PHYSIOLOGY IN THE SPACE ENVIRONMENT

VOLUME I
Circulation

NATIONAL ACADEMY OF SCIENCES
NATIONAL RESEARCH COUNCIL

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FOREWORD

At the request of the Office of Advanced Research and Technology of the National Aeronautics and Space Administration, the Space Science Board in 1966 undertook summer studies of the physiological problems of manned space flight. These studies were undertaken in two parts—respiratory physiology and circulatory physiology—by panels of experts selected for the purpose. The report of the panel on respiratory physiology* has already been published. The present volume constitutes the report of the panel on circulatory physiology.

Other reports—the Space Medicine Advisory Group Study of 1966 and the Space Science Board Summer Study of 1965—deal with general biomedical problems. The U.S. Air Force has undertaken a study of biomedical problems in support of its Manned Orbiting Laboratory program.

The possible effects of prolonged space flight on the circulatory system are extensive and complex. This volume, in addition to surveying in summary fashion what is now known, suggests directions that may be usefully taken in extending our existing knowledge. This is done with respect to (1) the various parts and functions of the circulatory system and (2) the various stress factors to which the system may be subjected. The panel also gives some attention to the possible benefits of applying a systems analysis approach to the task of acquiring further information on the behavior of the circulatory system under stress.

*Physiology in the Space Environment. II, Respiration, NAS-NRC Publ. 1485B, Nat. Acad. Sci.-Nat. Res. Council, Washington, D.C., 1967.

By way of illustrating how this may be approached, a number of diagrams and schematics were developed; they appear at appropriate places in the text.

This volume, which sets out the findings of the panel's deliberations during a very short period considering the extent and complexity of the subject matter, is necessarily essentially exploratory and suggestive and intended to shed light on problem areas and approaches for further study and investigation.

I am especially indebted to all those who participated in the summer study, particularly Dr. Lysle H. Peterson, who was Chairman of the circulatory physiology group, and to Dr. Herbert G. Shepler, who represented the Space Science Board secretariat for the group.

The report prepared by this group was reviewed by Dr. David F. Bohr, Dr. John T. Shepherd, and Dr. Peterson. Dr. Maurice B. Visscher served as an outside referee. Dr. H. T. Milhorn, Jr., and Dr. T. G. Coleman reviewed the control-system figures and legends and contributed valuable suggestions for the manuscript.

It is hoped that this report will carry the challenge of space physiology to scientists in the disciplines related to physiological investigation of the circulatory system.

Loren D. Carlson
Conference Chairman

PREFACE

The Study Group on Circulatory Physiology of the Space Science Board's Life Sciences Committee has met at intervals since the Spring of 1966. Its task was to predict the potential effects on the circulatory system of stresses associated with manned space flights lasting up to 1,000 days. This volume is the product of the Study Group's working sessions, the major portion having been developed at a two-week study at Woods Hole, Massachusetts, during the Summer of 1966.

Biomedical information currently available is not sufficient to meet operational requirements for development and execution of three-year manned space flights. After reviewing methods for obtaining the necessary information, the Study Group concluded that significant benefits could be gained by applications of systems analysis to the study of biological processes, particularly in those areas where experimentation and actual flights are especially costly in time and resources.

Since biological systems, such as the circulatory system, are very complex, the use of computer models to simulate the biological systems should be helpful for systems analyses. Stresses of space missions are also complex and are multiple. In a "systems approach" to the problem of predicting effects of multiple stresses on a complex system, the use of simulated stresses applied to a computer simulation of the biological systems should serve as an important aid to the manned space program.

The Study Group considered the circulatory system to include, in addition to cardiovascular function, those nervous, endocrine, and other factors that control cardiovascular functions. It was not

possible in the time available to the Group to conduct a detailed analysis of all components of the circulatory system nor to assemble them into an over-all system. The Group did, however, begin the task, and this report is illustrative of an approach rather than being a complete systems analysis of the effects of multiple stresses on a complex biological system for extended time periods.

Part I presents a summary of the contents of the report, arranged in the same sequence in which they appear in the text, and the principal recommendations of the Study Group. Part II discusses the control and regulation of the cardiovascular system and its functions in the light of current knowledge. Part III summarizes stress factors characteristic of manned space flight, also in the light of current knowledge.

A very gratifying and valuable aspect of the 1966 Summer Study, and the subsequent efforts related to it, has been the association with members of the Study Group and the invited representatives of the National Aeronautics and Space Administration and the Department of Defense. I wish to express my warmest appreciation for their insight, interest, and knowledge and for the high level of their scientific and practical effort throughout the study.

Lysle H. Peterson, Chairman
Study Group on Circulatory Physiology

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CONTENTS

PART I

SUMMARY AND RECOMMENDATIONS

1

SUMMARY

We present here a summary of the deliberations and conclusions of the Study Group on Circulatory Physiology. These are set out below in the sequence in which they are discussed in succeeding pages.

ELEMENTS OF THE CARDIOVASCULAR SYSTEM (PART II)

Control and Regulation of Vascular Function (Chapter 3)

Mechanical Properties (Tone) of Blood Vessels

The mechanical properties that determine the physical behavior of blood vessels are described. These are the properties that govern, for a cylindrical vessel, the radius of the vessel for a given distending pressure and that define vascular tone. Equations describing these properties have been derived and evaluated. The magnitude of these properties can now be measured quantitatively under experimental conditions. Thus, it should be possible to evaluate, analytically and experimentally, the effects of space-flight conditions on vascular tone. 3

Vascular Reactivity

The term "vascular reactivity" describes the mechanical response of vascular smooth muscle to stimulation. The mechanism

by which such factors as electrolyte concentration, pH, and pO_2 alter vascular reactivity must be considered in terms of their specific effects on the several components of the over-all contractile response: (1) membrane excitation, (2) excitation–contraction coupling, (3) protein contraction, and (4) energy metabolism. One of more of these components must change if vascular reactivity is to be altered. Although they represent real changes in the intrinsic properties of the vascular smooth muscle cell, it must be realized that they are initiated by changes in the cell's environment. When an environmental change produces a maintained, intrinsic alteration in the vascular smooth muscle, which alters its response to acute stimulation, the chronic influence, such as might be produced by an electrolyte shift or change in pO_2, is said to have produced a change in vascular reactivity.

Capillary Exchange

It is possible to differentiate two well-established processes responsible for movement of substances across the capillary wall. These are filtration and diffusion. Filtration depends on hydrostatic and osmotic pressure gradients and is the process by which the distribution of water between the intravascular and extravascular spaces is determined. The balance of these forces may be altered in the weightless state. Diffusion is determined by the concentration differences and random mobility of molecules and ions. Diffusion is mainly responsible for transcapillary movement of gases and for bulk (in contrast to net) movements of other materials. Pinocytosis may play some role in movement of large molecules or particles across the capillary walls.

The Veins

The veins' functions as capacitance and compliance systems are noted. Methods of study, nervous-system control, and humoral effects are described. As a capacitance system, the veins play an essential part in cardiovascular function by compensating for the effects of gravity on the entire system. Preliminary measurements indicate that, following weightlessness, the peripheral veins may change their pattern of response to tilt.

Mechanoreceptor Functions

An important factor in the control and regulation of the cardiovascular system is the role of the neural receptors. They lie within the walls of the blood vessels and generate sensory nervous impulses that travel to the central nervous system, providing information on the properties and behavior of the cardiovascular system. In turn, they assist in regulating those properties

and behavior. Their characteristics may become "reset" during weightlessness.

Cardiopulmonary Reflexes

When blood volume increases, stretch receptors in the atria initiate impulses that travel via the vagus nerve to the hypothalamus-neuro-hypophyseal ADH system. This results in an inhibition of ADH release, and water diuresis ensues, tending to restore blood volume to normal. This regulatory system could induce diuresis if relative blood volume in the atria and thorax increases in the weightless environment. The Bainbridge reflex, which describes an increase in heart rate resulting from an increase in right atrial pressure, has occupied a highly controversial position in physiological literature for the past 50 years. The Bezold-Jarisch reflex, hypotension intitiated by activation of receptors in the wall of the heart, is a reality, but the physiological mechanism for its excitation is not clearly established.

The Autonomic Nervous System and Cardiovascular Function

The heart and blood vessels respond to the controlling influences of several levels of the central and peripheral nervious systems. Some of this cortical control is mediated through the hypothalamus; some is not. The cardiovascular "center" in the medulla is a synaptic way station for certain control pathways of cardiovascular neural control. Efferent control of the heart is implemented by an interplay between the sympathetic and parasympathetic nervous systems. This is true of heart rate, and recent evidence indicates that, although control of myocardial contractility is regulated primarily by the positive inotropic influence of the sympathetic nervous system, the parasympathetic system may have a negative inotropic influence. Neurogenic vascular control is mediated primarily by means of sympathetic adrenergic vasoconstriction influence. The sympathetic nervous system also has important dilator influences. The parasympathetic nervous system has little influence on the vascular system. It is predictable that such stress factors as weightlessness and emotion encountered in manned space flight will alter the control of the autonomic nervous system on the heart and blood vessels. Adaptive changes of this control system may cause deconditioning.

The Adrenal Medullae

Secretion of catecholamines by the adrenal medullae is regulated by preganglionic fibers of the sympathetic nervous system.

The effect on the cardiovascular system of circulating catecholamines has not been satisfactorily quantified. These hormones do have effects on arousal and blood-sugar level. While in space, emotion should certainly cause an increase in secretion of epinephrine and norepinephrine by the adrenal medullae, while weightlessness might be expected reflexly to reduce this secretion.

The Renin–Aldosterone–Electrolyte Control Loop

A control system whose primary function appears to be the regulation of body-sodium metabolism is composed of a feedback loop involving endocrine secretions of the kidney and the adrenal cortex. An increase in body sodium inhibits the release of renin either by direct action on the renal secretory system or indirectly by a neurogenic regulatory system whose sensor has not yet been identified. The concentration of circulating angiotensin is thereby reduced, diminishing the stimulus for aldosterone secretions. Reduction in aldosterone concentration permits a greater loss of sodium, correcting the elevated body-sodium content. Other poorly quantified hemodynamic, electrolyte, humoral, and neurogenic influences modulate the level of activity of this feedback system.

Control and Regulation of Organ Circulation (Chapter 4)

Cerebral Circulation

Anatomical factors in cerebral circulation are outlined, with special reference to those most likely to be affected by spaceflight conditions. Anatomical variations of the cerebral arteries are listed since, if present in astronauts, they may affect cerebral vascular compensatory mechanisms during flight. Estimates are given of brain blood flow and pressure, and the stresses and physiological variables that can alter the flow and pressure are described. Particular attention is given to the roles of carbon dioxide and oxygen.

Coronary Circulation

Coronary blood flow is regulated by the interplay of coronary perfusion pressure and myocardial fiber shortening (intravascular compression) with the metabolic and neuromuscular factors acting on the coronary vessels. Stimulation of sympathetic adrenergic nerves and infusion of catecholamines result in vasodilation. A 30-to-60° head-up tilt in the dog increases coronary blood flow, as do emotional stresses and exercise. Whether local

metabolic factors or the sympathetic nervous system are primarily responsible for controlling the caliber of the coronary vessels is still unresolved.

Pulmonary Circulation and the Distribution of Blood and Gas in the Lungs

Gravity appears to be a significant factor affecting the distribution of both blood and gas within normal lungs. The mechanisms through which gravity works on blood and gas within the lungs, and their operation under both increased and decreased gravitational fields, are reviewed. Discussion is essentially limited to mechanical factors affecting the pulmonary circulation and ventilation, with emphasis on the relationships between alveolar, intrapleural, and vascular pressures. These relationships are illustrated with mechanical models. Prolonged space travel appears to offer no significant problems regarding the distribution of blood and gas in the lungs. On the contrary, the relations between blood flow and ventilation are likely to be optimal in the weightless state. Acceleration may produce adverse effects, however, and it is important to be able to evaluate risks and the physiological tolerances involved. The effects of gravity are so profound in altering the distribution of blood and gas within the lungs that many problems in basic pulmonary physiology can be studied more effectively under weightlessness than in a normal gravitational field. One of the dividends of space flight will be the opportunity to carry out experiments on the lungs that are impossible on Earth.

Renal Circulation

The juxtaglomerular complex is described, and its relation to and the factors involved in the production and release of renin are discussed. Renal circulation in man, normally about 20 percent of the cardiac output, can be regulated by a myogenic mechanism and by changes in sympathetic vasoconstrictor activity. The latter controls the distribution of flow between the outer cortex and the juxtaglomerular cortex; changes in distribution are associated with changes in sodium excretion. Exercise and the upright posture cause a reflex constriction of the renal vessels. The possible effects of prolonged hypoactivity of the sympathetic nerves on renal function during space flight require further study.

Circulation in Muscle, Skin, and Bone

The humoral and nervous control of the veins and capillaries in human tissues are discussed. Reference is made to the vascular

reflexes that could be evoked during space flight to maintain the activity of the autonomic nervous system when the postural reflexes cease to operate.

Splanchnic Circulation

The splanchnic circulation operates as a whole because the liver, spleen, and gastrointestinal tract are functionally linked and all drain through the portal vein. It can be regarded as a variable-capacity system mainly controlled by pressure gradients and by changes in the blood level of glucose, insulin, sympathetic innervation, and catecholamines. The reflex changes in splanchnic vascular resistance that normally occur with changes in position will be absent in the weightless state.

Control and Regulation of Blood Volume and Cardiac Output (Chapter 5)

Blood Volume

The factors that control and regulate red-cell mass and plasma volume are summarized, and methods in current use for the measurement of blood volume are outlined. Since analysis of this system depends on accurate measurement, advances can be made only by an understanding of the theory and its limitations. The description of the regulation of the red-cell mass and the plasma volume emphasized our ignorance in many areas, especially in connection with the concept of "volume receptors." Stresses likely to be encountered in space flight are analyzed; the effects of prolonged weightlessness on the hematopoietic system and on the control of plasma volume are not known.

Cardiac Output

Cardiac output is determined by stroke volume and heart rate. The mechanical, humoral, and neural factors that influence stroke volume and heart rate, and the interrelations with the vascular system and blood volume, are described briefly and illustrated diagrammatically. The role of vascular resistance in preventing cardiac emptying is discussed.

STRESS FACTORS IN MANNED SPACE FLIGHT (PART III)

Stress Factors in Manned Space Flight (Chapter 6)

Gravitation, Acceleration, and Vibration

The gravitational and inertial forces expected in prolonged space missions may be tolerable when considered independently, but their effects when combined with other environmental stresses, especially unplanned severe vibration, heat, radiation, atmospheric changes, and emotional factors, are essentially unknown. They may be severe, particularly when stresses are imposed upon the space-adapted state (so-called "deconditioning"), for tolerance may then be diminished markedly. Investigation of the effects of simple stresses and of complex interactions among them, and the development of countermeasures, are urgently needed. The acquisition of relevant biological data will be extraordinarily time-consuming and costly if ordinary investigative techniques are used, suggesting the utilization of systems analysis in biomedical investigations.

Weightlessness and Inactivity

The absence of gravity, or weightlessness, is the most unique change occurring in space flight. The circulatory system will adapt to prolonged weightlessness, although altered metabolic and vestibular function may affect the system indirectly. Weightlessness and a lack of physical exercise may induce physiological deconditioning, which might, in turn, diminish the ability of the cardiovascular system to withstand other stresses. Deconditioning, if it occurs, will assume special importance during exit from, and during and after entry into, the atmospheres of the Earth and other planets. It is likely that biological functions affected by weightlessness will change progressively with prolonged weightlessness until some different steady state or equilibrium is obtained. Because many such functions, possibly having different new steady states and time constants, interact, the net effect of prolonged weightlessness is not easily predictable. The effect of physical activity—or more properly, inactivity in confinement—has not been dissociated from the effects of weightlessness. Some of the changes in responses of the system may be similar.

Atmosphere

Within the limits of the changes in composition and pressure expected in the cabin and space-suit atmospheres, no marked effects on the circulatory system are anticipated. Physiological

changes attributable to altered total atmospheric pressure (from 187 to 760 mm Hg) will probably be unimportant, as will those due to variations in inspired pO_2 levels (150 to 630 mm Hg) because of only brief exposures to hyperoxia. Longer exposures to high oxygen-tensions could have undesirable effects on the hematopoietic system. The effect of prolonged exposure to trace contaminants in the atmosphere is essentially unknown and is cause for concern.

Heat

The principal effects of increased temperature on the cardiovascular system are the contribution of cutaneous blood flow to changes in tissue conductance and the resulting increase in cardiac output. Extended heat load results in alterations in blood volume and electrolyte "metabolism." Heat stress during space flight should remain within physiological limits, particularly since it is possible to design the environmental control system and to program activities to minimize the cardiovascular load. The major heat stress is expected to occur during re-entry. As a component of multiple stresses or as a factor superimposed on deconditioning, heat has not been completely studied.

Radiation

Ionizing radiations in the ranges anticipated in space flight affect the formed elements of the blood, the hematopoietic system, and capillary permeability. The effect of radiation doses on those components of the circulatory system is known in general terms, but the dose-rate effect is not known.

High Magnetic Fields

The use of electromagnetic propulsion or high magnetic fields to shield against ionizing radiation could expose astronauts to high magnetic fields during prolonged space missions. Electromagnetic fields have been shown to influence biological systems; direct effects on the circulatory system have not been demonstrated but do not seem unlikely.

Circadian Rhythms and Sleep

Circadian rhythms and sleep are not stress factors per se for the cardiovascular system. Circadian periodicity is endogenous in origin and is evident in a number of cardiovascular functions. A 24-hour cycle can be established by "zeitgebers" (time-givers) such as light-dark cycles or activity patterns. Attention must be given in space flight to providing zeitgebers of sufficient intensity to entrain the rhythm, since the "free-running" condition

can cause alterations in physiological functioning. It is known that sleep influences cardiovascular function also, but its effects are not completely separable at this time from those of circadian periodicity. If proper rhythms and sleep patterns are maintained during prolonged space flight, cardiovascular function will not be impaired.

Nutrition and Water Balance

None of the nutritional or water-balance problems encountered in space flight to date appear to be serious with regard to the cardiovascular system. The advent of synthetic diets, a not-unlikely possibility in prolonged space flights, may introduce problems heretofore unknown with respect to cardiac or smooth muscle, blood proteins, formed elements, and capillary integrity. Individual variations in nutritional requirements and in dietary preferences may also assume importance. Alterations in electrolyte and water balance and the consequent control system called into play have an influence on the cardiovascular system. Sodium, potassium, and calcium levels are known to affect the heart with respect to both the conduction system and its contraction mechanisms. The mechanical properties of the vascular wall are also sensitive to electrolyte alterations. Changes in electrolyte and water balance are indicated from present space-flight data, but the data are equivocal and the causes of the changes are not precisely identified.

Cardiovascular Responses in Space Flight and Simulation Studies

Qualitative changes in components of the cardiovascular system that have occurred in manned space flights to date and in simulation studies are charted. Factors affecting the accuracy of the measurements are described.

2

FINDINGS AND RECOMMENDATIONS

We present here the principal findings and recommendations of the Circulatory Physiology Study Group. Conclusions and recommendations relating to specialized topics may be found in the appropriate sections in Parts II and III of this report.

1. To secure a level of knowledge of the circulatory system and the effects on it of space-flight stresses that permits long-duration manned missions to be planned with assurance, a systematic program of ground-based and in-flight experimentation and testing is essential. We recommend a program that will include complementary series of experiments with animals and man, simulations, laboratory investigations, comprehensive literature studies, and physiological measurements pre-, post-, and in-flight. Because of in-flight constraints, the program must seek to obtain all possible data from ground-based work, limiting flight experiments to those requiring weightlessness and other conditions that cannot be reproduced on the ground. We suggest that special attention be given to the effects on the system of multiple, simultaneous, and sequential stresses and to the development of countermeasures to stress factors.

2. We identify improvement of instrumentation and techniques for biomedical measurements and monitoring as a pressing need. We note that the control, regulation, or precise functioning of particular critical elements of the circulatory system can be determined if new methods of measurement are devised or standard methods improved. Bioinstrumentation and telemetering devices presently available for manned space flights are, in our opinion, not adequate to obtain physiological data required

for mission safety on long flights, quite apart from assembling data scientifically or operationally needed for the long term.

3. The utilization of biomedical systems analysis should be seriously entertained as a technique, in conjunction with other methods, to obtain and rationalize information on physiological systems and to identify areas of needed research. During the 1966 Woods Hole Study, we took initial steps in implementing this concept relative to the circulatory system, developing preliminary models defining input stress factors, and considering data available to test the validity of output functions. The results of this effort have encouraged us to recommend that operating agencies continue to explore the feasibility of such a program. Clearly, much more must be done in feasibility studies, program analysis, and planning. We are satisfied, however, through our exploratory examination of one phase of the problem, that a biomedical systems-analysis program can contribute much to advancing and accelerating knowledge of the functions, control, and regulation of the circulatory system under space conditions.

