volume of oxygen in muscle cells</td>
</tr>
<tr>
<td>Q02</td>
<td>nonmuscle total cellular oxygen</td>
</tr>
<tr>
<td>QPO</td>
<td>rate of blood flow into pulmonary veins and left atrium</td>
</tr>
<tr>
<td>QRF</td>
<td>feedback effect of left ventricular function on right ventricular function</td>
</tr>
<tr>
<td>QRN</td>
<td>basic right ventricular output</td>
</tr>
</tbody>
</table>
tissue are similar to that of the nonmuscle, nonrenal precapillary and postcapillary resistances in the original Guyton model with the following exceptions.

First, the passive distention effect resulting from hydrostatic pressure was not included as a determinant of the leg arteriolar resistance. This exclusion was based on the belief that, upon standing, a strong myogenic local reflex acts to constrict arteriolar vessels (as well as capillary sphincters) in response to the high hydrostatic load. The myogenic reflex opposes the passive distention effect. It was felt that the passive distention effect should be removed until the myogenic effect is included in the model. Otherwise, the effect of standing would create arteriolar distention great enough to overcome autonomic vasoconstriction, a condition that does not normally exist in the real physiological system.

Second, the veins are not known to participate in the myogenic response but, rather, should be highly responsive to passive distention under the high hydrostatic pressures of standing. Consequently, a passive distention effect was added to the leg venule resistance. This formulation permitted a 0.13-kN/m² (1 mmHg) change in pressure to cause a 1-percent change in resistance in accordance with data reviewed by McDonald (ref. C-7). The net effect of excluding the passive distention effect in the leg arterioles and adding this effect to the leg venules is to favor a higher precapillary/postcapillary resistance ratio upon standing which tended to reduce leg capillary pressure towards leg venous pressure. According to Mellander (ref. C-8), this is an appropriate response to limit outward filtration of plasma in the erect posture.

**EFFECT OF GRAVITY ON PRESSURE GRADIENTS**

The average hydrostatic pressure gradient in the legs \( (P_{GL}) \) due to gravity has been expressed as

\[
P_{GL} = H_L \times F \times \sin \phi \quad (C1)
\]
The hydrostatic gradient at the baroreceptors is the hydrostatic pressure at these important sensors. The tilt angle changes must also be included since the tilt angle changes output of the leg venous compartment, where it opposes flow. Material compartment, where it aids flow, and at the pulmonary effect in a lumped leg compartment.) The average hydrostatic pressure is taken as the distance (in centimeters) from the heart to the knees. (The knee was used as a convenient reference point to find the average hydrostatic effect in a lumped leg compartment.) The term \( F \) converts pressures from centimeters water to millimeters mercury, whereas \( \phi \) is the angle (in radians) of body tilt measured from the horizontal. The pressure gradient \( PG_L \) is introduced into the formulation for leg flow at the input to the leg arterial compartment, where it aids flow, and at the output of the leg venous compartment, where it opposes flow.

The gravity effect on the carotid baroreceptors must also be included since the tilt angle changes the hydrostatic pressure at these important sensors. The hydrostatic gradient at the baroreceptors is given by an equation similar to equation (C1) except that the term \( H_L \) is taken to be the distance between the heart and the carotid receptor. The pressure gradient so calculated is subtracted from the effective blood pressure sensed at the carotid body during a tilt simulation. Any angle of tilt may be simulated by adjusting \( \phi \), and other postures such as sitting may be studied by reducing the height \( H_L \).

### VENOUS VALVES

The effect of venous valves has been added by permitting blood flow from the venous leg compartment to assume only positive values.