PART II
ELEMENTS OF THE CARDIOVASCULAR SYSTEM

3

CONTROL AND REGULATION OF VASCULAR FUNCTION

INTRODUCTION

In this chapter and the two that follow, elements of the cardiovascular system and functions of the nervous, renal, and endocrine systems involved in its control and regulation pertinent to the special questions of prolonged manned space flight are described. This information is then used to construct systems-analysis diagrams of aspects of vascular function.

The cardiovascular system has been divided into three subsystems for convenience in discussion although it is recognized that, in practice, the system must be treated as a totality. The subsystems are the vascular system, including the vasculature of the various organ beds, and its control and regulation (Chapters 3 and 4); the blood and blood volume and its control and regulation; and the heart and the control and regulation of its output (Chapter 5).

The vascular system forms a ramifying conduit through which blood is propelled by a force developed by the pumping action of the heart. Large arteries serve as a compliant reservoir that stores the rapidly ejected volume of blood during ventricular systole. The resistance to blood flow of the small arteries and arterioles governs the outflow of blood from this large-artery

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Contributors to this chapter are David F. Bohr, Loren D. Carlson, Edward W. Hawthorne, Raymond H. Murray, Lysle H. Peterson, H. T. Milhorn, Jr., and T. G. Coleman.

reservoir. Small-artery resistance serves two distinct functions: to maintain arterial pressure high enough so that all organs are adequately perfused with blood, though not so highly as to be damaging to the pump and conduit; and to regulate the distribution of flow to meet the highly variable metabolic demands of the several tissues. The arterial system culminates in the capillary bed, which serves as the only exchange area between the tissues and blood. The venous system, through its large and variable capacity, is the primary system for control of the return of blood to the heart.

Circulation of blood through the vascular system is determined by the properties and behavior not only of the blood vessels but also of the blood. The rheological properties of blood are very complex. It is a non-Newtonian liquid whose viscosity is a function of both its velocity and the geometry of its surroundings. The velocity profiles within the vascular system vary from streamlined to turbulent. Abnormalities can develop in the rheological properties of blood—e.g., blood sludging or aggregation of formed elements—under many conditions. These properties, although relevant to the proper behavior of the cardiovascular system in extended space flight, are not treated here in detail. The roles of certain other body systems in cardiovascular function have not been given full consideration in this study. For example, the vestibular system has not been considered; similarly, a variety of humoral substances which have secondary effects on the cardiovascular system—e.g., thyroxin and steroids—are mentioned only in passing.

MECHANICAL PROPERTIES (TONE) OF BLOOD VESSELS

The conditions of extended space flight are believed to affect the blood vessel. It is thought, for example, that the deconditioning associated with prolonged weightlessness simulation is related to an alteration in vascular tone. This section attempts to define the mechanics that determine the properties and behavior of blood vessels with regard to resistance to blood flow, blood pressure, and blood volume, and in the regulation of the cardiovascular system. While these mechanical properties apply to all blood vessels, the following discussion is limited to vessels having cylindrical geometry. Furthermore, the only external loading of the vessel wall considered is that of pressure.

The mechanical properties described are those that define vascular tone and the consequent effects on vascular resistance. The tone of blood vessels directly affects the behavior of vascular mechanoreceptors and thus the nervous regulation of the cardiovascular system. Although all vessels contribute to the

peripheral resistance, some authors find it convenient to distinguish between "resistance" and "capacitance" vessels, the former having relatively small and constant radii and the latter having radii that are relatively large and variable. These terms are qualitative, and there is no discrete separation of resistance and capacitance vessels within the body.

Resistance to flow is, of course, due to the viscous properties of the blood and the velocity characteristics of flowing blood, as well as to vascular radii. The effects of radius predominate, however, in the control of blood-flow resistance in health and in most forms of hypertension. Indeed, most of the significant biological functions of blood vessels relate to their radii. This discussion will therefore be concerned with those factors that determine vascular radius. The distribution of cardiac output to the organs and tissues of the body, and the work performed by the heart in so doing, varies primarily according to vascular radii. Furthermore, as will be noted later, communication between the vascular system and the central nervous system via so-called pressure and volume receptors is a function of vascular radii since the receptors that generate the nerve impulses might well be called radius receptors.

Vascular radius is a function of three general factors:

1. The distending pressure: the difference between the pressure inside (P_i) and that surrounding (P_o) the vessel, or $P_i - P_o$
2. The geometry of the vessel, i.e., the wall thickness (δ) and the radius (r)
3. The elastic (E) and the viscous (R) properties of the vessel wall material

The combined effects of 2 and 3 above determine how far a vessel will become stretched for a given distending pressure, and thus they specify vascular tone.

A more detailed examination of the manner in which distending pressure stretches a vessel and determines its radius indicates that the distending pressure which acts radially must generate a tangential force, for this pressure tends to compress the wall while the tension within the wall, which tends to cause stretch, acts in a different direction. The magnitude of the stretching stress (tension or T) that results from the distending pressure is determined by the geometry of the vessel, and is expressed by Eq. (1):

$$T = \frac{(a^2 P_i - b^2 P_o)}{(b^2 - a^2)} + \frac{(P_i - P_o)a^2 b^2}{r^2 (b^2 - a^2)}, \qquad (1)$$

where a is the inner and b the outer radius of the vessel.

If the pressure surrounding the vessel is assumed to be zero, the equation reduces to the form:

$$T = \frac{a^2 P_i}{(b^2 - a^2)} \left(1 + \frac{b^2}{r^2}\right). \qquad (2)$$

This equation may not apply to vascular beds where pressure surrounding the vessels may be quite high or where intravascular pressure is low compared with extravascular pressure, such as in skeletal muscle or in veins.

A further simplification of the equation may be assumed for "thin-walled" vessels where wall thickness is small relative to the vessel's radius, i.e., where the difference between a and b is small.

$$T = P(r/\delta), \qquad (3)$$

where $b - a = \delta$. The error involved in this assumption is a function of the ratio between radius and wall thickness, such that if the ratio is 10, the error is about 10 percent; if the ratio is 20, the error is about 3 percent.

Equations (1), (2), and (3) demonstrate the often-confusing relationship between pressure, which tends to compress the vessel wall, and tension, which tends to stretch the wall. These equations also illustrate another important condition which exists within the wall. Several investigators have considered the distribution of tension within the walls of structures as they become passively stretched. An equation known as the law of Laplace has been applied by certain investigators:

$$T = Pr. \qquad (4)$$

This equation applies to an extremely thin-walled structure, such as a soap bubble. However, some authors suggest that it may be applied also to walls that are not extremely thin, such as those of blood vessels, heart, and urinary bladder, since they may be considered as concentric series of extremely thin layers. The equation cannot be applied to thick-walled structures, for it implies a distribution of forces within the vessel wall which is probably not true. For example, Eq. (4) predicts that the tension in the wall should increase with each successive layer for a given distending pressure since the radius increases with each layer. Equations (1) and (2), however, show that when a vessel is passively stretched the tension is greatest at the innermost part of the wall and decreases in a curve toward the outer aspect of the wall. Furthermore, the dimensions of T in the two cases are different. In the Laplace equation, tension is force per unit length of circumference; whereas, in Eq. (1), (2), or (3), tension is force per unit area of wall material.

Thus, the geometry of the vessel is an important factor in determining its radius for a given distending pressure. It should be repeated that the relationships so far discussed apply only to cylindrical segments, and the pressures and tensions considered have been only those in the radial and tangential (circumferential) directions, respectively. Also, in the stretched arteries within the body, longitudinal tensions exist which tend to stretch the vessel in its long axis. Radial tensions also exist within a stretched vessel wall which tend to cause the wall to thin. The longitudinal and radial stresses are small but not necessarily insignificant in comparison with the tangential or circumferential stress.

The above equations refer to the amount of stress, or force per unit area, exerted on a vessel for a given distending pressure but do not indicate how much the vessel will be stretched. The extent of stretch depends not only upon the stretching force but also on the stiffness or resistance to stretch of the material of which the wall is composed, e.g., muscle, connective tissue. While stretch is a good qualitative term, another term, strain, is used to describe quantitatively the extent of stretch that results from an applied force. Since a given material will stretch twice as much under the same applied stress if it is initially twice as long, the ratio of the elongation to the initial length is used (Peterson, 1962). This ratio is strain.

$$\Delta 1/1_0 = \epsilon = \text{strain}, \tag{5}$$

where 1 = the change in length due to stretch and 1_0 is the initial or unstretched length. For a cylinder having an initial radius r_0 and the new or stretched radius r, then

$$\epsilon = \frac{r - r_0}{r_0} = \frac{\Delta r}{r_0} . \tag{6}$$

Thus, it is possible to compare large and small blood vessels with regard to the stiffness of the wall.

The walls of blood vessels exhibit two kinds of stiffness, elastic and viscous. The differences in the two can be described if it is assumed that in one case the material is purely elastic and in the other purely viscous. In the former case, the material will be strained a given amount by a given stress no matter how rapidly the stress is applied. In the latter case, the amount of strain will depend upon the time duration of the stress, or conversely, the velocity of the strain will be a function of the applied stress. Vessel walls have both qualities, i.e., they are viscoelastic.

The simplest cases can be described mathematically. For a purely elastic material

$$T = E\epsilon, \tag{7}$$

where E is the modulus of elastic stiffness. Thus, the greater E is, the smaller is the strain (ϵ) resulting from a given applied stress (T). For a purely viscous material

$$T = R\,(d\epsilon/dt), \tag{8}$$

where $d\epsilon/dt$ is the strain velocity. The case for a viscoelastic material where the viscous and elastic elements are considered in parallel can thus be expressed (the Voight model)

$$T = E\epsilon + R(d\epsilon/dt). \tag{9}$$

Hence, a viscoelastic material is stiffer when stretched rapidly rather than slowly, or, in other words, the stiffness is a function of the velocity or frequency of strain.

It has been shown (Peterson et al., 1960) that the stress–strain relations of the aorta and its major branches can be described by Eq. (9), i.e., as a relatively simple viscoelastic case. This simple linear relationship with constant coefficients is the result, among other things, of the fact that arterial strain is small. For example, along the aorta, demoral, or carotid artery where the pressure may change by 30 to 50 percent during a cardiac cycle, the change in radius is usually only 1 to 2 percent. For such small strains, the behavior of the material approaches linearity. If the vessels are stretched over greater ranges, the moduli tend to be different over different parts of the range. Thus, when vasomotor tone is stable, it is possible to evaluate the moduli of elasticity and viscosity of a vessel by simultaneously measuring the stress and strain. Since physiological changes in E and R due to vasoconstriction or dilatation are slow compared with a cardiac cycle, the degree of linearity or constancy of E and R with strain can be distinguished from changes in E and R due to vasomotor effects.

It is now possible to measure quantitatively the distending pressure and the radius of the vessel wall instantaneously and to evaluate an equation that numerically defines vascular tone. The equation is:

$$T = Pr + E\epsilon + R(d\epsilon/dt). \tag{10}$$

There are several points to make from this equation for thin-walled vessels. First, the strain is a function of five variables: distending pressure (P), vessel radius (r), wall thickness (δ), elastic modulus (E), and viscous modulus (R). Second, the radius–wall thickness ratio is important in determining the tangential tension (T) developed in the wall for a given distending pressure; thus, a vessel of large radius and relatively thin wall behaves as if it were less stiff. Conversely, the smaller the radius, the more effectively stiff is the vessel. For example, capillaries are mechanically stiff structures, resisting stretch by distending pressure even though their walls are thin because their radii are very small.

Third, factors that determine tone or stiffness can now be quantitatively evaluated under experimental conditions (Peterson et al., 1960). The elastic moduli of blood vessel walls are similar to those of good gum rubber, and the viscosity of the wall is of the order of one million times that of blood (Peterson, 1964). As mentioned earlier, vessel strains are normally small during the cardiac cycle. Even differences between vessels markedly constricted and dilated are of the order of 10 percent. Since, however, resistance varies exponentially with radius (of the order of the fourth power), these changes in radius provide large changes in resistance. Although most of the energy loss and the drop in pressure along the arterial system are usually thought to relate to blood viscosity, that is, result from overcoming the viscous resistance to blood flow, it is likely that a considerable loss is due to stretching of the highly viscous vessel walls during the cardiac cycle. No quantitative estimate of this loss has yet been verified. Since the vessel wall is nearly, but not exactly, isovolumetric (Poisson ratio approximately 0.5), if the tangential or circumferential strain is about 1 percent, then the radial and longitudinal strains on the wall will be less than 0.1 percent. Tethering of the wall by branching vessels and surrounding tissue further reduces longitudinal strain. Intralumenal, radial, and longitudinal tensions are complex theoretically and difficult to measure. It has been found (Attinger, 1964) that flexing or extending a limb can produce large changes in the longitudinal strain and moduli of elasticity and viscosity of vessels. It has also been shown that the posture of the head and neck may markedly affect cerebral blood flow (Toole, 1966).

Finally, the earlier, and still used, concept of critical closing of vessels may be open to question despite the fact that flow may cease while a distinct pressure gradient exists. The earlier explanation was that during vasomotor activity the active forces in the wall would exceed the passive stretching forces (as defined earlier) and that the vessel radius would be reduced to zero. It should be pointed out that the inner radius of a cylindrical vessel is unlikely ever to be less than the wall thickness. The inner aspects of the wall could buckle and protrude into the lumen, but, in this case, the vessel wall is no longer cylindrical (Van Citters et al., 1962; Van Citters, 1966).

It is interesting to consider next the factors that alter the mechanical properties of the vessel wall such that its radius changes in response to distending pressure. This, of course, is a central problem in hypertension. Normally, changes in wall properties are produced by alterations in the state of vascular smooth muscle, i.e., vasoconstriction or vasodilation. Vasomotor changes are usually thought of as being induced by catecholamine release from the sympathetic nerve endings in the vicinity of the vascular smooth muscle. In actuality, several

factors affect the contractility of vascular smooth muscle: catecholamines released by the autonomic nervous system; blood-borne vasoactive substances such as catecholamines, aldosterone, and other steroids; locally produced vasoactive substances; the "intrinsic" pacemaker activity of the muscle itself; the water and electrolyte content of the vessel wall; and the mechanics of the vessel wall itself. The prevailing vascular tone in arteries or veins is dependent on the totality of these factors and their interaction. Extended weightlessness or immobility is likely to affect one or more of these factors and result in alteration of vascular tone.

VASCULAR REACTIVITY

Active vasoconstriction or vasodilation results from an interaction of the contractile machinery of the vascular smooth muscle cell with some neurogenic or humoral influence. A vascular response occurs when either the intrinsic contractile machinery of the cell or the vasoactive influence of the cell's environment is altered. If an intrinsic change develops in the smooth muscle cell, there is said to be a change in vascular reactivity. Changes in this intrinsic, myogenic property of smooth muscle constitute the subject of this section. Such changes have important physiological influences on vascular resistance and, hence, on the regulation of blood pressure and the distribution of blood flow. For instance, if some property of the cell changes so that ionized calcium acquires more ready access to the myofibrillar area of the cell, a great contraction results. If this occurs throughout the body it leads to an increase in total peripheral resistance and results in hypertension. On the other hand, if the partial pressure of oxygen inside the cell falls so that the energy available is inadequate for optimal contraction, reactivity of the muscle declines, and vasodilation and an increase in blood flow to the affected part result. It is possible that hypoxia, by depressing vascular reactivity, may play an important role in both active and reactive hyperemia and in the autoregulation of blood flow.

To study these basic mechanisms, the simplest and most rigidly regulated environment must be used. In situ, the vascular smooth muscle cell is able to perform its function because it is acutely sensitive and responsive both to local metabolic changes and to remote regulation by neurogenic and humoral control systems. In this in situ environment of potent, variable, but poorly understood regulatory influences, experiments intended to examine the basic cellular contractile mechanism are difficult, if not impossible, to control, and results are uninter-

pretable. The major contributions to our understanding of the contractile process of vascular smooth muscle have come through the use of smooth-muscle preparations that have been isolated from these in situ control systems. Very reasonably, these systems, which are all important in regulating the vascular system in situ, must be understood in terms of what they do to the basic components of the contractile process; however, in order to investigate their action it seems most realistic at present to use techniques that allow each influence to be imposed, individually, on the isolated vascular smooth muscle in a rigidly controlled environment.

Methodology

Before proceeding with specific evidence bearing on the details of the contractile process and on the factors that alter it, a brief assessment will be made of the techniques that are used in the study of the reactivity of isolated vascular smooth muscle. These studies are of two types. One involves direct recording of the contraction and relaxation of a piece of vascular smooth muscle; in the other, these processes are inferred from changes in resistance of an isolated perfused blood vessel, as measured by changes in pressure and of flow through its lumen. In the current state of the art there is no important argument favoring one of these approaches over the other. Defenders of the "isolated strip" technique emphasize the problems involved in quantifying a smooth-muscle response from observed changes in vascular resistance. A recorded change in the resistance to flow reflects primarily a change in the length of the muscle cell; yet, accompanying such a shortening there will be a decrease in tension in the wall if the vessel is perfused at a constant pressure (Laplace's law), or a tendency for tension to increase if the vessel is perfused at a constant flow rate. The matter may be improved somewhat by calculations of the work done during the constriction (Hinke, 1965), but such calculations involve extensive and indirect observations. Furthermore, in all types of perfusion studies one is dealing with a population of cells subjected to widely varying passive tensions, high at the inflow end and low at the outflow end of the tube.

Studies of the reactivity of the isolated strip of vascular smooth muscle are also subject to criticism. Inevitably there are many damaged cells along the cut edges of the piece of vessel wall. Furthermore, it is difficult to obtain a strip whose long axis parallels the long axis of its contractile fibers. It is reassuring to find that in spite of weaknesses in both methods, there is a high degree of consistency in the results obtained with them.

Many different themes may be imposed on these two funda-

mentally different approaches to the evaluation of vascular reactivity. It is possible to record contractile tension of strips from vessels as small as 250-μ o.d. (Zuberbuhler and Bohr, 1965) and, by mounting a strip in a small blood-perfused bath, to study it in an environment that approaches its normal habitat (Vick, 1965; Zuberbuhler and Bohr, 1965). Variations in environment may also be evaluated in the isolated perfused vessel. With the latter preparation it is possible to assess the relative potency of vasoactive agents when they are delivered to the luminal side, in contrast to the adventitial side, of the vessel wall. Apparently, a much higher concentration is required for a given response if the agent is presented to the adventitial rather than the intimal surface (Hinke et al., 1964). With the perfusion technique, it is possible, also, to vary the tension on the smooth muscle either by altering the intraluminal pressure or by changing the pressure outside the vessel when it is enclosed in a rigid plethysmograph (Davignon et al., 1965). Many techniques have been used recently, in parallel with observations of mechanical reactivity, aimed at investigating the behavior of one or more specific components of the over-all contractile process. These include measurements of electrolyte content and fluxes (Bohr, 1964; Briggs and Shibata, 1966; Burnstock et al., 1963; Daniel, 1965; Daniel and Nash, 1965; Friedman and Friedman, 1965; Garrahan et al., 1965; Hageneijer et al., 1965; Headings and Rondell, 1964; Peterson, 1963; Tobian and Chesley, 1966; Wallach et al., 1964), monitoring of electrical activity (Cuthbert and Sutter, 1965; Cuthbert et al., 1964; Funaki, 1960, 1961; Funaki and Bohr, 1964; Keating, 1964; Roddie, 1962; Speden, 1960; Su and Beven, 1965; Takenaka, 1964), measurement of oxygen utilization (Dury et al., 1957; Howard et al., 1965; Kirk, 1962; Kosan and Burton, 1966), substrate utilization (Kirk, 1962; Lundholm and Mohme-Lundholm, 1962; Mulcahy and Winegrad, 1962; St. Clair et al., 1966), characterization of the oxygen requirements (Carrier et al., 1964a, 1964b; Detar and Bohr, 1965; Howard et al., 1965), and metabolite requirements (Coe et al., unpublished observation; Kirk, 1962; Mulcahy and Winegrad, 1962; St. Clair et al., 1966). Further insight into the components of the contractile cell has arisen from electromicrographic studies (Rhodin, 1962) and from work with its contractile protein (Filo et al., 1963, 1965; Huriaux et al., 1965; Laszt and Hamoir, 1961; Mallen, 1965; Ruegg et al., 1965; Schirmer, 1965; Yur'ev, 1961).

Content and Mobility of Electrolytes

Since vascular reactivity is highly dependent on electrolytes, a review of current information on electrolyte content and mobility of vascular smooth muscle may be useful.

The electrolyte situation in vascular smooth muscle is sufficiently dissimilar from that in cardiac or skeletal muscle that it is unsafe to draw conclusions from these latter, more extensively studied, tissues. There does appear, however, to be reasonable similarity in this respect between vascular smooth muscle and other smooth muscle. Recent reviews (Bohr, 1964; Burnstock et al., 1963) and studies (Bülbring and Kuriyama, 1963a, 1963b; Kuriyama, 1963) have dealt with electrolyte content and mobility of smooth muscle in general. Items in these reviews that have particular bearing on problems of vascular reactivity, and the results of more recent pertinent studies on vascular smooth muscle will, therefore, be summarized.

One characteristic in which smooth muscle in general and vascular smooth muscle in particular differs from skeletal muscle is its very high sodium and chloride content and mobility and its low potassium content (Daniel, 1965; Daniel and Nash, 1965; Friedman et al., 1962; Garrahan et al., 1965; Hageneijer et al., 1965; Headings et al., 1960; Peterson, 1963). Several factors combine to cause the high content of sodium in the normal vessel wall: (1) extracellular fluid volume (estimated to be between 30 and 50 percent) (Friedman and Sréter, 1963; Headings et al., 1960; Norman et al., 1959, Prosser et al., 1960) is greater than in skeletal muscle, (2) intracellular sodium concentration is probably high but cannot be comfortably estimated [perhaps 50 mM (Garrahan et al., 1965)] because (3) there is a large and poorly defined amount of sodium sequestered in bound, electrochemically inactive form. The amount of sodium in the medial layer of a dog carotid artery, after it was damaged so that the cell membrane no longer formed a barrier to ion distribution, was much greater than could be accounted for as being in equilibrium with the sodium in the physiological salt solution in which it was bathed (Headings et al., 1960). The excess amounted to 125 mg of sodium/kg of tissue solid. Recent isotopic studies (Garrahan et al., 1965) of rates of sodium efflux have demonstrated that much of the excess sodium resides in a compartment whose efflux rate is indistinguishable from that of ionized sodium in the extracellular space. It was concluded that the association and dissociation of sodium and a negatively charged polyanion in the extracellular space must be so rapid that it cannot be distinguished from diffusion. This is in agreement with earlier predictions (Crane, 1962; Headings et al., 1960) that the acid mucopolysaccharide, chondroitin sulfate, which is abundant in the vessel wall and has a high anionic charge, may be the site of this sodium binding. The increased content of mucopolysaccharides in the walls of blood vessels of animals with experimental hypertension (Crane, 1962; Headings and Rondell, 1964) may well be causally related to the high sodium content (Daniel and Dawkins, 1957; Gross and Schmidt, 1958; Koletsky

et al., 1959; Peterson, 1963; Tobian and Chesley, 1966) of these animals' blood vessels. Challenging problems are raised by the recent observation that the biological half-life of ^{22}Na in the vascular tissue of hypertensive rats is greater than it is in that of normotensive controls (Zech and Pellet, 1965).

Significant and interesting differences in electrolyte content have been described for vessel wall from different levels of the arterial tree (Friedman and Friedman, 1965; Peterson, 1962, 1963).

Although the passive movement of sodium and potassium through the vessel wall is extremely rapid (Dawkins and Bohr, 1960; Garrahan et al., 1965), the active transport of these ions is slow (Barr et al., 1962; Daniel, 1965). The uphill movement of these two monovalent cations against a concentration gradient is sensitive to temperature and ouabain and is inhibited by various metabolic inhibitors (Garrahan et al., 1965; Peterson, 1963). These factors argue that the active transport mechanism of vascular smooth muscle is dependent on an energy-supplying system plus the proper functioning of a membrane ATPase similar to that of cardiac and skeletal muscle.

One of the greatest concerns in the use of isolated vascular smooth muscle as a model from which insight can be gained into the determinants of vascular reactivity is the well-established observation that although these tissues are capable of maintaining and even re-establishing transmembrane ionic gradients, the gradients fall short of those that exist in situ (Barr et al., 1962; Daniel, 1965; Dawkins and Bohr, 1960; Headings et al., 1960). In the dog carotid, for instance, potassium concentration recovered to only about one half of its normal value (125 mEq/1 of intracellular water) when it was incubated in physiological salt solution at 38° C. Furthermore, when the potassium concentration in the physiological salt solution was increased to four times normal, intracellular potassium still failed to reach its in vivo concentration (Barr et al., 1962). Incubation in plasma at 30° C did no more to support the re-establishment of a transmembrane gradient than did incubation in physiological salt solution (Daniel, 1965; Dawkins and Bohr, 1960). The problem involved here hopefully is related to the large number of damaged, nonresponsive, and probably dead cells that exist along the margins of the excised tissue. The failure of these cells to establish a transmembrane gradient would mask the fact that the living cells may, in situ, have normal transmembrane concentration gradients. Unfortunately, mechanical handling does not seem to be the only factor responsible, since after 90 min of perfusion of an intact rat with physiological salt solution, the potassium concentration of the aorta had fallen, and the sodium content had increased, to values similar to those of a rat aorta removed and incubated in an iso-

lated bath for this period of time (Dawkins and Bohr, 1960).

The calcium content of vascular smooth muscle is higher than that of other muscle tissues (Cohen and Stoclet, 1965; Wallach et al., 1964). Isotopic studies indicate that this calcium is present in at least three compartments (Bülbring and Kuriyama, 1963a), one of which is firmly bound (Feis, 1959). The association of the mobility of calcium with contraction and relaxation of vascular smooth muscle strongly implicates this cation as the primary determinant of the mechanical response (Briggs, 1962; Briggs and Melvin, 1961). This dependence of contraction on intracellular calcium concentration together with the observation of an elevated calcium content in arteriolar smooth muscle of the hypertensive animal (Tobian and Chesley, 1966) suggest that an abnormal cellular handling of calcium may be responsible for an increased vascular reactivity in hypertension.

Component Events of a Vascular Contractile Response

Because muscle contraction is not a one-step process, consideration of vascular reactivity requires that the several individual events that normally lead to a change in muscle tension or length be examined. From studies carried out primarily with the larger, more easily approached, skeletal muscle cell, it has been possible to identify four separate but interdependent steps. These are: membrane excitation, conversion of chemical to mechanical energy by the contractile protein, excitation–contraction coupling, and energy metabolism. An alteration in any one of the four may lead to a change in the end result of mechanical activity—either contraction or relaxation. However, a given change in a cell may alter more than one of these events. It becomes difficult to interpret responses in terms of mechanisms involved when this alteration influences individual components of the response in such a way that they have opposite effects on the final contraction. A useful concept is that one component may be rate-limiting and hence have predominant influence in the outcome of the change involved. For example, energy metabolism, excitation–contraction coupling, and the chemomechanical transduction of actomyosin may be operating optimally in a situation in which the membrane is poorly excitable and is limiting contraction. In this type of smooth muscle the first three components named might be changed extensively without altering the observed response, yet a slight change in membrane excitability would alter the response.

Factors Influencing Vascular Reactivity

At the outset, vascular reactivity was described as the ability of vascular smooth muscle to contract or relax, as determined by the intrinsic properties of the vascular smooth-muscle cell. It is now evident that each of four separate components of an over-all contractile response may influence the response from which vascular reactivity is deduced. The unrealistic goal of this section is to characterize the nature of the change in any or all of the four components that may be responsible for a change in vascular reactivity.

The difference between the influence of an environmental change (stimulant or relaxant) and an intrinsic change in vascular smooth muscle (vascular reactivity) may be hard to define. In general, when a specific chemical agent is added to the cell environment and causes contraction or relaxation, it is thought of as an environmental influence. However, if such an environmental change produces a maintained, intrinsic change in the vascular smooth muscle which alters its responsiveness to acute environmental changes, then the chronic influence, such as might be produced by an electrolyte shift or some factor present in plasma, may be said to have produced a change in vascular reactivity.

Electrolytes

One hypothesis which has crystallized within the last five years is that all physiologically significant changes in vascular reactivity initiated by changes in electrolyte composition intracellularly or in the cell's environment or in the concentration gradient between the environment and the inside of the cell, are mediated through a single, final common pathway: an alteration in the concentration of ionized calcium in the environment of the myofilament. Electrolyte changes which cause an increase in this concentration will enhance reactivity, and those which decrease it will depress reactivity. This concentration of ionized calcium is known to determine the level of the active state (contractile activity) of the muscle (Podolsky and Costantin, 1964). The precise and parallel dependence of tension development by the contractile protein on this concentration of calcium has been demonstrated for both skeletal and vascular smooth muscle (Filo et al., 1965).

Granted the concentration of ionized calcium as the final common pathway, an overwhelming wealth of possibilities remain whereby an alteration in any electrolyte might influence this prime mover of the contractile protein. It should be useful to examine these possibilities in the framework of the components of the contractile response.

In the first place, changes in intracellular calcium concentration may be altered through the effects on the membrane of changes in concentrations of various electrolytes. It is not clearly established whether vascular smooth muscle behaves in an all-or-none fashion in response to action potentials, or whether contraction is effected by a specific increase in calcium permeability which permits graded amounts of this ion to reach active sites in the myofilament area. The latter seems hypothetically possible in view of the fact that the physiological concentration of ionized calcium outside the cell is over 1,000 times that necessary to produce a maximum response of the contractile protein. With this enormous difference in concentration between the outside and the inside of the cell, a slight change in membrane permeability to calcium should greatly alter vascular responsiveness. It is probable that an increased concentration of potassium in the environment of the cell is capable of effecting such an increase in membrane permeability to calcium (Waugh, 1962).

If, on the other hand, it is assumed that the primary access of calcium to the myofilament area is by way of processes initiated by action potentials as it is in skeletal muscle (Blanchi, 1961), then there are several aspects of membrane phenomena whose influence, by shifts in electrolyte concentration, may alter the rate of delivery of calcium to the critical area. Sandow et al. (1965) have presented evidence that the extent of active state (and therefore calcium availability to the myofilaments) is a function of both the duration and the extent of depolarization during an action potential. Probably the most evident way in which electrolyte concentration may alter excitability of the membrane and, hence, the ease with which action potentials may be stimulated, is by producing a change in resting membrane potential. If the magnitude of this potential decreases, the threshold for excitation will decrease. Although this reviewer knows of no careful study of the dependence of resting membrane potential on ion gradients in vascular smooth muscle, such studies in other smooth muscles indicate that here, as in most excitable tissue, the primary determinant is the transmembrane concentration gradient of potassium (Burnstock et al., 1963). However, in contrast with the situation in skeletal muscle, sodium concentration gradient also plays a significant role. An increase in the $(Na_o):(Na_i)$ gradient produces depolarization which should increase excitability.

A second membrane phenomenon that is intimately dependent on electrolyte environment and that must be a critical determinant of the reactivity of vascular smooth muscle is its intrinsic pacemaker activity. This activity is clearly evident in vascular smooth muscle in which the excitatory process initiated in the pacemaker is propagated throughout the muscle (Bohr, 1964;

Cuthbert and Sutter, 1964; Johansson and Bohr, 1966; Sparks, 1964), but it may also be an important factor in the tonic responses of vascular smooth muscle that is incapable of cell-to-cell propagation. Here the magnitude of the contraction depends on the frequency of nonsynchronous pacemaker firing of individual units. Interesting antagonistic effects may be evident in a given ionic shift, the direction of change being dependent on whether the determining influence is on membrane depolarization or on pacemaker frequency. Thus, an increase in potassium outside the cell brings about depolarization and thereby an increase in excitability, whereas this same shift by virtue of increasing membrane permeability to potassium causes a slowing of pacemaker activity and relaxation (Johansson and Bohr, 1966). Trautwein (1963) has presented an extensive assessment of the determinants of cardiac pacemaker activity, but no such understanding is available for that of vascular smooth muscle.

A third factor in the relationship of the influence of the membrane on access of calcium ions to the myofilament area is the level of stability of the membrane (Shanes, 1958). Interestingly, calcium itself is the most important physiological stabilizer of membrane excitability. An increase in calcium outside the cell stabilizes the membrane, depressing its excitability. Magnesium has similar effects (Sparks, 1964).

A final membrane property which must play an important role in excitation and, hence, in the amount of calcium gaining access to the myofilaments, is the ease with which the excitatory process is propagated from cell to cell. The greater the number of cells involved in an individual response, the greater will be the vascular reactivity. Since some vascular smooth muscle contains an abundance of intercellular bridges (nexuses) (Dewey and Barr, 1964), a structural basis for propagation exists. However, it is probable that cell-to-cell propagation in this tissue is decremental and highly susceptible to changes in electrolyte environment.

Excitation–Contraction Coupling

The second component of the over-all contractile process is the one most directly related to the access of calcium to the area of the myofilaments. This is excitation–contraction coupling, through which the excitatory events of the cell membrane cause release of sequestered calcium from the membrane or from the sarcoplasmic reticulum. The concentration of calcium in the environment and the amount sequestered have a direct bearing on the amount that can be made available to the myofilaments at the time of membrane excitation. An important determinant of the sequestration of calcium is the activity of

membrane ATPase. This enzyme is influenced by the presence of potassium and sodium, and it is possible that these monovalent cations may in some way compete with calcium for the transport activity of this enzyme.

Protein Contraction and Energy Metabolism

Little can be said about the influence of electrolytes on the other two components of the contractile process. In vascular smooth muscle protein contraction is influenced by total ionic strength and possibly by magnesium in physiological ranges of concentration (Filo et al., 1965). The possibility has been considered that vascular smooth muscle contains an unusual protein, tonoactomyosin (Laszt and Hamoir, 1961), and that the tonic state of the muscle depends on the relation between this protein and the potassium ion concentration. The influence of electrolytes on the energy metabolism of vascular smooth muscle has not been studied.

It may be of interest to cite a final example to emphasize, first, the known role of calcium as a determinant of vascular reactivity, and second, the fact that other electrolytes influence the state of vascular contraction or relaxation through as yet undefined pathways. If vascular smooth muscle is stored at 4° C overnight in physiological salt solution (PSS) so that metabolic activities are stopped, electrolyte distribution then runs downhill (Barr et al., 1962). Intracellular sodium rises, intracellular potassium lowers, and sequestered calcium is released from its traps. If this tissue is immediately transferred from the cold PSS to a warm, oxygenated bath it develops tension which lasts for 20 to 30 sec before commencing a protracted relaxation. The tension development is to be expected because of the presence of calcium in the environment of the myofilaments. The relaxation results from sequestration of this calcium by the active pump system operated by membrane ATPase. If, however, the transfer is made to otherwise normal but potassium-free, warm PSS, the contraction occurs but there is no subsequent relaxation. The absence of relaxation in this case may well reflect the requirement for potassium of the membrane ATPase; in its absence no sequestration of calcium occurs and a fixed tension development persists.

Influence of pH on the Contractile Response

It is probable that each of the four components of the contractile response can be altered by shifts in pH over a physiological range. For the past century, investigators have observed the effects of pH changes on muscle contractility in general and vascular responsiveness in particular. Such studies have found

impetus by the disparity of results, for a given shift in pH may have opposite influences on the individual components of the response; i.e., an increase in $[H^+]$ may increase excitation–contraction coupling while simultaneously decreasing membrane excitability. Nevertheless, a clear consensus has emerged that a shift in pH causes vascular reactivity to change in the same direction. Examples of this generalization are seen in the observation of Carrier et al. (1964a, 1964b) that the decrease in pH from 7.4 to 7.15 is accompanied by a decrease in vascular resistance of an isolated perfused small muscular artery. Tobian et al. (1959) observed a decrease in reactivity to norepinephrine of the isolated rat aorta when pH was shifted over the same range. Bohr and McVaugh (1959) have obtained diametrically opposite results in perfusion studies of the rat hind limb. Responses either to epinephrine or to constrictor concentrations of KCl were enhanced when the pH was reduced over this same range by any of several methods (increasing pCO_2, adding HC, changing phosphate buffer). Present knowledge clearly permits no comfortable interpretation at a mechanistic level, and, from a practical standpoint, we do not know how to manipulate the effect of a given pH change on vascular reactivity. However, under most circumstances, acidosis depresses vascular responsiveness.

Autoregulation

Although it is hardly appropriate to consider autoregulation as a single factor influencing vascular reactivity, the general types of responses involved are relevant and some of them have been demonstrated in the isolated vascular smooth-muscle preparation. The mechanism for the maintenance of constant blood flow despite wide variations in perfusion pressure that has been most studied in this manner is the so-called myogenic mechanism. Here, contraction of vascular smooth muscle occurs in response to an increase in passive tension in the wall. It is reported (Davignon et al., 1965; Somlyo et al., 1966; Sparks, 1964) that smooth muscle of the human umbilical artery contracts in response to quick stretch. Most vascular smooth muscle, however, is unpredictable in this respect. Quite apart from factors involved in the quick-stretch phenomenon, vascular smooth muscle has two characteristics, the combination of which would require that myogenic autoregulation occur in vivo: (1) resistance vessels in situ are partially constricted due to tonic contraction of their vascular smooth muscle, and (2) stretch increases muscular contractility. This basic physiological principle has recently been demonstrated to apply to vascular smooth muscle (Gordon and Nogueira, 1962; Sparks and Bohr, 1962; Speden, 1960). This being true, when a resistance vessel is

stretched by an increase in distending pressure the existing contraction of its smooth muscle must also be increased. Another possibility that has been proposed (Folkow, 1964) is that an increase in tension may elicit an increase in frequency of pacemaker activity of the spontaneous firing of a vascular smooth-muscle cell. Observations on active vascular smooth muscle in the isolated bath have shown that increases in tension are capable of increasing the frequency of spontaneous phasic activity (Johansson and Bohr, 1966; Sutter, 1965).

A second mechanism which may play an important role in autoregulation of blood flow involves the partial pressure of oxygen in the blood. Carrier and associates (1964a, 1964b) have observed that the spontaneous tone of an isolated, blood-perfused, small artery is a direct function of the pO_2 of the perfusing blood. In other studies, it has been found that tension development by the isolated vascular strip in response to stimulation with epinephrine is a direct function of the pO_2, over a range of 0–100 mm Hg (Carrier et al., 1964a, 1964b; Detar and Bohr, 1965). By this possible autoregulatory mechanism an increase in blood flow resulting from an increase in perfusion pressure might increase arteriolar pO_2, enhance the contractility of the vessel, and thereby increase local vascular resistance. It seems unlikely that substrate concentration may be a rate-limiting factor for contraction of vascular smooth muscle. Physiological concentrations and endogenous stores of glucose are well in excess of those which would place any limits on tension development (Coe et al., unpublished observation).

A third mechanism which may maintain a constancy of flow when arterial pressure changes, depends on the production of vasodilator metabolites by the parenchyma surrounding the resistance vessels (Stainsby, 1964). An increase in perfusion pressure initially causes an increase in flow rate; this washes out the vasodilator metabolite so that its concentration and, therefore, its vasodilator efficiency are reduced. Vasoconstriction will result, and blood flow will return toward control levels. CO_2 may well play the role of such a vasodilator metabolite in the brain; adenosine is a likely candidate in the heart (Berne, 1964).

CAPILLARY EXCHANGE

Living tissue has contact with the outside world only by means of the exchange that takes place through the capillary wall. Substances move through this wall by three different processes: (1) bulk flow, or filtration, which carries not only plasma water but also small molecules of solute capable of traversing pores

in the wall. This exchange process is responsible for regulation of distribution of water between intravascular and extravascular compartments; (2) diffusional exchange, which is much more rapid than bulk flow and is the important process for the movement of blood gases across the capillary wall; and (3) pinocytosis, a process for which the electron micrographer has presented extensive evidence, but whose function has not been established. Johnson and Wilson (1966) have recently presented a model of the capillary exchange system and reviewed the mathematical considerations relevant to transcapillary movements.

Capillary Filtration

The factors governing this form of exchange across the capillary wall are the hydrostatic pressures on each side of the wall and the colloid osmotic pressure of the plasma and of the interstitial fluid (Starling, 1896). While Landis (1928) verified the proportionality between the hydrostatic pressure gradient and the outward flow of water in a single capillary, normally only one of the four variables concerned in filtration (i.e., the plasma colloid osmotic pressure) can be measured with any precision. Direct measurements of pressure in a single capillary are not usually possible and if achieved would not be representative of the total capillary bed of that tissue or organ. No direct measurements of the pressure in the tissue spaces are available because of their minute size and the distortion caused by any measuring device (Kitchin, 1963). Guyton (1963) measured the pressure inside a perforated capsule implanted in the tissues of dogs and observed negative tissue-pressure values.