#### TABLE C.1.—Steady-State Values of Major Physiological Parameters in Modified Guyton Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood volume, liters</td>
<td></td>
<td>Blood flow, liters/min</td>
<td></td>
</tr>
<tr>
<td>Right heart</td>
<td>0.109</td>
<td>Cardiac output</td>
<td>6.47</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0.413</td>
<td>Renal</td>
<td>1.20</td>
</tr>
<tr>
<td>Left heart</td>
<td>0.431</td>
<td>Leg (muscle)</td>
<td>0.98</td>
</tr>
<tr>
<td>Total cardiopulmonary</td>
<td>0.953</td>
<td>Nonrenal, nonmuscle</td>
<td>4.30</td>
</tr>
<tr>
<td>Upper artery</td>
<td>0.714</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg artery</td>
<td>0.146</td>
<td>Body fluid volume, liters</td>
<td>5.003</td>
</tr>
<tr>
<td>Total artery</td>
<td>0.860</td>
<td>Blood</td>
<td>3.007</td>
</tr>
<tr>
<td>Upper veins</td>
<td>2.750</td>
<td>Plasma</td>
<td>1.999</td>
</tr>
<tr>
<td>Leg veins</td>
<td>0.440</td>
<td>Red cell</td>
<td>12.013</td>
</tr>
<tr>
<td>Total veins</td>
<td>3.190</td>
<td>Intestinal</td>
<td>0.545</td>
</tr>
<tr>
<td>Total stressed volume</td>
<td>0.877</td>
<td>Free fluid</td>
<td>11.467</td>
</tr>
<tr>
<td>Total unstressed volume</td>
<td>4.126</td>
<td>Gel</td>
<td>40.038</td>
</tr>
<tr>
<td>Total upper body volume</td>
<td>4.417</td>
<td>Total body water</td>
<td>15.042</td>
</tr>
<tr>
<td>Total leg volume</td>
<td>0.586</td>
<td>Extracellular</td>
<td></td>
</tr>
<tr>
<td>Total blood volume</td>
<td>5.003</td>
<td>Intracellular</td>
<td>24.996</td>
</tr>
<tr>
<td>Blood pressure, kN/m²</td>
<td></td>
<td>Metabolic rate, ml O₂/min</td>
<td></td>
</tr>
<tr>
<td>Upper arterial</td>
<td>13.35</td>
<td>Nonmuscle, nonrenal</td>
<td>252</td>
</tr>
<tr>
<td>Leg arterial</td>
<td>12.24</td>
<td>Leg (muscle)</td>
<td>58</td>
</tr>
<tr>
<td>Upper venous</td>
<td>0.61</td>
<td>Total</td>
<td>310</td>
</tr>
<tr>
<td>Leg venous</td>
<td>0.65</td>
<td>Concentration, mg/liter</td>
<td></td>
</tr>
<tr>
<td>Right heart</td>
<td>0.08</td>
<td>Plasmasodium</td>
<td>142.0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>2.52</td>
<td>Plasma potassium</td>
<td>5.00</td>
</tr>
<tr>
<td>Left heart</td>
<td>0.129</td>
<td>Plasma protein</td>
<td>70.1</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper arterial</td>
<td>100.1</td>
<td>Hematocrit, vol.%</td>
<td>39.95</td>
</tr>
<tr>
<td>Leg arterial</td>
<td>99.3</td>
<td>Stroke volume, liters</td>
<td>0.088</td>
</tr>
<tr>
<td>Upper venous</td>
<td>4.55</td>
<td>Heart rate, beats/min</td>
<td>73.3</td>
</tr>
<tr>
<td>Leg venous</td>
<td>4.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right heart</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>18.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left heart</td>
<td>0.970</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

where \( H_L \) is taken as the distance (in centimeters) from the heart to the knees. (The knee was used as a convenient reference point to find the average hydrostatic effect in a lumped leg compartment.)
this leg compartment can only be filled by arterial
blood (rather than reverse venous flow from upper
body veins), transient conditions can exist in which
outflow to the veins is extremely low. This occurs,
for example, during the onset of lower body nega-
tive pressure simulation. This situation was not
possible in the original Guyton formulation.

**LEG PLASMA/INTERSTITIAL FILTRATION**

A mechanism was added to permit plasma to
filter into a new interstitial leg compartment. This
mechanism is illustrated in figure C-2 in schematic
form. Blood flow in the leg tissues is driven under
an arterial-venous pressure gradient \((PAL - PVL)\)
across an arterial resistance \(RAL\) and a venous
resistance \(RVL\). The capillary pressure \((PCLG)\) is
computed as a function of upstream and
downstream pressures and the precapillary/
postcapillary resistance ratio, in accordance with
the Landis-Pappenheimer formulation:

\[
PCLG = \frac{RCLG \cdot PAL + (1 - RCLG) \cdot PVL}{RCLG}
\]

where \(RCLG = \frac{RVL}{RVL + RAL}\). Filtration
rate into the leg interstitium \((QLEG)\) is based on
the transcapillary hydrostatic pressure and oncotnic
pressure gradients multiplied by a leg capillary
filtration coefficient \((CFLG)\).

\[
QLEG = (PCLG - PILG - PPC) \cdot CFLG
\]

where \(PILG\) is the leg interstitial pressure and \(PPC\)
is the plasma colloid osmotic pressure. It is
assumed that interstitial colilolic osmotic pressure is
negligible. The value of \(PILG\) is determined from
the leg interstitial volume \((VILG)\) and the tissue
compliance \((CTLG)\).