In man, plethysmography has been used to assess the total capillary filtration rates in the limbs. These rates depend on the area available for filtration in addition to the factors outlined above. Two approaches have been used:

1. Changes in limb volume during venous occlusion. The initial increase in volume when the venous outflow is suddenly arrested represents the rate of arterial inflow; when the pressure in the veins reaches the occlusion pressure, venous outflow equals arterial inflow and the subsequent slow increase in limb volume is assumed to be due to filtration into the interstitial space. Sequential filling and delayed compliance of forearm veins contribute in an unknown way to the slow increase in volume; also the effective filtration pressure is unknown, and as soon as filtration starts, tissue pressure increases. The results are therefore difficult to interpret.

2. The volume of the limb is measured with the blood vessels temporarily emptied by external pressure, before and after a

period of venous congestion. The increase in the measured volume is due to increased interstitial fluid and not to variations in blood content (Krogh et al., 1932).

Measurements made in the forearm using these methods indicate that only when there is increased metabolic activity does the capillary filtration rate increase; nervously mediated vasodilatation is reported to decrease the rate (Kitchin, 1963). Increased capillary filtration will occur in areas where intravascular pressures are elevated; the amount filtered will be limited by the compliance of the interstitial tissue spaces. Weightlessness would cause tissue fluid to accumulate in dependent parts.

Increased knowledge of capillary filtration and of the relations of filtration to blood flow will depend upon the development of more precise methods of measurement. Recently, the protein concentration of the capillary filtrate has been measured in cat limbs by an isotope technique to give an estimate of the permeability of the capillary membrane (Appelgren et al., 1966). Wiederhielm (1966) has estimated the filtration rate in occluded capillary segments with a densitometric method; his work indicates that the venous end of the capillary network is more permeable to water than is the arterial end. This permeability gradient provides a safety margin against edema formation by its shift of the capillary fluid balance toward reabsorption. Indicators such as ^{133}Xe, which diffuse freely through all membranes, have provided an additional method to study the behavior of the minute vessels (Lassen et al., 1964). These new developments offer increasing opportunities to evaluate the response of the microcirculation to prolonged space flight.

Weightlessness

The change to a weightless environment causes the relatively sudden loss of gravitational hydrostatic gradients; the only vascular pressures remaining are those produced by body tissues, e.g., myocardial and skeletal muscle, and elastic tissue. Since intra-tissue pressure is much less affected by hydrostatic gradients, little change is expected in this factor during weightlessness; and, since plasma and interstitial osmotic pressures will not be directly affected, the balance of pressure will favor the absorption of interstitial fluid and an initially increased effective blood volume. Compensatory responses moderate and soon reverse this initial effect; simulation and space-flight studies suggest that a new equilibrium condition is reached rapidly with blood volume levels becoming and remaining below normal levels for an indefinite period. The effects of this hypovolemia on regional capillary exchange are uncertain.

Diffusion

The direction, magnitude, and rate of the exchange of small molecules through the capillary wall are determined by (1) transmembrane concentration gradients usually established by tissue metabolism and dependent on rate of blood flow; (2) the size and shape of the molecule; and (3) lipid solubility, related to the oil–water partition coefficient of the substance (see Zierler, 1967).

THE VEINS

In addition to conducting blood back to the right ventricle of the heart, the veins function as a capacitance system. Approximately 70 percent of the systemic blood volume is in the veins. They also form a compliant system which normally has a low internal pressure except in the erect position when the hydrostatic column adds to the pressure in the dependent limbs. The veins contain functional valves that assist propulsion of blood by a muscle-pumping action. As a capacitance system, the veins play an essential part in cardiovascular function by compensating for the effects of gravity on the entire system. Preliminary measurements indicate that, following weightlessness, the peripheral veins may change in their pattern of response to tilt.

Methods of Study

There are two principal methods of studying veins in man, both of which are restricted to the limbs. Pressure–volume curves may be established by occlusion techniques. The basic disadvantage of this method is that other blood vessels may contribute to the volume change. The initial volume is unknown, and there may be a dilation caused by elevated venous pressure. A second method involves the isolation of a vein and measurement of pressure change in an isovolumetric system. This method requires the temporary isolation of a small segment of a vein and the introduction of a needle or catheter. There is a temporary arrest of flow and, as the segment is not perfused, reflex changes only can be studied with time.

The Nervous Control of the Veins

The veins are supplied by sympathetic adrenergic nerve fibers, stimulation of which causes an increase in tension of the smooth

muscle of the vein wall. When the lumbar sympathetic chain is stimulated electrically, the limb veins, like the resistance vessels, constrict at stimulus frequencies of less than one impulse per second, and a maximum response is reached at about 10 impulses per second. Thus, the effector system has the potential of great sensitivity of response to different stimuli.

In man, stimuli causing reflex constriction of the capacity vessels in the limb are muscular exercise, respiratory maneuvers, and emotional stress (Bevegard and Shepherd, 1965). The receptors and afferent pathways are unknown. With exercise, reflex venoconstriction is proportional to the severity of the exercise. If this reflex venoconstriction is widespread, it must aid the muscle pump to maintain the filling pressure of the heart and produce the additional blood needed to fill the expanded systemic vascular bed. Surprisingly, tilting a subject to the 70 percent head-up position does not cause a sustained constriction of the veins in human limbs (Samueloff et al., 1966). A constriction may occur at the moment of tilting, but it is transient and cannot, unlike the reflex constriction of the resistance vessels, be correlated with the shift of blood from the thorax to the legs. Whether the wall tension of the veins in the dependent parts is increased by means of a local myogenic mechanism as a consequence of increased transmural pressure is not determined. A decrease in carotid sinus pressure, which causes reflex constriction of the resistance vessels, is not accompanied by similar reflex changes in venous wall tension. In fact, to this stimulus, there is preferential increase in efferent impulses in the sympathetic adrenergic fibers to the resistance vessels.

Humoral Effects

A component of blood plasma has been shown to be a potent vasoconstrictor (Bohr and Johansson, 1966). This factor has not been isolated, but it apparently has functional significance. Epinephrine and norepinephrine given intravenously also cause constriction of the limb veins in man. While there is evidence from isolated vein studies that the constriction is caused by activation of both alpha and beta receptors, stimulation of the alpha receptors predominates in vitro.

Angiotension given intravenously in animals has no effect on the venous capacitance system, but there is evidence that it causes venoconstriction in the limbs of normal man. Studies of isolated veins demonstrate that the portal veins respond vigorously to angiotension, whereas the renal veins exhibit no response. Its effects on other veins fall between these two extremes.

MECHANORECEPTOR FUNCTIONS

The central nervous system plays a major role in the control and regulation of the cardiovascular system. Nervous-system control involves a feedback loop that begins with the mechanoreceptors embedded in the walls of large vessels such as the carotid sinus and the aortic arch. Mechanoreceptors emit nerve impulses which are transmitted to the central nervous system, whose efferent impulses to the heart and blood vessels take precedence over autonomic nervous-system controls. It is often said that mechanoreceptors control blood pressure; however, it is more accurate to say that they control vessel wall strain and strain rate.

The major aspects of a regulating system are outlined by Peterson (1960). For the purposes of this discussion, they can be summarized as follows:

1. The system that regulates a given function (which must be identified and defined) must contain a mechanism that specifically measures the existing value of the function within the area of regulation.
2. The system must possess "information" on the value to which the function must be held. This is usually the normal or ideal value and is often called the "set" value.
3. The system must possess some mechanism for comparing the existing value with the ideal value in order to determine whether the existing value is too high or too low, i.e., in error.
4. The system must possess mechanisms to dispatch information relating to the degree and sign of the error to machinery that will correct the error.
5. The machinery for correcting the error must, of course, be able to increase and decrease the existing value of the function. These mechanisms control the value of the function.
6. All these mechanisms are related to each other in a "closed loop," so that if the value of the function becomes either greater or less than its set value the error will be corrected.

These attributes tend to keep the value of the function constant. Furthermore, the constancy may be set at various levels as, for example, in fever, body temperature is reset. It should be stressed, however, that constancy itself is not necessarily a result of regulation: a building tends to remain constant in position and structure, yet, if blown over, it will not right itself. Blood pressure will be considered in some detail as an example of a regulated function.

The first characteristic of a regulating system, noted above, states that there must be a measuring device, or in physiological

terminology, a receptor. Thus, if blood pressure is regulated there must be receptors that specifically measure blood pressure. It has long been recognized that the so-called pressure receptors respond to stretch rather than to pressure per se. Thus, if they are effective pressure receptors, then the relationship between blood pressure and receptor activity should be reasonably linear. Many investigators have applied various substances to the carotid sinus wall in attempts to change the stiffness of the wall and thus to alter the relationship between blood pressure and sinus wall strain (Heymans and Von Den Heuvel-Heymans, 1951; Palme, 1944; Landgren, 1952). They have demonstrated that reflex control of blood pressure can be altered by the application of many substances. The question remains, however, whether natural events can alter properties of the carotid sinus wall or whether these findings were pharmacological curiosities.

The second characteristic implies that the nerve impulses passing between the receptors embedded within vessel walls and the central nervous system relate to blood pressure. Item number three suggests that these impulses are in some way integrated with other electrical activity within the central nervous system related to blood pressure levels. Item number four implies that the efferent autonomic nervous activity acting upon the functions of the heart and blood vessels serves to correct any existing error in blood pressure.

Investigations have been made of the relation between stress (pressure) and strain (stretch) in the carotid sinus walls, the electrical response of the receptors to their wall strain, the interaction of receptor activity with other functions of the central nervous system, and the factors that affect arterial tone generally.

Relation of Blood Pressure and Vessel Wall Stretch

Many functions of the vascular system are related to the radii (r) of the blood vessels. For example, resistance to blood flow is a function of r^x, where x may be between 2 and 4. Blood volume is a function of r^2. It has already been noted that the activity of volume and pressure receptors is a function of the radius of the container vessels.

The radius of a vessel is, of course, a function of the distending pressure and the mechanical properties or stiffness of the vessel itself. Indeed, the word "tone" signifies those properties that determine the radius a vessel will assume for a given distending pressure. Conversely, a rigorous definition of those properties would provide a rigorous definition of vascular tone.

Methods have been devised that permit the simultaneous

measurement, in vivo, of distending pressure (P), vessel radius (r), wall thickness (δ), wall elasticity (E), wall viscosity (R), and wall mass (m). These parameters can be equated to give a precise expression for vascular tone (Peterson et al., 1960):

$$P(\frac{r}{\delta}) = E\epsilon + R\frac{d\epsilon}{dt}, \qquad (11)$$

where ϵ is strain. Strain, which is the proportional change in radius, is a function of the radius wall-thickness ratio, and of the wall's elasticity, viscosity, and inertial stiffness. In the time-frequency ranges encountered in the arterial system, mass may be neglected as a factor affecting change in radius as a function of change in pressure.

The water and electrolyte content of the arterial wall is labile and affects the wall's mechanical properties in at least four ways. An increase in water content increases the wall stiffness physically by (a) increasing the wall thickness, (b) decreasing the vessel's internal radius, and (c) as a result of its own noncompressibility. [Equation (11) shows that the radius wall-thickness ratio plays a prominent role in determining wall stiffness. In addition, the decreased lumen will in itself increase resistance to blood flow.] Changes in electrolyte concentration indirectly alter stiffness by (d) affecting the contractility of vascular smooth muscle. These relationships are indicated in Figure 1 (see page 56).

These considerations relate to the regulation of blood pressure as follows:

1. Since the so-called pressure receptors are in fact stretch receptors, the magnitude and rate of stretch will be determined by the elastic and viscous stiffness of the vessel wall within which they are contained, as well as by the pressure and rate of change of pressure within the vessel.

2. Arterial blood pressure is a function both of the mechanical properties of the arterial walls and of the heart's output. The arterial walls affect blood pressure in two related ways: by affecting the resistance to blood flow and by affecting the manner in which the arterial pressure pulse wave becomes distorted as it travels along the arterial system.

3. Any factor(s) that may affect the mechanical properties of the blood-vessel walls will, therefore, affect blood pressure not only by direct action but also by inducing changes in receptor activity.

The Carotid Sinus and Pressure Regulation

As noted above, previous experiments have shown that the application of vasoactive substances to the walls of the carotid

sinus result in reflex alterations of arterial blood pressure. The investigators concluded that either these substances affect the receptors directly or they cause alterations in the stiffness of the sinus wall. After it became possible to differentiate these effects experimentally, studies were conducted in which the intrasinus pressure, the motion of the sinus wall, and the electrical activity of receptors were simultaneously measured.

Afferent information about the cardiovascular system, which is transmitted to the central nervous system via Hering's nerve, is a function of seven factors: (1) geometry of the carotid sinus, (2) elastic modulus of the sinus wall, (3) viscosity of the sinus wall, (4) receptor coefficient (a), (5) receptor coefficient (b), (6) arterial pressure, and (7) rate of change of pressure. This is considerably more than a simple relationship between receptor activity and pressure alone.

The elastic and viscous moduli of the carotid sinus are variable. Application of vasoactive substances to the carotid sinus wall can cause constriction and dilation of the sinus wall as a result of alterations in elastic and viscous moduli. Presumably, these changes are mediated by vascular smooth muscle in the sinus wall. It has been found that such changes occur reflexly. Thus, if the cardiovascular system is stimulated in such a way as to elicit generalized reflex vasoconstriction, the carotid sinus wall shares therein. Such changes in the sinus wall are not due to nonlinear properties of the wall and can be prevented by denervating the sinus wall. Preliminary findings indicate that the generalized alterations in vessel wall water and electrolyte content during hypertension also affect the sinus wall. Studies to date have not indicated that the coefficients (a) and (b) for a given receptor vary significantly. It may be, however, that with age and in conditions not as yet studied the characteristics of the receptors themselves may change.

The rate of change of pressure, which also significantly affects receptor activity, is itself the result of complex factors. The contour of the arterial pulse may be considered to be composed of the sum of a series of sine waves differing in frequency, amplitude, and phase. The fundamental frequency is that of the pulse rate; additional, higher harmonics define the contour of the pressure pulse. It is well known that the contour of the pressure pulse changes as it travels from the root of the aorta toward the periphery. In general, as the pulse travels peripherally it tends to develop a higher pulse pressure and to loose higher-frequency components. This distortion is due essentially to two general phenomena—reflected waves, and to what is called harmonic dispersion and damping. Such dispersion and damping are due to the fact that the transmission velocity of a disturbance in a viscoelastic medium is a function both of the frequency of the disturbance and of the viscoelastic properties of the medium.

Thus, higher-frequency components travel along the arterial tree at a more rapid rate than do those at lower frequencies. In summary, the rate of change of pressure is a function of the temporal pattern of cardiac contraction and of the mechanical properties of the blood and the vessel walls.

Preliminary observations also indicate that the manner in which the neuroelectrical activity in Hering's nerve is introduced into the central nervous system is not simple. Electrodes have been introduced into the solitary tract of the medulla at the site of the entrance of Hering's; they indicate that only a small proportion of the cells in that area fire in sychrone with the receptors. In other works, these cells are intermingled with large numbers of cells whose firing is, at least grossly, unrelated to carotid sinus receptors.

CARDIOPULMONARY REFLEXES

The Gauer-Henry Reflex

The observations of Gauer and Henry (1963) and Gauer et al. (1961) suggest that when blood volume increases, the atrial walls are stretched and receptors in them are activated. It appears that receptors located in the low-pressure side of the circulation could best measure the condition which Peters (1935) called "fullness of the blood stream." These receptors which sense changes in volume, are located mainly in the left atrium and are sensitive to distention of the atrial wall (Gauer et al., 1961). The work of Schaefer (1950), Jarisch and Zotterman (1948), Pearce and Whitteridge (1951), and Paintal (1953) demonstrated that the afferent impulses from these receptors pass over the vagus nerves.

The course of atrial impulses after the vagus nerve has entered the medulla has been studied. Von Baumgarten et al. (1959), and Bonvallet and Sigg (1958) have shown that only the rostral end of the series of rootlets entering the medulla from the jugular and nodose ganglia carry cardiovascular afferents discharging in time with heart beat. By cutting these rootlets it has been shown that degeneration occurs in a small region adjacent to sensory nuclei of the vagus nerve. This region lies at the rostral end of the tractus solitarius and dorsal to it and contains very small nerve cells. Hellner and Von Baumgarten (1961) have been able to record regularly bursts of spikes related to heart rate when microelectrodes were placed in this restricted area. Tracing of the atrial afferents beyond these secondary neurons serving atrial receptors is not complete. According to Gauer and Henry it is believed that the impulses either travel directly or by multisynaptic pathways in the periaqueductal gray to the midbrain limbic region near the nuclei of Gudden

and Bechterew in the central tegmentum. Thence, as Nauta (1958) has shown, there are strong connections with the supraoptic region which control the release of antidiuretic hormone. The final efferent limb of this reflex is not completely known; however, it is suspected that a direct reflex arc is not involved.

Gauer et al. (1954) observed that in dogs negative pressure breathing promoted an increased urine flow that began after about 10 min and reached its peak in 30 to 50 min. Drury et al. (1947) have reported that positive pressure breathing promoted a decrease in urine flow. These observations were confirmed by Sieker and associates (1954) and Hulet and Smith (1959), and it is clear that this effect bears on the excretion of water and that there is no primary effect on the rate of excretion of sodium or other solutes. The response can be blocked with vasopressin, and there is no increase in urine flow while the subject is under maximum water diuresis, and the secretion of ADH is presumably suppressed, as reported by Boylan and Antkowiak (1959) and Murdagh et al. (1959). The antidiuretic response to positive pressure breathing can be partially or completely inhibited with alcohol (Gauer and Henry, 1963). Surtshin and his collaborators (1955) have demonstrated that the diuresis which occurs during negative pressure breathing is not significantly affected by renal denervation. The efferent arm of this reflex seems to be diminished supply of antidiuretic hormone rather than some peripheral neural component.

In assessing the significance of this reflex, the findings of Ledsome and colleagues (1961) should be emphasized. These investigators were not able to find support for the concept that the diuresis induced by stretch of the atrial receptors is due to decreased release of antidiuretic hormone. Further, they observed that the diuretic response to stretch of atrial receptors was small and exceedingly variable. In addition, it was noted that only small increases in the excretion of sodium, potassium, or total urinary solutes occurred. Thus, the basic mechanism of operation of the Gauer-Henry reflex is still open to question, and more investigation is required before an adequate explanation can be offered. Henry et al. (1956) reported that changes in blood volume from -30% to +30% influences pressure concordantly throughout the circulatory system and concluded that stretch receptors in the left atrium could therefore be influenced by changes in volume. It must be emphasized that this reflex only influences the excretion of water.

Findings from the Gemini space flights, reported by Dietlein and Judy (1966), suggest that "the retention of electrolytes and water following re-entry is consistent with the hypothesis that atrial and thoracic stretch receptors are of physiological importance with changes from a condition of one gravity to null

gravity and vice versa. Change from null gravity to an erect position in one gravity would result in a pooling of blood in the lower extremities and an apparent decrease in blood volume as experienced in the atria and thorax." This would produce an increased output of ADH and aldosterone and result in water and electrolyte retention.

In weightlessness the increased volume of blood in the thorax and atria should produce a diuresis by a reversal of the above mechanism. These investigators concluded that their findings are consistent with the assumption that the Gauer-Henry atrial reflex would be activated by the change from weightlessness to the one-gravity environment.

The Bainbridge Reflex

In 1915, Bainbridge observed that a rise in venous pressure produced by infusion of saline solution or blood caused cardiac acceleration partly by reduction of vagal inhibition and partly through stimulation of the accelerator mechanism (see Wiggers, 1949). Several investigators (Ballin and Katz, 1941; Aviado et al., 1951; McCrea and Wiggers, 1933) have failed to confirm the existence of this reflex response. However, recently, evidence has been presented by Kinnison et al. (1965) to confirm the existence of the Bainbridge reflex by experiments in which the selective inflation of balloons in the pulmonary artery, inferior vena cava, and aorta allowed right atrial pressure and aortic pressure to be independently controlled. Increases in right atrial pressure elevated cardiac frequency by an average of 9.6 per minute for each centimeter (water) increase in right atrial pressure. This work was done in the closed-chest, anesthetized animal. The authors suggest that their success is in part due to the intact thoracic receptors. It may also be of interest to study this phenomenon in the unanesthetized animal.

The Bezold-Jarisch Reflex

Almost any condition that irritates the left ventricle is followed by a mild reflex decrease in arterial pressure. For instance, injection of Veratrine into the coronary system, which causes spontaneous firing of nerve fibers in the ventricles, immediately causes bradycardia decrease in arterial pressure and apnea. This reflex is called the Bezold-Jarisch reflex (see Guyton, 1966). Paintal proved that the drug powerfully excited ventricular and atrial receptors. This finding suggests that the Bezold-Jarisch reflex is an abnormal manifestation of the potency of cardiac receptors in promoting a reflex bradycardia and hypotension (Wright, 1961).

THE AUTONOMIC NERVOUS SYSTEM AND CARDIOVASCULAR FUNCTION

Classically the autonomic nervous system includes the hypothalmus and the sympathetic and parasympathetic nervous systems. Since, however, the central nervous system as a whole participates in the control of the cardiovascular system, the circulatory physiologist is tempted to define a "functional" autonomic nervous system: the sum total of all those pathways in the central and peripheral nervous system that are involved in the autonomic and reflex adjustment of the heart and blood vessels. Most reflexes that regulate vasomotor and cardiac function involve participation of the cortex, hypothalamus, medulla, and outlying ganglia and spinal cord. Several excellent reviews on the subject of control of the circulation (Eichna and McQuarrie, 1960; Folkow, 1955; Rushmer and Smith, 1959) attest to the difficulty of separating aspects that are controlled by the autonomic nervous system from those that are not. The primary channels through which the central nervous system exerts influence on the heart and blood vessels have been suggested by Bard (1960) to be the following autonomic outflows:

"(a) The widely distributed sympathetic is a vasoconstrictor fiber, a certain proportion of which are tonically active (i.e., are discharging nerve impulses) at bodily rest;

"(b) the sympathetic and parasympathetic innervations of the heart, both of which are tonically active under basal conditions;

"(c) sympathetic vasodilator cholinergic fibers to the vasculature of the skeletal muscles;

"(d) the sympathetic preganglionic (cholinergic) innervation of the adrenal medulla, whose output of catecholamines can and does influence the cardiac and smooth musculatures of the circulatory system;

"(e) secretomotor fibers which, in activating the salivary gland, the sweat glands, and possibly other glands, indirectly bring about local vasodilation through the formation of bradykinin."

Cortical Regulation of Cardiovascular Function

A number of investigations have been reported that deal with cortically evoked cardiovascular responses in humans. These have added greatly to our knowledge of the subject, since most earlier information was derived from animal studies in both anesthetized and unanesthetized preparations.

It was shown in 1939 (see Hoff, 1950) that electrical stimulation of the prefrontal lobes can cause significant hypertension

in a patient undergoing surgery for removal of a brain tumor. Chapman and associates (1949; 1950a; 1950b; 1960) have shown that increases in arterial pressure and changes in heart rate can be induced by stimulation of selected cortical areas. Of interest is their finding that electrical stimulation of the posterior orbital surface of the frontal lobe caused three types of responses: elevation of systolic and diastolic arterial pressure with little or no change in breathing; partial or complete arrest of respiration in the expiratory phase without change in blood pressure; and elevation of blood pressure together with arrest of respiration during a given stimulus.

In assessing cortical effects on cardiovascular function, it seems most desirable to examine investigations of the effects of cortical stimulation. Superficial and deep surgical implantation of indwelling electrodes has allowed long-term study of the effects of various stimulation programs in the unanesthetized animal and man. With this technique, Hoff et al. (1959) studied the pressor responses elicited by repeated instances of cortical stimulation over periods of 3 to 6 months in cats and dogs. In these experiments, transient pressor responses could be obtained by stimulating loci in the frontal orbital and anterior temporal regions, even when the stimulus threshold was below that necessary to evoke skeletal motor response.

The studies of Delgado and Livingston (1948) and Delgado (1960) have greatly expanded our understanding of the influence of the cerebral cortex on cardiovascular function. They have found areas affecting the cardiovascular system in the top of the frontal lobe, the orbital cortex, the motor and premotor areas, the hidden motor area, the anterior part of the temporal lobe, the insula, and the cingulate gyrus. Their studies have been conducted in unanesthetized man, monkeys, and cats.

Stimulation of some areas slows the heart without causing arrhythmia, while stimulation of other areas such as the subiculum causes ectopic beats. Delgado has shown as well that the pattern of ECG ventricular extrasystoles depends upon the cerebral locus stimulated. It was observed that changes such as pressor responses and ECG changes could be produced without modifications occurring in the EEG. Recently, Hoff et al. (1963) made an extensive review of the studies on cerebral cortical control of cardiovascular function. Some of their conclusions are of interest here. For example, they state, "1) that probably cortical levels exert more specific autonomic control than do diencephalic or mesencephalic levels . . . ," and "2) clinical and experimental studies reveal generalized as well as localized cardiovascular and other autonomic disturbances from cortical and subcortical brain lesions. In experimental animals, stimulation of cerebral loci over prolonged periods of several months through indwelling surgically implanted electrodes has

resulted in enduring pathological changes in the vascular system, with medial hyperplasia and hypertrophy and intimal proliferation in coronary, pulmonary and bone marrow arteries and arterioles. Chronic changes also include alterations in behavior, temporary hypertension, symptomatic polycythemia and myocardial infarcts."

It seems clear that the cerebral cortex can influence the autonomic system independently of the hypothalamus. There apparently are "autonomic projections" from the motor cortex that pass through the pyramids and are concerned with the immediate cardiovascular changes that accompany initiation of muscular activity of cortical origin (Bard, 1960). Wall and Davis (1951) found, for example, that the changes in blood pressure produced by stimulation of either the anterior temporal lobe or the Rolandic area can be abolished by section of the pyramids but are unaffected by destruction of the hypothalamus. These authors in their study of the monkey's cortex concluded that "there exist three systems in the cortex which affect the autonomic system; the sensory motor cortex, the posterior orbital-anterior indula system, and the temporal-cingulate system." It appears further, according to Bard (1960), that the "first and last of these exert their effects over extrahypothalamic paths while cardiovascular effects (but not respiratory) obtained from the second depend on a hypothalamic projection."

Hypothalamus, Amygdala, and Other Subcortical Areas

According to Smith (1965), "the subcortical regions affecting the circulation have direct anatomic connections with these areas concerned with cardiovascular function." He cites extensively from the literature in support of this view.

Although there are several well-defined anatomical connections between the cortex and autonomic subcortical regions, such as the amygdala, hypothalamus, and hippocanpus, very little is known about their functional interactions. Spiegel and Hunsicker (1936) showed a possible relation between the hypothalamus and the posterior orbital cortex and the anterior insula. Their studies revealed that destruction of the hypothalamus abolished the pressor responses to stimulation of these cortical areas.

The importance of subcortical and other areas in cardiovascular function is shown also by the studies of Carroll et al. (1961). Pressor responses, changes in heart rate, and cardiac arrhythmias (including ventricular fibrillation) were produced through stimulation of various loci in the hypothalamus, amygdala, central gray, and von Bechterew's nervis centralis segmenti superior. A number of other studies (Bronk et al., 1940;

Koikegami et al., 1953; Nauta, 1960; Bruno et al., 1961) likewise show the importance of these subcortical areas in cardiovascular function.

Smith and associates (1960) suggested that the hypothalamus may not necessarily be the main coordinating control system for cardiovascular adjustments in animals. They pointed out that "certain diencephalic regions are critical for the emergence of normal cardiovascular adjustment patterns . . . ." The authors emphasized that almost any combination of cardiovascular effects can be produced by stimulating one or another hypothalamic area.

Emotional Behavior, Fear, Anger, and Exercise

The hypothalamus plays an important role in modulating cardiovascular responses, especially in relation to the elaboration of emotional behavior. Its involvement is most readily demonstrable in the cardiovascular responses to fear, anger, anxiety, and exercise. One of the most interesting reports bearing on this observation is that of Heath and Mickle (1960), who reported results of a seven-year study involving the use of depth electrodes in man. Electrodes were implanted and left in place for two-year periods. It was observed that excitation of the rostral hypothalamus caused anxiety, tachycardia, and other clearly autonomic effects. Smith et al. (1960), in animal studies, found that bilateral destructive lesions of the paraventricular area of the hypothalamus prevented the change in heart rate that normal accompanies eating and that the changes in systolic pressure were actually the reverse of normal. In the same animal, the heart-rate response to exercise was not affected while the systolic pressure response was eliminated. Experimental stimulation of some hypothalamic foci (Nakao, 1958) elicits behavior that mimics that displayed by animals subjected to threatening situations. This set of responses reflects the cardiovascular components of the behavioral pattern of fear. According to Nakao (1958) stimulation at other sites produces aggressive reactions similar to those observed in animals angered by natural stimuli or situations.

The most common cardiovascular reactions within this total behavioral picture are changes in heart rate, blood pressure, and cardiac "force of contraction and contractility." All these changes are consistent with Cannon's "fight or flight" concept.

Chapman et al. (1950b) conclude from their studies that the amygdala represents one of the links in a neurophysiological unit involved in autonomic, emotional, and other behavioral states. They found striking increases in blood pressure and heart rate on stimulation of the amygdala region in patients with temporal lobe epilepsy.

Adaptative cardiovascular adjustments occur, however, in situations other than those eliciting fear or anger. Simple muscular exercise, no matter how motivated, is accompanied by prompt adaptive changes in the heart and vascular tree. Rushmer et al. (1960) monitored the cardiovascular response in dogs to treadmill exercise. Electrical stimulation of the diencephalon in the region of the fields of Forel induces cardiovascular changes in dogs which mimic those induced by exercise. When bilateral lesions are inflicted on these same regions, exercise no longer elicits these cardiovascular adjustments.

Brainstem and Midbrain "Centers"

According to Smith (1964) "There is no evidence for (a) critical integrative cardiovascular center between the diencephalon and the medulla oblongata." Responses are, however, produced by stimulation of the brainstem and the pons. Oberholzer (1960) in reviewing this subject concluded "that a) no specific vasomotor bundle can be found at the pontomedullary level, b) electrical stimulation of the reticular formation, especially the lateral, may affect both nerve cells and descending fibers, c) vasodilatorcholinergic fibers may be stimulated in the lateral reticular formation . . . , d) some vasomotor fibers travel in the pyramidal tracts." Thus, responses elicited by stimulation of areas on the midbrain and pons are likely due to excitation of fiber tracts passing through this region of the brain. There are many descending fiber tracts here with efficient circulatory function (Smith, 1964). For example, there are the important midline pathway below the median longitudinal fasciculus which ends in the duomedial inferior olive, a path through the reticular formation, and a fine fiber system in the periventricular gray. There are also important sites of synaptic interaction between inputs into the region from higher centers and incoming information from cardiovascular afferents connected to receptors in the inferior olive and the thoracic regions of the spinal cord. These interactions probably result in the final output to the effector organs (Rushmer et al., 1960).

Medullary Integration and Regulation of Cardiovascular Function

The notion of "centers" of cardiac and vasomotor control in the medulla has recently been attacked by Manning (1964), Manning and Peiss (1960), Peiss (1964), and Smith (1964), and it is not now generally believed that medullary centers provide the main input to the preganglionic neurons supplying the outflow of neural information to the heart and circulatory system. It has not, for example, been possible to demonstrate anatomically large num-

bers of nerve pathways directly from the medulla to the intermediate cell columns in the cord. As a matter of fact, most of the direct input to these cells as indicated by Smith (1964; 1965) comes from the hypothalamus. In addition, it has been suggested that the higher levels of the nervous system may equally serve with the medulla and brainstem as regions of integration and control of cardiac circulatory function. Certainly it appears from the studies of Pitts and Larrabee (1941) that much interaction between the afferent impulses (particularly from the mechanoreceptors and chemoreceptors located in the aortic arch, along the common carotids, and in the carotid sinus region) and the efferent impulses from higher levels of the brain occurs at the medullary level.

Nervous Control of Cardiac Function

The final pathways by which the central nervous system affects cardiac control involve two inputs into the heart, one chemical or humoral and the other neural. The former input is indirect; it results from increases in circulating humors such as catecholamines, cholinergic substances, angiotensins, various hormones, and other substances produced in areas remote from the heart. The latter input to the heart is autonomic and consists of sympathetic innervation and parasympathetic innervation through the vagus nerve. The sympathetic effects on myocardial function are ultimately due to changes in myocardial catecholamine concentration, as previously described by Hawthorne and Ison (1965).

The importance of the vagus in control of cardiac function is best described by Braunwald (1966): "It is well known that increases in vagal tone cause slowing of the heart and decrease conduction. Furthermore, the recent studies of Levy et al. (1966) strongly support the view that change in vagal activity is not solely concerned with change in heart rate but as well depressed myocardial contractility, and thus, in effect antagonize the ventricular myocardial effects of sympathetic nerve stimulation."

The central nervous system appears to modulate ventricular performance in animals from moment to moment chiefly through changes in heart rate. Recordings made from unanesthetized dogs suggest the variety of changes in cardiac dimensional and aortic pressure that can occur as a result of the changes in inputs from the central nervous system to the heart and systemic circulation.

THE ADRENAL MEDULLAE

The secreting cells of the adrenal medullae are pheochromocytes or modified ganglion cells. They are innervated by preganglionic fibers of the sympathetic nervous system. Under normal resting conditions, tonic low-frequency (1–5 impulses/sec) stimulation of the adrenal medullae results in rates of secretion of approximately 0.2μg/kilo/min of norepinephrine and approximately 0.07 μg/kilo/min of epinephrine into the general circulation. Release of these hormones into the blood contributes to the plasma catecholamine concentration, which is also established by the "spill over" into the blood of norepinephrine produced as a result of general adrenergic sympathetic nerve activity. Stimulation of the splanchnic nerves to the adrenals causes a marked increase in the amount of hormone released, while section of the splanchnic nerves is said to abolish secretion. The rate of adrenal medullary secretion of the epinephrines is controlled by the central nervous system at cortical, hypothalamic, and medullary levels. The studies of Ferguson and colleagues (1957) showed that threshold stimuli on the cortex produced an increase in adrenal medullary secretion of the order of 0.2 to 0.4 μg/min, whereas stimulation of the hypothalamus frequently resulted in secretion rates of more than ten times this amount. Stimulation of loci in the medulla oblongata have been shown to produce even greater effects than hypothalamic stimulation. Areas of the cortex, such as the anteriomedial part of the orbital surface of the cerebral cortex in cats, have been shown by Folkow and Von Euler (1954; Von Euler and Folkow, 1958) to selectively decrease epinephrine secretion by the adrenal medulla.

Despite considerable evidence for central nervous control of adrenal medullary secretion of the epinephrines, Von Euler and Folkow assert that adrenal medullary secretion does not normally appear to play a major role in vasomotor control of autonomic effector cells, especially when activated at low stimulation rates, a view previously presented by Celander (1954).

Epinephrine, however, profoundly affects liver metabolism and skeletal muscle cells and also appears to have definite arousal effects on the central nervous system and an action on mental function: evidence suggests that hypoglycemia specifically and almost exclusively affects the secretion of epinephrine by the adrenal medullae (Gaunt et al., 1949). This suggests that factors other than sympathetic nerve stimulation play a role in adrenal medullary function.

Stimulation of the carotid sinus mechanoreceptors alters the input of sympathetic impulses to the adrenal medullae. Lowering of endosinal pressure causes, reflexly, an increase in adrenal sympathetic nerve activity, while raising endosinal

pressure causes the reverse effect. Astronauts under the weightless conditions of space flight are deprived of the $+G_Z$ effect of the 1-G environment of earth. As a result, especially during extended rest periods, their endosinal pressures will be higher (by approximately 20 to 25 mm Hg) when compared with man in the head-up position on Earth. This should result in a significant reduction of the tonic sympathetic activity of the nerves supplying the astronauts' adrenal medullae and therefore a decrease in the adrenal secretion of epinephrine and norepinephrine.

It is not known just what effects chronic absence of tonic sympathetic stimulation would have on the adrenal medullary tissue. A study of the effects of denervation on adrenal medullae function seems indicated.

THE RENIN–ALDOSTERONE–ELECTROLYTE (RAE) CONTROL LOOP

The closed loop involving endocrine secretions of the kidney and adrenal cortex, and electrolyte metabolism, is important in regulation of the cardiovascular system. The three major variables of this loop are the renin–angiotensin system from the kidney, aldosterone from the adrenal cortex, and electrolyte concentration and distribution.

Renin Regulation

Extensive evidence suggests that cardiovascular dynamics also has a direct controlling influence on this closed loop. This evidence has been reviewed by Skinner and associates (1964) and supported by their observation that the secretion of renin by the kidney varies inversely with renal arterial pressure. They propose renal baroreceptor as a sensing system for the regulation of renin release. Vander and Miller (1964) similarly found that renin secretion by the kidney into the renal vein increases when renal arterial pressure is reduced to 90 mm Hg or less by tightening a clamp on the renal artery. They also observed that this clamping resulted in a decrease in sodium excretion in the urine. This latter observation raised the question of whether renin secretion occurs as a response to the fall in arterial pressure (baroregulated) or to the secondary decrease in sodium excretion. To answer this question, they repeated the clamping procedures during osmotic and chlorothiaziels-induced diuresis which maintained the sodium excretion. Under maintained sodium excretion, the renal artery clamping and the consequent fall in renal artery pressure failed to cause a renin release. From these and other confirmatory observations it may be concluded

that renin secretion is not controlled by blood pressure directly but by the flow or composition of intratubular fluid. Sodium appears to be the most important element forcing the sensing system that probably resides in the macula densa of the distal tubules. A decrease in sodium excretion through this tubule causes an increase in renin secretion by the nearby juxtaglomerular apparatus surrounding the afferent arterioles. Renal arterial pressure is an indirect determinant of renin secretion in that it can influence glomerular filtration and hence the rate of sodium excretion through the distal tubule. Recent studies suggest that the sodium-sensing, renin-secreting system may be neurogenically regulated (Brubacher and Vander, 1966).

Angiotensin Formation

The enzyme renin hydrolizes angiotensinogen, an alpha-2-globulin normally present in the plasma, to yield a decapeptide angiotensin I. A converting enzyme present in both plasma and tissues then splits two amino acids from angiotensin I to yield the active octapeptide, angiotensin II. Normally renin is the rate-limiting variable for the production of angiotensin II. Under abnormal conditions, however, the concentrations of angiotensinogen may be important. In liver disease its concentration falls, and when hydrolisis by renin is impaired, angiotensinogen may reach 4 to 15 times its normal concentration.

Aldosterone Regulation

Aldosterone is secreted by the zona glomerulosa of the adrenal cortex. In reviewing the control systems for aldosterone, Davis et al. (1966) stress that angiotensin is the most potent stimulus for its secretion. Sodium and potassium concentrations in the plasma may play a minor role in aldosterone secretion, and ACTH appears to be "supportive" but not essential.

The loop of this control system is closed by the sodium-retaining action of aldosterone in the renal tubules. As the amount of sodium in the body builds up, a level will be reached where any more will spill over into the distal tubule. This increase in sodium excretion, acting via the macula densa, will reduce renin secretion, initiating a negative feedback system for aldosterone secretion.