Because of the lack of detailed information
regarding the leg tissues and tissue pressure
changes during standing, this represents a highly
simplified model of leg filtration having the follow-
ing major assumptions.

1. Leg tissue fluid volume is equal to 1.5 liters in
   supine steady state.
2. Linear compliance permits tissue pressures to
   rise by about 5.3 kN/m² (40 mmHg) during stand-
ing when the fluid volume is increased by approx-
imately 500 milliliters because of plasma filtration.
   This large pressure increase is necessary to oppose
   excessive filtration because of the equally high
   change in capillary pressure.
3. The effects of lymph flow, tissue colloidal
   concentration, and tissue gel have not been in-
cluded.

The total resistance to blood flow through the
leg muscle is given by the sum of the two variable
resistances

\[
RL = RAL + RVL
\]

and the blood flow rate of the leg is taken to be the
difference of pressure between the leg arteries
\((PAL\) and veins \((PVL)\) divided by the resistance

\[
QL = \frac{(PAL - PVL)}{RL}
\]

**EXTERNAL LEG VASCULAR PRESSURE**

An external pressure term \((PXV)\), shown in
figure C-2, was included in the formulation for leg
arterial and venous pressure, as was an external
tissue pressure term \((PXT)\). These terms are nor-
mally zero. By setting \(PXV\) and/or \(PXT\) to values
less than zero, the effects of lower body negative
pressure can be simulated. Values higher than zero
will simulate various events such as positive pres-
sure leg garments, water immersion, dehydration
of the legs, and a muscle pump mechanism, all of
which have the effect of reducing venous leg blood
volume and aiding in venous return during stand-
ing.

**INSTANTANEOUS STRESS RELAXATION
EFFECT**

A term representing instantaneous stress relaxa-
tion was added to the stress relaxation block of the
original model. This term appears as a constant fac-
tor (normally zero), which was found to be neces-
sary to aid venous return during tilt simulation. In
that case, reverse stress relaxation was used. Its
physiological counterpart may be a combination of
stress relaxation and the abdominal compression
postural reflex, as well as a central venoconstrictor
effect.

**MODIFIED RED BLOOD CELL PRODUCTION
ALGORITHM**

A new algorithm for red cell regulation was also
implemented in the recompartmentalized Guyton
model. This new block was based on the
erythropoiesis regulatory simulation model previously described in Section III. This model has greater capability than the blood cell subroutine in the original Guyton model, especially with respect to the simulation of hemopoietic responses to hypoxia, red cell infusion, and bed rest. A detailed description of this algorithm, as it appears in the modified Guyton model, is presented in reference C-3.

The new red blood cell algorithm was based on a kidney sensor of oxygen partial pressure located in tissue of constant metabolic rate and perfused with venous capillary blood, flowing at a constant rate. These restrictions permit erythropoiesis to be responsive primarily to changes in hematocrit and arterial oxygen partial pressure, shifts of oxy-hemoglobin dissociation, and disturbances in oxygen-carrying capacity of hemoglobin.

**RENIN-ANGIOTENSIN SYSTEM**

The original version of the Guyton model did not possess a detailed representation of the renin-angiotensin system. In particular, renin secretion as such was not present, and the model did not respond correctly to low-level angiotensin II infusion. This original model contained what was essentially a black box, with angiotensin level dependent on tubular sodium flow. To extend the range of applicability of the model, the black box was replaced with a more physiologically oriented section. A flow chart of the added system is contained in appendix A (fig. A-3). The new system improved the mechanism for releasing angiotensin into the circulation and permitted thirst and salt intake as well as renal afferent and efferent arteriolar resistances to depend on angiotensin levels.
BARORECEPTOR SYSTEM

The baroreceptor system in the original Guyton model was changed by direct inclusion of separate aortic and carotid effects and by separate inclusion of the autonomic influence on both contractility of the heart and whole-body unstressed volume. Appropriate delays and resetting mechanisms were used. A flow chart for the modified system is given in figure C-3.

VASCULAR STRESS RELAXATION

Stress relaxation of the vascular system was extended by the inclusion of new components with different time constants for action. These new components are associated with 6-hour and 14-day relaxation phenomena.

FIGURE C-3.—Block diagram of baroreceptor system.
REFERENCES