Stress Factors of Space Flight on RAE Loop

If, as is believed, the most common physiological stimulus to renin production is the erect position, i.e., +1 G_Z, alterations

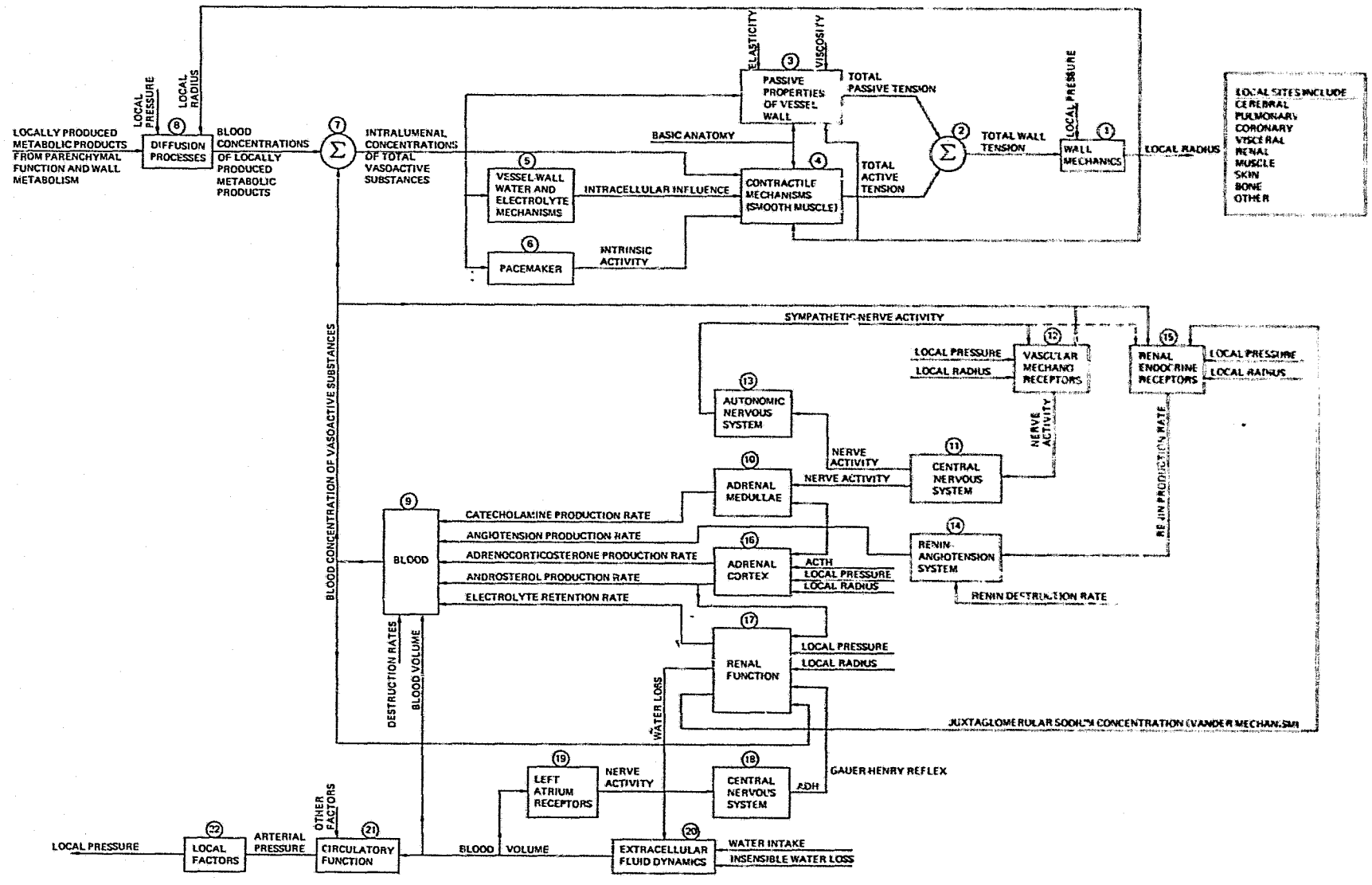

FIGURE 1. Regulation of vascular radius.

in gravitational forces encountered transiently at lift-off and re-entry and during weightlessness will be stress factors, or "forcing functions," on this control loop.

In connection with the increase in renin that occurs on Earth in the erect position, it is interesting to note that it takes place in the face of an increase in renal artery pressure brought about by the hydrostatic column between the level of the heart and that of the kidney, which adds 40 mm Hg to the distal pressure at the kidney. Yet there is no increase in renal blood flow nor in glomerular filtration rate. This argues that neurogenic and myogenic control systems have effectively constricted renal resistance vessels to compensate for the increase in renal artery pressure. In view of the current hypothesis that the regulation of renin secretion is dependent on sodium in the distal tubule, it may be inferred that this renal vasoconstriction has reduced sodium excretion in the urine. The absence of +1 G_Z during weightlessness should remove this common stimulus for renin release. Therefore, it is possible that the entire loop may be reset at a lower level resulting in a decrease in aldosterone secretion by the adrenal cortex and an increase in sodium loss.

Another forcing function of space travel that deserves consideration in this control loop is emotional stress; it may well have an opposite effect to that of weightlessness. Renal vasoconstriction resulting from emotional stress would be expected to increase renin secretion and hence aldosterone secretion and salt retention.

Investigation of the RAE Loop in Space

Methods are available for monitoring all three variables of this closed loop. Renin and aldosterone assays are reliable but difficult (Skinner et al., 1964; Vander and Miller, 1964; Davis et al., 1966), and sodium balance studies can best define the electrolyte variable. These direct measurements should do much to determine the level of activity of the RAE loop in man subjected to weightlessness.

If, as has been proposed, the level of activity of this loop is low during weightlessness it would be relevant to determine whether the responsiveness of the system to known stimuli is altered during short and long exposures, and whether the loop develops a "disuse atrophy." Two simple stimuli whose normal response could be quantified and compared with responses under protracted weightlessness are lower body negative pressure and sodium-free diet (Brubacher and Vander, 1966).

To illustrate how the systems approach can be useful, the factors governing the regulation of the vascular radii of various areas of the circulation are summarized in Figure 1. The radius

of an individual vessel (local radius) is determined by the law of Laplace, which depends upon total wall tension and local pressure (block number 1). Total wall tension is the sum of total passive tension and total active tension as shown by block number 2 (Σ). Block number 3 (passive properties of vessel wall) shows that the total passive tension is determined by the basic anatomy of the vessel, its elasticity, its viscosity, the intraluminal concentration of vasoactive substances, and the radius of the vessel itself. The total active tension, as shown by block number 4 (contractile mechanisms), is determined by the basic anatomy of the vessel, the intraluminal concentrations of vasoactive substances, the intracellular influence of water and electrolytes, and the intrinsic activity of the smooth muscle. Block number 5 (vessel-wall water and electrolyte mechanisms) shows that the intracellular influence of water and electrolytes is dependent upon the intraluminal concentrations. Block number 6 (pacemaker) shows that the intrinsic activity of smooth muscle is determined by the intraluminal concentrations of vasoactive substances. The intraluminal concentrations of vasoactive substances, as shown by block number 7 (Σ), result from the sum of the blood concentrations of locally produced metabolic products and the blood concentrations of vasoactive substances. The blood concentrations of locally produced metabolic products, as shown by block number 8 (diffusion processes), are determined by the rate of production of these products by parenchymal function and wall metabolism, the local pressure, and the local radius. The radius and pressure are important to the diffusion process because they determine the rate of blood flow through the vessel.

Vasoactive substances in the blood consist of catecholamines, angiotensin, adrenocorticosterone, androsterol, and various electrolytes. The concentrations of these substances in the blood, as shown by block number 9 (blood), are dependent upon their production and destruction rates and the blood volume according to the formula

$$\text{concentration} = \frac{1}{\text{blood volume}} \int (\text{production rate} - \text{destruction rate})\,dt.$$

Catecholamine production rate is determined by nerve activity produced by the central nervous system and by the angiotensin production rate as shown by block number 10 (adrenal medullae). The nerve activity from the central nervous system is produced by nerve activity of the vascular mechanoreceptors as shown by block number 11 (central nervous system). Block number 12 (vascular mechanoreceptors) shows that this nerve activity is produced by sympathetic nerve activity, the blood concentrations of vasoactive substances, the local pressure, and the local radius; these latter two determining the blood flow to the receptors.

Block number 13 (autonomic nervous system) shows that sympathetic nerve activity is determined by the action of the central nervous system on the autonomic nervous system. The angiotensin production rate is determined by the renin production and destruction rates as shown by block number 14 (renin–angiotensin system). Block number 15 (renal–endocrine receptors) shows that the renin production rate is determined by the blood concentration of vasoactive substances, the juxtaglomerular sodium concentration, and possibly sympathetic nerve activity. The local pressure and local radius determine the blood flow to these receptors. Block number 16 (adrenal cortex) shows that the adrenocorticosterone and androsterol production rates are determined by the ACTH production rate, the angiotensin production rate, the local pressure, and the local radius. Block number 17 (renal function) shows that the electrolyte retention rate, the rate of water loss, and the juxtaglomerular sodium concentration are determined by the androsterol production rate, the local pressure, the local radius, the ADH production rate, and the blood concentrations of vasoactive substances. The ADH production rate is determined by the nerve activity from the central nervous system as shown by block number 18 (central nervous system). Block number 19 (left atrial receptors) shows that the nerve activity from these receptors is determined by the blood volume (actually the pressure in the left atrium resulting from the blood volume). Block number 20 (extracellular fluid dynamics) shows that blood volume is determined by the sum of water loss by the kidneys, water intake, and insensible water loss. The blood volume is therefore determined as follows. Changes in blood volume alter the pressure in the left atrium to produce nerve activity which acts on the central nervous system to cause alteration of the secretion rate of ADH, and thereby the rate of water loss by the kidney. The blood volume along with other factors then acts through various aspects of circulatory function (block number 21) to produce the arterial pressure. Arterial pressure then acts through local factors (block number 22) to produce the local pressure.

This systems diagram and the preceding discussion have dealt with the factors regulating the vascular radii of various areas of circulation. Systems diagrams for the regulation of splanchnic blood flow, regulation of blood volume, and regulation of cardiac output will be presented in Chapters 4 and 5.

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4

CONTROL AND REGULATION OF ORGAN CIRCULATION

INTRODUCTION

This chapter examines circulation to individual vascular beds in terms of the relative importances of perfusion pressure and of nervous, humoral, and metabolic factors in determining the blood flow. The role, direct and reflex, normally played by gravity in determining the caliber and responsiveness of the resistance and capacity vessels is described, and attention is directed to changes that may result from prolonged space flight.

In the weightless state, the distribution of blood and gas within the lung becomes optimal and the possibility of atelectasis is at a minimum. Since sympathetic nerves have, at most, a minor influence in the control of the pulmonary vessels, a reduction in their activity during space flight is expected to have small effect. In a 1-G environment, systemic arterial blood pressure is maintained in supine man by reflex constriction of the resistance blood vessels in the muscle, kidney, and splanchnic region. This reflex is not activated in the weightless state; if as a consequence of prolonged weightlessness it becomes hypofunctional, systemic arterial blood pressure will decrease when the subject is again exposed to gravity. The brain circulation which can only compensate for modest changes in perfusion pressure will decrease below a critical level, and loss of consciousness will follow.

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Numerous stimuli, other than those initiated by gravitational changes, activate autonomic efferent fibers to the heart and blood vessels. Some of the stimuli, such as exercise and emotions, could be evoked at intervals during space flight to maintain normal function of the autonomic nervous system. This chapter illustrates the need to integrate present knowledge of cardiovascular regulatory systems and to plan experiments to study the consequences of prolonged weightlessness on the patterns of response of the nervous system to known stimuli.

CEREBRAL CIRCULATION

The cerebral vascular bed and its blood stream constitute a support system whose function is to provide the brain with a continuous supply of nutrients (mainly glucose and oxygen) and to dissipate the products of metabolism (heat, carbon dioxide, etc.) with sufficient rapidity to allow neuronal function.

Because the retina is a direct extension of the brain, and because its physiologic functions so closely resembly those of the brain, these two structures will be discussed together. The vestibular apparatus derives its blood supply from vessels that supply the brain, so its blood supply will also be considered here. The features of vascular anatomy and blood flow to the brain, retina, and vestibular apparatus which relate to factors that may be encountered in space flight are sketched.

Cerebral Anatomy of Importance in Space Flight

Arteries

In contrast with the two external carotid arteries which divide into numerous branches soon after they arise, the two internal carotid arteries ascend without significant branching through the neck into the skull to the level of the cavernous sinus. They then give rise to the ophthalmic arteries which supply the structures within the eye. The central retinal arteries, which branch from the ophthalmic, supply the retina. The internal carotid arteries anastomose with the vertebral–basilar system via the posterior communicating arteries. Soon thereafter the carotids end by dividing into the anterior and middle cerebral arteries which perfuse a large portion of the cerebral hemispheres.

The two vertebral arteries, one on either side, usually arise as the first branches of the subclavian arteries in the root of the neck. They enter osseous and ligamentous canals that lie within the transverse processes of the upper six cervical vertebrae and which also contain vertebral veins and sympathetic

nerves. The vertebral arteries join to form the basilar artery within the skull at the pontomedullary junction. The basilar artery ascends to the level of the midbrain, where it ends by dividing into the two posterior cerebral arteries. The vertebral basilar system supplies the "vital" areas of the brain, such as the upper spinal cord, the entire brain stem, the cerebellum, part of the hypothalamus and thalamus, and the medial temporal and occipital lobes of the cerebrum. The vertebral or basilar arteries, or one of their branches, also give rise to the internal auditory artery which supplies the cochlear and vestibular apparatus.

Anatomical variations occur frequently in the cerebral arteries and can affect the functioning of the compensatory mechanisms that regulate cerebral blood flow. Some of the variations that could produce adverse effects in space flight are:

1. There may be anomalous arrangements of the vertebral arteries or of the structures at the root of the neck, such as fibrous bands or aberrant muscles that press on the arteries when the head or arms are placed in certain positions (Patel and Toole, 1965).

2. The configuration of the vertebral arteries in relation to the atlas and the axis is such that rotation of the head may compress one or both of them (Janeway et al., 1966).

3. One of the vertebral arteries may be hypoplastic or, occasionally, absent so that the structures supplied by the vertebral-basilar system are dependent upon one artery rather than two, thereby limiting reserve capacity.

4. The circle of Willis may be inadequate for shunting blood from the vertebral-basilar to the carotid system or from one carotid to the other (Toole, 1966).

5. Because the ophthalmic artery is a branch of the internal carotid artery, vision may be affected by factors that influence carotid artery pressure or flow.

6. Because the vertebral-basilar system supplies the vestibular and cochlear apparatus, factors that affect pressure or flow in this system may also affect cochlear and labyrinthine function.

Veins

Drainage of blood from the brain is carried out by two systems of veins, one deep, the other superficial. Both empty into the dural sinuses which are noncollapsible. The dural sinuses usually join at the confluens sinuum, then separate and continue bilaterally as the transverse and sigmoid sinuses, leaving the skull via the jugular foramen. There they form the internal jugular veins which descend through the neck. The internal jugular veins are collapsible, and venous pressure may or may not be subatmospheric depending upon hydrostatic effects and the phase of respiration.

Cerebral Vascular Physiology Relevant to Space Flight

The brain consists of about 60 percent gray matter and 40 percent white matter. Gray matter receives approximately three times more blood than the white, and the metabolic requirements of gray matter are estimated to be three to eight times greater than those of the white. Metabolic activity varies in different cellular groups within the gray matter. For example, lamina 3, 4, and 5 of the cerebral cortex have a far greater blood supply and metabolic requirement than layers 1, 2, and 6. The red nucleus of the midbrain has an unusually rich blood supply and indeed derives its name from this observation.

Current techniques for measuring blood flow in the human brain can estimate over-all flow, but almost none of them can estimate the flow in any of the subdivisions of the brain (Lassen, 1959; Kety, 1961; Hedlund, 1965). Investigators using the Kety-Schmidt technique or one of its modifications have determined average brain blood flow to be approximately 52 ml per 100 g of tissue per minute. If calculated on the basis of an average brain weighing 1,400 g in a young healthy adult resting in a supine position, total flow is estimated to be about 750 ml per minute. Using other techniques, investigators have obtained results ranging to 1,200 ml of blood per minute to the brain (McHenry, 1966).

In most normal people, brain blood flow can be reduced by 20–30 percent before detectable impairment of cerebral function occurs. Mild exercise decreases the proportion of cardiac output which the brain receives and also causes a slight decrease in total brain blood flow, perhaps because of hypocapnia. During sleep, brain blood flow increases slightly, perhaps because of hypoventilation and hypercapnia. However, provided that the rate of change is not too rapid and that the compensatory limits of cerebrovascular autoregulation are not exceeded, anxiety or change in systemic arterial blood pressure is not accompanied by a change in the brain blood flow.

Tilting the body into the head-up position causes no decrease in brain blood flow when measured at 20°, but in the 65° head-up position, brain blood flow has been found to decrease to about 80 percent of that in the recumbent position. This has been considered by some to be secondary to increased ventilation which reduces pCO_2 and by others to be a hydrostatic effect (Shenkin et al., 1949; Sheinberg and Stead, 1949; Patterson and Cannon, 1951; Patterson and Warren, 1952; Kleinerman and Sancetta, 1955; Eckenhoff et al., 1963). Whether this decrease in brain flow is maintained for long periods of time is not known.

Blood flow through each internal carotid artery has been found to average 400 ml per minute and between 50 and 100 ml through each vertebral artery in a small number of anesthetized supine human beings (Hardesty, 1960; Hardesty et al., 1963). No

simultaneous measurements of flow through both internal carotid arteries and both vertebral arteries have been made in man.

The mean arterial pressure of the cerebral branches of the carotid in normal recumbent man is about 90–100 mm Hg (Carlyle and Grayson, 1955). Effective pressure in the ophthalmic artery is reduced to 70–80 mm Hg by the constant 16–20 mm Hg intraocular pressure. Consequently, when pressure in the carotid system is reduced, retinal perfusion is affected first. Peripheral vision fades when the mean arterial pressure of the ophthalmic artery falls rapidly to about 40 mm Hg. Blindness occurs at 20 mm Hg (Duane, 1954; Duane et al., 1963).

In space flight, the stresses that may affect brain blood flow are anticipated to be the following:

Preflight Emotional stress causing hyperventilation and consequent reduction of arterial CO_2 could result in a decrease in brain blood flow (Gotoh et al., 1965).

Lift-off A decrease in brain blood flow could result from hyperventilation due to excitement and from the superimposed effects of acceleration in the $+G_X$ axis, or in a vector of the $+G_Z$ axis, depending on the position of the head and the body (McNutt et al., 1963; Sem-Jacobsen and Sem-Jacobsen, 1963). Retinal blood flow would tend to decrease most in the $+G_X$ axis.

In-flight Weightlessness has not had recognizable effects on brain blood flow. Astronauts have felt fullness in the head, which has been attributed to decreased venous return, but there has been no visible fullness in the jugular veins. Possible effects of prolonged weightlessness have not been assessed (Kety et al., 1948).

Re-entry The effects of re-entry on cerebral circulation are similar to those at lift-off but would probably be more severe if deconditioning were present.

Postflight Deconditioning of the cardiovascular system during prolonged weightlessness may result in great reduction in cerebral perfusion pressure on standing erect in a gravity environment. Upon assumption of the upright position, pooling of blood may cause cerebral perfusion to fall below tolerable levels causing loss of consciousness (Weissler and Warren, 1959). The effects of cardiovascular deconditioning upon the cerebral circulation may be pronounced, and one might anticipate deconditioning of the cerebral vascular bed as well. Reconditioning of the cardiovascular system would allow the compensatory mechanisms that regulate cerebral blood flow to reassert themselves, and no long-term effects are anticipated.

Variables Affecting Brain Blood Flow

Flow of blood through different portions of the cerebral vascular bed is adjusted continuously to meet the metabolic needs of the brain (Lassen, 1964). This autoregulation is thought to occur at the arteriovenous level and to be related, principally, to the following seven factors: aortocranial arterial pressure, jugular venous pressure, cerebrospinal fluid pressure, carbon dioxide content of blood, oxygen content of blood, glucose content of blood, and nerve supply of cerebral arteries.

Aortocranial Arterial Pressure When arterial pressure is reduced, the cerebral resistance vessels dilate and, conversely, when pressure increases, the vessels become smaller. If blood pressure decreases rapidly, compensatory dilation of the cerebral vessels may not occur quickly enough to prevent loss of consciousness.

Jugular Venous Pressure In human beings whose jugular-venous return has been obstructed, increased intracranial pressure has sometimes developed and has resulted in papilledema and cerebral edema.

Cerebrospinal Fluid One of the functions of the cerebrospinal fluid is to minimize the hydrostatic effects of gravity on the arterial and venous columns of blood.

Carbon Dioxide The cerebral and retinal vascular beds are exquisitely sensitive to arterial pCO_2 (Woodbury and Karler, 1960). Reduction in level of arterial pCO_2 is accompanied by constriction of the vascular bed and decrease in cerebral blood flow. Levels may fall to the point where neuronal activity is impaired, as evidenced by changes in the electroencephalogram, by loss of consciousness, and, in some instances, by convulsions. This is described clinically as the hyperventilation syndrome.

Elevation of arterial pCO_2, as it occurs in pulmonary disease or in breathing atmospheres rich in carbon dixoide, results in remarkable increases in over-all cerebral blood flow. If very high levels of arterial pCO_2 are sustained, intracranial pressure may increase to the point where brain function is impaired, progressing from euphoria to stupor or coma, and ending in cerebral edema. Such problems would arise in space flight only in the event of a systems failure.

Oxygen The healthy adult brain consumes about 3.5 ml of oxygen per 100 g of tissue per minute. This approximates 50 ml per min for the entire brain or 20 percent of the total oxygen

consumed by the resting body (Lambertsen, 1965). Retinal oxygen requirement is thought to be about 8 ml per 100 g of tissue per minute (Hickam and Frayser, 1966). Under normal circumstances, total oxygen requirements of the brain remain unchanged during sleep, wakefulness, and, so far as can be determined, during intellectual activity. Local oxygen requirements of areas within the brain during neuronal activity have never been determined in man. Fear, convulsion, epinephrine infusion, and extreme anxiety increase the brain's oxygen requirements. Hypothermia and hypothyroidism decrease oxygen consumption. The brain and retinal requirements for oxygen should remain fairly constant throughout long space flight. Barring failure of the life support system, no problems are anticipated.

Limits of tolerance to hyperoxia or hypoxia are narrow (Behnke et al., 1935; Donald, 1947; Ohlsson, 1947; DuBois, 1962; Dunn, 1962; Michel et al., 1965). Tolerance is affected to a certain degree by the level of carbon dioxide and glucose in the blood and tissue. Neither brain nor retina has a reserve supply of oxygen nor will they function anaerobically. Consequently, if the oxygen supply is interrupted, impairment of perceptual and intellectual functions is noticeable within 5 to 6 sec. These effects progress to blindness and unconsciousness within 15 sec. There then ensues a variable interval of up to 30 min before neuronal death occurs. Cellular death does not occur simultaneously at all neuronal levels: cells having the highest metabolic rates die soonest. If consciousness is restored, there may be permanent impairment of perceptual and intellectual performance.

Glucose Requirements Both brain and retina have a respiratory quotient of about 1 and are almost totally dependent upon glucose metabolism (Hickam and Frayser, 1966). Brain utilization of glucose is about 5.5 mg per 100 g of tissue per minute or about 80 mg per min. Those requirements are not expected to alter during space flight.

Nerve Supply of Cerebral Arteries Although there is a rich supply of sympathetic and parasympathetic nerves to the cerebral arteries (Fang, 1961), their purpose is much debated. Some investigators believe that these nerves are functionless because stellate ganglion block in the healthy adult or in patients suffering with atherosclerotic forms of cerebral vascular disease has had no measurable effect on cerebral blood flow as measured by the Kety-Schmidt technique. These studies, however, are inconclusive, for they do not necessarily measure blood flow in a situation in which the arteries are able to respond to nerve stimulation (Krog, 1964). With regard to autoregulation of the brain vessels, it seems that the nervous supply has little, if

any, effect and that autoregulation is largely under the control of myogenic reflexes which lie within the vessels themselves. The question of function of the sympathetic and parasympathetic nerves to the brain arteries must thus remain open.

Among the vascular reflexes relevant to cerebral circulation during space flight are the oculocardiac reflex, which may result in changes in cardiac rate or rhythm and loss of consciousness, and the carotid sinus reflex (Gurdjian et al., 1958; Toole, 1959; Silverstein et al., 1960; Lown and Levine, 1961). The carotid sinus reflex plays a part in controlling cerebral blood flow by initiating reflex response to changes in carotid artery pressure. Its effector pathway travels vagal and sympathetic outflow tracts. Some investigators believe that it also induces direct intracranial reflex responses. The carotid sinus reflex should not pose difficulties during space flight unless high levels of $-G_z$ were encountered.

Recommendations

1. Physical examinations for the selection of astronauts have not included detailed examination for anomalies or disease within the cerebral-vascular tree. Auscultation of the head and the neck for the presence of murmurs has not been carried out, nor has determination of the sensitivity of the oculocardiac or carotid sinus reflexes, nor measurement of the retinal artery pressure. These examinations are probably not necessary for short-duration flights. For long-term flights, however, such anomalies could be a basis for disqualification. Data from these examinations would be of great benefit for preflight and postflight comparison and to evaluate any loss of consciousness during flight.

2. It is suspected that weightlessness may cause jugular venous pressure to rise. Investigations should be made of the possible effects of such an increase on intracranial pressure and on brain blood flow.

3. There should be continuing investigation of the effects of alterations in blood gases on total and regional brain circulation.

4. Better methods are needed to determine intracranial arterial pulsations and regional distribution of blood flow in the brain.

CORONARY CIRCULATION

The function of the heart is to provide a proper pressure and flow of blood in the capillaries of the body organs and tissues so that the supply of nutrients and removal of waste products

are optimally maintained during all levels of activity. It demonstrates broad flexibility in its ability to use a variety of metabolites to produce energy without a qualitative or quantitative change in work. Thus the heart's performance is largely independent of fluctuations in its chemical environment, and there is no evidence that lack of substrates limits its work capacity. The heart's muscle mass and conducting system is supplied with nutrients by way of small coronary vessels built into the myocardium.

Properties and Behavior Peculiar to Coronary Circulation

The coronary circulation has certain peculiar features not found in most vascular beds. The purpose of some of these features is unknown. Others are of doubtful benefit to cardiac function and still others serve as built-in safety factors. These features will be discussed below.

During each ventricular contraction, while the heart is providing the pressure head for aortic flow, the increase of pressure within its wall lessens coronary arterial flow and increases coronary venous outflow. The tissue pressure in the right ventricle is nevertheless so small that the rate of coronary systolic inflow exceeds the diastolic rate, but in the left ventricle the coronary systolic rate of inflow is considerably less than the diastolic rate. In both ventricles, the net effect is to impede coronary flow.

Although about 85 percent of total flow into both sides of the heart drains through corresponding superficial coronary veins, up to 15 percent of the left coronary flow drains directly into the right ventriclular and left atrial cavities.

Myocardial tissue pressure, which determines the extravascular component of coronary resistance, must, on theoretical grounds, be considerably greater than the prevailing systolic blood pressure in the inner half of the left ventricular wall and somewhat less in the outer half. If it were not normally compensated by a reverse gradient in the vasomotor component of coronary resistance, the tissue pressure gradient would produce a nonhomogeneous flow at different depths and in different areas of the myocardium. Present experimental data do not permit conclusions on the importance of this effect.

About two thirds of the oxygen normally supplied to either the right or left ventricle is extracted from the blood with an arteriovenous difference of 12 to 14 ml and a coronary sinus value of about 5 ml/100 ml of blood. Under heavy stresses encountered in everyday life, the latter can fall to 1 to 2 ml. This means that the myocardium is primarily flow-dependent for its oxygen requirements and during strenuous activity must operate

with very little reserve. However, some help is available through compensatory mechanisms. An increase in circulating erythrocytes (considerable in animals and moderate in humans) results in an increase in arterial and coronary venous oxygen content and thus is capable of supplying the myocardium with an extra 3 to 4 ml of O_2/100 ml of blood/min. Presumably, only a small proportion of the myocardial capillaries is perfused at rest (one present estimate is 20 percent) while under heavy stress all might be operational. It would be helpful if the heart could carry out sizable anaerobic metabolism, but cardiac muscle is capable of only about 8 percent of the maximum oxygen debt that an equivalent weight of skeletal muscle can endure.

Much of the oxygen used by the heart is not related to useful external work (i.e., overcoming peripheral resistance). For example, in the presence of a constant coronary perfusion pressure, a heart doing no external work and either in asytole (empty or full) or empty and beating can have an oxygen-consumption value up to 35 percent of that of a heart performing a normal amount of external work.

These characteristics of the heart of unknown or doubtful positive benefit are counterbalanced by certain built-in safety factors. Following the release of a temporary coronary artery occlusion, coronary blood flow and oxygen usage increases by 500 to 700 percent and far exceeds the flow and oxygen consumption that would have occurred during the period of flow stoppage. This response is probably the most characteristic and important hemodynamic response of the coronary bed to myocardial hypoxia. The underlying mechanism is unknown. Presumably, it occurs with every heart beat following ventricular contraction; it can be decreased or eliminated by massive coronary-bed dilation through the impact of natural stress or by inducing coronary insufficiency (reduced coronary flow) through constriction of the coronary arteries.

Finally, in contrast with most vascular beds, the sympathetic nervous system and catecholamines act on coronary circulation predominantly through vasodilation.

Control Mechanisms

Basically, coronary blood flow is regulated by the interplay of coronary perfusion pressure and myocardial fiber shortening (intravascular compression) with the coronary bed's active vasomotor state (estimated from the ratio of late diastolic coronary pressure to late diastolic coronary flow). The myocardial fiber shortening and the vasomotor state are controlled through local changes in the coronary vessels and myocardium, induced by a variety of blood-borne metabolites, inorganic ions, and hormones;

by reflex stimulation of the cardiac sympathetic nerves whose afferent input is known to be in the central nervous system; and by mechanoreceptors in the carotid sinus, left ventricular wall, coronary arteries and veins, and in other parts of the cardiovascular system. Hypoxia is one of the most potent physiological stimuli known for evoking coronary vessel dilation.

Although coronary circulation has very little reserve, it is able to respond promptly to emergencies. Its pattern of response to most stresses, including hormone and drug injections, is vasodilation, which can at times be massive. (Exceptions are angiotensin and vasopressin which cause coronary constriction). Possibly the best examples of its ability to respond are found in its reactions to the extremes of ventricular loading. When outflow is obstructed in either right or left ventricle, coronary flow, especially in the right coronary artery, can increase greatly throughout the cycle despite the presence of very high ventricular pressure and somewhat lowered coronary perfusion pressure. Conversely, reduced ventricular loading due to such stresses as hemorrhagic shock, hypotension from ganglionic blockade, alpha blockade, or anesthesia, very often leads to extreme coronary vessel dilation throughout the cardiac cycle to help maintain blood flow at relatively high levels.

Responses to Stresses Relevant to Space Flight

Responses of the coronary circulation to positional change, physical exercise, and emotional stress have been studied in the unanesthetized man and dog. The increases in coronary blood flow are the result of active vasodilation and are brought about primarily by cardiac acceleration and to a lesser extent by increased coronary flow occurring throughout the cycle and per heart beat.

Tilting a well-trained dog shows the traditional changes in systemic circulation. With a 30° to 60° head-up tilt, heart rate increases mildly, blood pressure increases moderately, and cardiac output decreases per stroke and per minute with a marked increase in peripheral resistance. By contrast, coronary flow increases by 30 to 40 percent throughout the cardiac cycle, and in late diastole coronary resistance decreases significantly. This coronary vasodilatation apparently is effected through activation of the cardiac sympathetic nerve by mechano-

receptors in the carotid sinus.

Various types of emotional impacts, such as fear, anger, and pain, can increase coronary flow by 100 to 400 percent. Left coronary flow is initially increased by cardiac acceleration and blood pressure elevation and later by vasodilation of the coronary bed. Rapid increase in heart rate within the first 2 sec or so

essentially maintains the coronary flow per minute throughout the cycle despite a decreased pulse pressure, systolic ejection time, stroke volume, and stroke coronary flow. The delayed rise in coronary flow per minute is associated with a continued increase in heart rate, widening of the pulse pressure, further increase in blood pressure, augmentation of stroke volume, and a marked rise in both systolic and diastolic flow per heart beat in the presence of markedly reduced duration of systole and diastole. At this stage of response, the flow per heart beat increases greatly, at times by 300 percent, and thus accounts for 60 to 90 percent of the increased mean coronary flow, the remainder arising from the increased ventricular rate. Massive dilation occurs because of the great increase in late diastolic coronary flow and a slight rise in late diastolic coronary pressure. Since the characteristic response of coronary flow to various types of excitement is quite similar to that which usually follows cardiac sympathetic nerve stimulation in chronic animals (left stellate ganglion previously separated from sympathetic chain and spinal nerves to eliminate peripheral effects of stimulation), this mechanism may be responsible for the response.

Heavy treadmill exercise (15 mph) can increase coronary blood flow by 300 to 400 percent. Most of the increase is due to sustained cardiac acceleration, but a third or more of the increased flow per minute can arise from an increased stroke coronary flow. Maintenance and augmentation of coronary flow per heart beat occurs almost entirely through adjustment of systolic volume flow which then approximates the diastolic flow. Under these circumstances, the heart is not entirely flow-dependent, at times 30 to 40 percent of the extra oxygen used being made available from an increased arterial oxygen content. The pattern of response to treadmill exercise is similar to that accompanying excitement except that the flow per heart beat is less exaggerated and the effects are maintained longer.

The mechanisms that control the massive dilation typical of stress states are not precisely known. They may be related to the very large increase in heart rate generally associated with stimulation of the heart by the sympathetic nervous system or to response arising entirely within the myocardium.

Heart-rate change alone can greatly affect coronary flow. In the experimentally blocked [atrial-ventricular (A-V) node sectioned] and paced heart, coronary flow continues to rise over a wide range of ventricular rates (60 to 280 beats per min). Sympathetic influences are not essential to this adjustment since similar changes are noted after beta-adrenergic blockade. However, the importance of the marked cardiac acceleration that is characteristically associated with stress is not entirely clear since, if the heart rate is fixed and low,

adaptation to a sizable ventricular load can be immediate and the dilation very large. The response in coronary flow to exercise and excitement is just as large in the experimentally blocked and paced heart as it is in a heart with natural conduction and increased heart rate; the former merely shifts from a mild increase in stroke coronary flow and a large increase in heart rate to a large increase in stroke coronary flow with the same heart rate. Possibly, then, hearts might function better with a smaller acceleration increment.

It has been shown in the unanesthetized dog, both with normal conduction and ventricular pacing, that intracoronary injection of catecholamines (Isuprel, epinephrine, or norepinephrine) generally increases coronary flow and decreases late diastolic coronary resistance before the occurrence of any myocardial or systemic effects. Intravenous beta blockade generally causes coronary blood flow to decrease; after beta blockade, intracoronary epinephrine, norepinephrine, or phenylephrine still further reduce coronary flow while the dilator effect of Isuprel is abolished. These results are consistent with the presence and functioning of both alpha and beta adrenergic receptors (predominantly beta) in the coronary vasculature.

Experiments designed to determine the function of the alpha and beta adrenergic receptors and their usefulness to the heart under the stress of everyday life have thus far been inconclusive. Following intravenous beta blockade in an unanesthetized dog with heart pacing after experimental A-V conduction block, the same moderate level of treadmill exercise that had previously produced large increases in coronary flow and cardiac work now generally had only a slight effect on coronary flow. Cardiac output and work were also largely unaffected. The reduction in cardiac output for the same external workload could indicate reduced requirements for cardiac output (marked decrease in flow through large regional arteries) or increased peripheral requirements for oxygen which could be met by an increased systemic oxygen extraction. Similarly, beta blockade reduces, but to a lesser extent, the coronary and systemic responses to excitement. However, beta blockade has no effect on coronary dilatation arising from hypoxia and from the injection of a number of substances such as Ca, K, and angiotensin. Thus, this question has not been resolved.

The sympathetic nervous system is apparently involved in the response of the left coronary circulation to various stresses. The experimental evidence for this is furnished by tilt-table experiments in which head-up tilting is found to cause coronary vasodilatation; by the appearance of catecholamines in the coronary sinus during stimulation of cardiac sympathetic nerves and during muscular activity; and by the fact that cardiac sympathetic nerve stimulation and intravenous and intra-

coronary catecholamines give a flow response similar to that found with excitement. Further, the belief is held (without proof) that sympathetic nerve activation may initiate the coronary vasodilatation that occurs in stress states, but that local metabolic factors within the heart are of primary importance in maintaining basal coronary vasomotor tone and in adjusting coronary blood flow to meet the fluctuating oxygen requirements of the myocardium. This problem of weighting local factors as opposed to central nervous system control of the coronary circulation may be resolved when studies of the coronary circulation are made using completely cardiac-denervated animals.

Recommendations

Since the heart and coronary circulation are known to be able to respond promptly to a wide variety of conditions, prolonged space flight is not expected to lead to coronary insufficiency or cardiac dysfunction. However, it is possible that the interaction of forces that tend to depress cardiac action, such as relative immobilization and weightlessness, with those that increase its action inefficiently, i.e., environmental and emotional stresses, may result in depletion of catecholamine stores, decreased neurohumeral drive, reduced cardiac metabolism and function, and eventual atrophy of the heart and its coronary system. These possibilities should be investigated using animals and man.

1. Cardiac capabilities during space flight could be tested in dogs and primates. Coronary flow and cardiac output can be determined by appropriately implanted flowmeters, and blood pressure by a microaortic strain gauge. Heart rate could be controlled and varied by a cardiac pacemaker during these experiments. In man, preflight and postflight determination of cardiac output can be accomplished by dye-dilution techniques, and coronary flow by xenon clearance.

2. It has been demonstrated in mechanically paced hearts that increasing the ventricular rate in increments from 60 to 280 per minute results in a progressive rise in coronary flow despite the drop in cardiac output which occurs when the ventricular rate exceeds 160 per minute. By the use of the methods mentioned above, for measuring coronary flow, cardiac output, and aortic pressure, it could be determined if this pattern of response is altered by the conditions of space flight.

3. A test for the detection of ventricular dysfunction, making use of angiotensin, is currently under study at the Heart Institute of the National Institutes of Health, and in the Department of Cardiology of the Johns Hopkins Medical School. This drug, although increasing cardiac work and blood pressure, con-

stricts the coronary arteries and thus prevents an increase in coronary flow. In performing this test, a catheter is passed into the left ventricle, and stroke work and left ventricular end-diastolic pressure are recorded during intravenous infusion of angiotensin. Ventricular function curves obtained in animals and man before and after space flight should aid in detection of ventricular dysfunction.

4. Serum enzyme determinations may prove to be of value in studying the effects on the various body systems, and particularly the heart, of environmental and emotional stresses encountered in prolonged space flight and in evaluating deconditioning. Every organ has its characteristic enzyme content. When tissue cells are damaged or undergo necrosis as a result of pathological or physiological conditions, their particular sets of enzymes are liberated into the blood stream in the same proportions in which they were present in cells. Hence, conclusions can be drawn about the condition of a particular organ on the basis of the determination of the levels in the serum of such groups of enzymes. The most important enzymes for this purpose include the transaminases (SGOT and SGPT), the alkaline and acid phosphatases, the lactic dehydrogenases, aldolase, creatine phosphokinase, and malic dehydrogenase. Of particular value are the five electrophoretically distinct forms of lactic dehydrogenase: since various tissues differ widely in their content of these isoenzymes, the tissues have distinctive patterns which are reflected in the serum in the event of injury. A recent finding that may be pertinent to space research is the demonstration of markedly elevated enzyme levels after strenuous exercise in men and animals untrained for such exertion, and the absence of changes in enzyme levels after prior muscular training.

Serum enzyme determinations on bloods drawn from astronauts and experimental animals during space flight and immediately before and after may be of value in the demonstration of tissues vulnerable to the stresses encountered. Comparison of preflight and postflight enzyme levels following the use of the exercise ergometer may also provide a useful clue to the degree of deconditioning. Such studies on changes in serum enzymes in animals that have been chronically exposed to a variety of cardiac stresses are currently under way at Walter Reed Army Institute of Research.

PULMONARY CIRCULATION AND THE DISTRIBUTION OF BLOOD AND GAS IN THE LUNGS*

Within recent years, considerable evidence has been accumulated that suggests that gravity is the major factor affecting the distribution of both blood and gas within normal lungs. I propose to review the mechanisms through which gravity works on blood and gas within the lungs and attempt to show how these mechanisms operate under both increased and decreased gravitational fields encountered in space travel. This review is essentially limited to mechanical factors affecting the pulmonary circulation and ventilation of the lungs, and I have concentrated on the relationships between alveolar, intrapleural, and vascular pressures. Some of these relations can be considerably simplified through the use of mechanical models, and the Starling resistor is one such model on which I have leaned heavily, fully realizing the dangers and limitations of reasoning from mechanical analogues. Nevertheless, the mechanical model allows the integration of a number of seemingly isolated facts into a coherent picture and suggests a variety of experiments that can be carried out to test its validity.

Of course, the pulmonary circulation and airways will be affected in space by all the factors that are at work on the surface of the Earth. There are hundreds of references on the effects of changes in blood gases and drugs on the pulmonary circulation and airways, some of which are of unquestioned importance, especially from the viewpoint of the composition of the air breathed, but this information is so well understood and the magnitude of the changes expected so small, that this aspect of the picture has not been covered in any detail in the present review.

Pulmonary Circulation

Starling Resistor Effect

Starling, in his heart–lung preparation, connected the aorta to a thin-walled collapsible tube traversing a chamber in which the pressure surrounding the tube could be controlled. Such a device has come to be called a Starling resistor. Although Starling resistors have been widely used in the laboratory, it

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was not until the recent work of Banister and Torrance (1960) that it became apparent that the Starling resistor might serve as a model to explain some of the pressure-flow relationships of the pulmonary circulation. More recently, the pressure-flow relationships of Starling resistors have been described in simple quantitative terms (Permutt et al., 1961; Permutt and Riley, 1963), although these quantitative relationships were implicitly set forth in the work of Duomarco and Rimini (1954).

Consider a thin-walled collapsible tube. Let P_I, P_O, and P_S be the inflow, outflow, and surrounding pressures, respectively.* The relationships between pressure and flow through such a tube can be characterized, as a first approximation, by the following statements (Permutt et al., 1961; Permutt and Riley, 1963):

1. When $P_S > P_I > P_O$, no flow through the tube occurs.
2. When $P_I > P_S > P_O$, flow through the tube is proportional to $P_I - P_S$, and changes in P_O have no influence on flow.
3. When $P_I > P_O > P_S$, flow through the tube is proportional to $P_I - P_O$, and changes in P_S have no influence on flow.

It is now reasonably clear that the small blood vessels of the lungs are easily collapsible and are surrounded by a pressure essentially equal to alveolar pressure (Permutt et al., 1961; Howell et al., 1961; Banister and Torrance, 1960). Therefore, flow through an alveolus of the lung can be described by the three statements above if the following substitutions are made: pulmonary arterial pressure (P_{PA}) for P_I, pulmonary venous pressure (P_{PV}) for P_O, and alveolar pressure (P_{ALV}) for P_S. A number of studies in excised lungs, intact dogs, and normal human subjects suggest that these pressure–flow relations obtain in normal lungs (Anthonisen and Milic-Emili, 1966; Banister and Torrance, 1960; De Bono and Caro, 1963; Fowler et al., 1966; Permutt et al., 1962; Sheehan, 1966; West and Dollery, 1965; West et al., 1964).

Starling Resistor Effect on Distribution of Pulmonary Blood Flow at 1G

Recent work of West and colleagues (1964, 1965), who used excised lungs of dogs, gives considerable support to the concept that the effective driving pressure for blood flow through

*Throughout this paper, the units of pressure and the reference level are not relevant except when specified. It is assumed, of course, that when relationships between pressures are considered, all pressures are in the same units and are measured from the same reference level.

the lungs is the difference between pulmonary arterial and alveolar pressure whenever alveolar pressure is greater than pulmonary venous pressure, and that changes in pulmonary venous pressure have no influence on flow under these conditions. West divides the lungs into three zones.

Zone 1 is that portion of the lung in which alveolar pressure is greater than pulmonary arterial pressure, which in turn is greater than pulmonary venous pressure. This zone has no flow because of the collapse of small vessels exposed to alveolar pressure.

Zone 2 is that portion in which pulmonary arterial pressure is greater than alveolar pressure, which in turn is greater than pulmonary venous pressure. In this zone, flow increases linearly toward the more dependent regions because $P_{PA} - P_{ALV}$ increases linearly.

Zone 3 is that portion in which pulmonary arterial pressure is greater than pulmonary venous pressure and both are greater than alveolar pressure. In this region flow tends to remain constant because the driving pressure ($P_{PA} - P_{PV}$) remains constant, gravity affecting both pressures by an equal amount. In this zone, West et al. (1964) find, however, that there is still some increase in flow toward the more dependent parts, presumably because the increasing transmural pressure causes distention of pulmonary vessels.

It now appears quite likely that these same factors are in large part responsible for the distribution of blood flow in the erect human subject in a normal gravitational field (+ 1 G_Z). Butler and Paley (1962) found that the mean P_{PA} was 6.9 cm H_2O in relation to atmospheric pressure at the angle of Louis in 13 erect normal subjects. Anthonisen and Milic-Emili (1966) showed by radiographs that the angle of Louis was, on the average, 10 cm below the top of the lung. If the pulmonary blood vessels act as Starling resistors, there should be no blood flow above the level at which $P_{PA} = P_{ALV}$. Thus, on the basis of the above average values, P_{PA} should be equal to P_{ALV} approximately 3 cm below the top of the lung, and the upper 3 cm of the lung should be unperfused with blood. Anthonisen and Milic-Emili (1966), using ^{133}Xe in a manner that allowed them to calculate relative blood flow per alveolus at different horizontal levels of the lung, found on the average in six normal subjects that the upper 2.9 cm of the lung was unperfused with blood. These figures suggest that the upper 3 cm of the lung in normal upright subjects is in West's Zone 1 and compare favorably with the conclusions of Bjurstedt et al. (1962) and Riley et al. (1959) who, on the basis of dead-space measurements, estimate that 6 percent and 14 percent of the alveoli become unperfused with blood on assuming the upright posture.

Butler and Paley (1962) also found that the pulmonary wedge pressure was 11.3 cm H_2O less than P_{PA}. If we assume that the pulmonary wedge pressure accurately reflects the pressure in the pulmonary veins, we can estimate that for a distance of 11 cm below the uppermost level of perfusion (where $P_{PA} = P_{ALV}$ and P_{ALV} is 11 cm above P_{PV}), P_{PA} should be greater than P_{ALV}, and P_{ALV} should be greater than P_{PV}. This is comparable to West's Zone 2; and within this zone there should be a linear increase in blood flow per alveolus as we go down the lung, since flow per alveolus is proportional to $P_{PA} - P_{ALV}$. Anthonisen and Milic-Emili (1966) found a linear increase in pulmonary blood flow per alveolus for a distance of 15.1 cm below the uppermost level of perfusion. Considering the limitations of the methods, the agreement appears to be reasonably good. At any rate, if the pulmonary blood vessels act like Starling resistors, there should be a Zone 2 of vertical distance approximately equal to the difference between mean arterial and left atrial pressures expressed in cm H_2O. Anthonisen and Milic-Emili (1966) found, in contrast with the findings of West et al. (1964) in excised lungs, that blood flow per alveolus did not show a significant increase within Zone 3. Their findings are compatible with those of Bryan et al. (1965) who concluded, on the basis of studies with the macroaggregated albumin technique, that the basal vessels of the lungs in normal subjects are close to the limit of their distensibility at + 1 G_z.

Several other studies in human subjects with the use of radioactive gases have not shown the distinct zones found by Anthonisen and Milic-Emili (1966), but rather have shown approximately linear increases in flow per unit volume of lung from apex to base (Ball et al., 1962; Bryan et al., 1964; Dollery and Gillam, 1963; West and Dollery, 1960). Anthonisen and Milic-Emili (1966) suggest that the distinct zones might have been obscured because the alveoli in the upper parts of the lung are larger than in the lower parts owing to the more negative intrapleural pressure. They, too, found an essentially linear increase in blood flow per unit volume of lung but not per alveolus. The gradient of intrapleural pressure with vertical distance would have presented no problem in West's work (West and Dollery, 1965) on excised lungs where the pleural pressure was uniform.

In the supine posture, there is agreement that the distribution of blood flow from apex to base becomes uniform. Yet the possibility remains that there is a difference in blood flow in the anterior–posterior direction. A recent study of Kaneko et al. (1966) shows that the blood flow per alveolus is evenly distributed in the anterior - posterior direction in normal men in a supine position. Wood et al. (1963) found in dogs in a supine position that mean left atrial pressure was + 3 cm H_2O in

relation to atmospheric pressure at middorsoventral chest level and that the average dorsal–ventral dimension was 20 cm. This would suggest that the upper 7 cm of the lungs were in Zone 2, which theoretically should have increasing flow in the ventral–dorsal direction.

Read and Fowler (1964) have attempted to account for the effect of gravity on the distribution of pulmonary blood flow in a somewhat different manner. They postulate that vascular smooth muscle tone can produce a critical opening pressure within pulmonary vessels. If one then presupposes a critical opening pressure that is relatively uniform throughout the lung, the effect of gravity on pulmonary arterial pressure causes a zone of no perfusion at the upper parts of the lungs above the level where pulmonary arterial pressure is less than the critical opening pressure. Read and Fowler also consider that extrapulmonary veins can act as Starling resistors in areas where the pulmonary venous pressure is less than intrapleural pressure. Under these conditions, the effective driving pressure is pulmonary arterial minus intrapleural pressure, and there should be a decrease in driving pressure toward the upper portions of the lungs even when pulmonary arterial pressure is greater than critical opening pressure.

Apparently Read and Fowler did not consider the possibility of a Starling resistor effect under conditions where pulmonary venous pressure is less than alveolar pressure. Since alveolar pressure is always equal to or higher than intrapleural pressure, the Starling resistor effect from venous collapse as postulated by Read and Fowler is probably irrelevant under most conditions because the Starling resistor that is farthest upstream is the controlling one. Nevertheless, West and Dollery (1965) showed that in excised lungs, under special circumstances where the hilum is considerably above the most dependent portion of the lung, collapse of extrapulmonary veins might be of significance in determining the distribution of pulmonary blood flow. Because the hilum in the human subject is well above the most dependent part of the lung, even in the supine position, a Starling resistor effect from collapse of the veins has to be considered, especially under conditions of increased G.

Effect of Increased Gravity on the Pulmonary Circulation

If we assume that the lungs continue to act as Starling resistors under conditions of increased G, the effects can be easily predicted if we know the mean pulmonary arterial pressure at heart level. Let $P_{PA'} = P_{PA}$ at the level of the heart. The height

in centimeters that the lungs can be perfused above heart level (h) is

$$h = \left(P_{PA'} - P_{ALV}\right)/G, \qquad (1)$$

when $P_{PA'}$ and P_{ALV} are expressed in cm H_2O and G is the magnitude of acceleration in relation to the normal gravitational acceleration. The expression is valid only under conditions where G is not equal to zero. For instance, if $P_{PA'}$ remained at 20 cm H_2O at + 5 G_z, the lungs could only be perfused to a distance of 4 cm above the level of the heart. Thus, all parts of the lungs more than 4 cm above the level of the heart would be in Zone 1.

By the same reasoning we can assume that the vertical distance of Zone 2 (assuming that there is a Zone 1), which we shall call h_{Z2}, is given by the following simple expression,

$$h_{Z2} = (P_{PA} - P_{LA})/G, \qquad (2)$$

when $P_{PA} - P_{LA}$ is the difference between the pulmonary arterial and left atrial pressure expressed in cm H_2O. Thus, if $P_{PA} - P_{LA}$ is 10 cm H_2O, the vertical distance of Zone 2 would be reduced from 10 cm at + 1 G_z to only 2 cm at + 5 G_z. The overall effect, then, of increasing G can be assumed to be an increasingly sharp division between the upper portions of the lungs with no blood flow and the lower portions of the lungs with relatively even blood flow (those portions in Zone 3). Let us see how these predictions compare with the few studies available.

Glaister (1965), using ^{133}Xe, found that the ratio of blood flow per unit volume of lung in the lower to the upper part was 2.7:1 at + 1 G_z, 5.9:1 at + 2 G_z; and at + 3 G_z blood flow to the upper part of the lungs was absent. Bryan et al. (1965) used equation (1), above, to analyze the result obtained with the macroaggregated albumin technique in normal subjects exposed to increasing + G_z, and found that the results were entirely in keeping with the predictions from the equation. These workers also found that the blood flow in the more dependent parts of the lungs was relatively evenly distributed with increasing + G_z in spite of the increasingly high intravascular pressures toward the more dependent regions.

At the present time it is somewhat uncertain whether the anterior parts of the lungs become unperfused with blood during increasing + G_x. If the work only of Wood et al. (1963) on dogs is taken into consideration, we must assume that the anterior portions of the lungs are not perfused with blood at + 6 G_x. Wood found that the pulmonary arterial pressure 10 cm below the most anterior portion of the lungs averaged 33 cm H_2O. Equation (1) suggests that the maximum height of perfusion would be only 5.5 cm above the level of the pressure measurement,

which means that 4.5 cm of the most anterior portions of the lungs would not be perfused at all. As the average anterior - posterior (or ventral - dorsal) dimension of the lungs was approximately 20 cm in Wood's study, we can estimate that more than 20 percent of the most anterior parts of the lungs was unperfused. On the other hand, Hoppin et al. (1967), using the macroaggregated albumin technique in normal human volunteers, found the same distribution of blood flow in the anterior - posterior direction at + 1 G_X, + 4 G_X, and + 8 G_X. They accounted for their results and explained as follows why they differed from those obtained at + G_Z:

> Under + G_Z, much of the lung being superior to the heart, may have had inadequate perfusion pressure. . . Under + G_X as in the present study, however, little of the lung would have been "uphill" from the right ventricle which is located forward in chest and is not markedly displaced under + G_X. . . Furthermore, there has been evidence suggesting that pulmonary artery pressures are elevated under + G_X. . . In man under + 5 G_X, pressures in the right atrium, radial artery, and esophagus were increased about 20 mm Hg. . . In dogs under + 5 G_X and + 10 G_X similar though variable increases in aortic, right atrial, and right ventricular pressures were noted. . . .

These same workers concluded that nearly all the lung must have been in Zone 3. They also reported that the blood flow was relatively evenly distributed in spite of changes in transmural pressures, estimated to be from 0 to 88 mm Hg, from the anterior to the posterior portions of the lungs. These findings contrast with those of West and Dollery (1965) who suggested that changes in transmural pressure within vessels in Zone 3 had some influence on the distribution of blood flow. The findings of Hoppin et al. (1967), more than any others to date, point to the relative unimportance of changes in transmural pressures in determining the distribution of blood flow, and this negative finding indirectly points toward the tremendous importance of the Starling resistor effect.

Although the increase in transmural pressure in the more dependent portions of the lungs does not appear to have a great deal of influence on the flow through these vessels, the high transmural pressure would be expected to cause transudation of fluid from the pulmonary capillaries into lung tissue and alveolar spaces. Wood et al. (1963) concluded that considerable transudation of fluid does occur on the basis of hemoconcentration during exposures to forward acceleration (6 G_X for 60 sec). These workers also found a significant decrease in right and left atrial pressures of 1 to 2 cm H_2O during the period of recovery compared with the control. On the basis of similar decreases in right atrial pressure in human subjects, Wood et al. (1963) estimated a decrease in plasma volume of nearly 400 ml.

Any increase in the extent of Zone 1, which certainly occurs under increased + G_Z and might occur under + G_X, would be expected to increase the extent of alveolar dead space, and minute volume would have to be increased in order to maintain a normal arterial pH and P_{CO_2}. Zechman et al. (1960) have found an increase in minute volume in normal subjects exposed to increased + G_X, and Barr (1962) found the same thing in normal subjects exposed to increased + G_Z. In addition, Barr found that the arterial pH did not change, and suggested that the increased minute ventilation was necessary to maintain the pH at a normal value in the presence of an increased alveolar dead space.

Extrapolation to the Gravity-Free State

It is immediately apparent from the above considerations that under zero G, all the blood vessels of the lung must be in either Zone 2 or Zone 3, but it is not immediately apparent which of the two zones they will be in under ordinary activity. If left atrial pressure were positive in relation to the ambient pressure and therefore in relation to alveolar pressure, all the blood vessels would be in Zone 3, but it is not at all certain that left atrial pressure is positive in relation to ambient pressure under ordinary conditions in the weightless state. The intrapleural pressure is negative, and it is quite possible that the left atrium could be distended sufficiently to provide an adequate filling pressure for the left ventricle during diastole even under conditions where the intraluminal pressure of the left atrium is negative in relation to ambient pressure. Whether this will occur at end-expiration, it is likely to occur at end-inspiration and almost certainly will do so if the subject increases his lung volume sufficiently. The reason is that assuming constant cardiac output, pulse rate, and myocardial contractility, the left atrial pressure is fixed in relation to intrapleural pressure. With a normal inspiration, assuming no major change in cardiac output, pulse rate, or myocardial contractility, the left atrial pressure would remain constant in relation to intrapleural pressure. At the same time, however, inspiration is always associated with an increase in alveolar pressure in relation to intrapleural pressure. Therefore, inspiration would be expected to cause an increase in alveolar pressure in relation to left atrial pressure. If the increase in alveolar pressure in relation to left atrial pressure is sufficient, the lungs will change from a Zone-3 state to a Zone-2 state.

Regardless of whether the lungs are in Zone 2 or Zone 3, the blood flow per alveolus would tend to be even because P_{PA} is even throughout and, as will be shown later, the same is likely

to be true for ventilation. Therefore, from the point of view of good distribution of blood and gas within the lungs, the weightless state is ideal, and it is reasonable to conclude the alveolar dead space and venous admixture would be at a minimum.

Even though the gravity-free state will insure even distribution of blood flow, the uniformity of the blood vessels' condition is not necessarily an unmixed blessing. Consider some of the problems that might arise if the pulmonary vessels remain in a constant Zone-3 state:

Those portions of the lungs near the apex would have considerably higher transmural pressures than would be present in the upright subject at + 1 G_Z. In fact, the cephalad portions of the lungs at zero G would be in the same state as they would be in a patient with mitral stenosis at + 1 G_Z. It is not inconceivable that this would result in reflex changes and structural alterations.

An increased tendency toward fluid transudation from the capillaries is also possible. When the blood vessels are acting as Starling resistors, the alveolar pressure is higher than the pulmonary venous pressure, and the pulmonary capillaries, which are surrounded by fluid pressure equivalent to alveolar pressure, are in a state of collapse and at virtually zero transmural pressure. We have found that, if a Starling resistor is made of a fairly large collapsible tube, even if the tube has 1-mm holes in it, fluid will still move from the area surrounding the tube into the tube and on into the outflow reservoir. If the flow is increased beyond a certain critical level, depending on the diameter of the collapsible tube, fluid will begin to move out of the collapsible tube into the area surrounding the tube, especially if the holes are placed at the upstream end of the tube. If the transmural pressure is even slightly positive, and the tube is no longer collapsed, fluid flows freely from the tube to the surrounding area. Now here we have a situation in which a change in transmural pressure of an exceedingly small amount can reverse the direction of fluid movement across the wall of the collapsible tube under conditions in which the tube changes from a collapsed to a distended state.

A similar reverse in fluid movement might occur as the pulmonary capillary changes from a collapsed to a distended state when pulmonary venous pressure becomes higher than alveolar pressure. It is even possible that pulmonary edema could occur. It is well known that if a person continues to lie in one position, fluid tends to accumulate in the most dependent portion of the lungs. Frequent movement occurs in the normal person, even when asleep, and this type of fluid accumulation is not often seen in the normal person unless he is highly sedated. At zero G, however, no matter how the person turns, he will never change his pulmonary capillary from a distended to a collapsed state.

Furthermore, any activity that leads to an increased left atrial pressure will accentuate the condition.

Finally, it is possible that at least some of the capillaries of the lungs have to be in a Zone-2 state to permit the lungs to filter out some of the cellular elements of the blood, which apparently is one of the functions of the lungs. One would expect collapsed capillaries to be better filters than fully distended ones.

The problems that might conceivably arise from uniformly collapsed capillaries relate to a possible increase in their filtering capacity. Might they tend to become plugged with cellular elements? Might there be an increased tendency for microthrombi? Is it possible that the blood might become altered in its continuous passage through collapsed capillaries? Unquestionably, if the capillaries were uniformly in a collapsed state, their diffusing capacity would be reduced. Nevertheless, the reserve under normal activity is so great that it seems unlikely that such a reduction could have any significant influence on blood–gas tensions.

Distribution of Ventilation and Perfusion

Effect of Gravity upon the Distribution of Ventilation

There now appears to be little question that gravity is the main factor determining the distribution of both blood and gas within the lungs under physiological conditions. Use of the radioactive xenon technique by several independent groups shows that both perfusion and ventilation per unit lung volume are greater in the lower than in the upper portions of the lungs, with more striking difference for perfusion than ventilation (Anthonisen and Milic-Emili, 1966; Bryan et al., 1964; Denison et al., 1964; Glaister, 1965; Kaneko et al., 1966). The differences are increased during positive acceleration (Bryan et al., 1966; Glaister, 1965) and are reversed when the subject is turned upside down (Glaister, 1965; Kaneko, 1966).

The effect of gravity on the distribution of blood flow can in large part be explained by mechanical factors, but the way in which gravity also causes a difference in ventilation between the lower and upper parts of the lungs is not yet generally agreed upon. It is possible that the diminution in blood flow itself causes a reflex diminution in ventilation by bronchial constriction. It now seems likely, however, that the major effect of gravity on the distribution of ventilation is also through mechanical factors.

The mechanical factor influencing the distribution of ventilation in relation to height is the "gradient" in intrapleural pressure from the lower to the upper parts of the lungs with the more negative values in the upper parts (Daly and Bondurant, 1963; Krueger et al., 1961; Milic-Emili et al., 1966; Turner, 1962; Wood et al., 1963). Neither the magnitude of the gradient nor the mechanism governing it has been clearly delineated. Krueger et al. (1961) suggested that the air-filled lung tissue has the properties of homogeneous fluid of the same mean density as the lungs. Mead (1961) and Turner (1962) suggested that differences in supporting forces applied to the surface of the lungs might be responsible for the difference in intrapleural pressure. Whatever its origin, the gradient in intrapleural pressure appears to be gravity dependent and has been shown to increase under conditions of positive acceleration (Milic-Emili et al., 1966; Wood et al., 1963). The magnitude of the gradient at + 1 G has been found to be approximately 0.2 cm H_2O/cm by Krueger et al. (1961), Daly and Bondurant (1963), and Milic-Emili et al. (1966). On the other hand, Wood et al. (1963) have reported gradients in excess of 0.5 cm H_2O/cm.

The mechanism by which the gradient in intrapleural pressure causes differential ventilation between the upper and lower parts of the lungs appears to be related to the relatively greater volume of the alveoli in the upper parts of the lungs. If the compliance of the lungs were homogeneous throughout, the more negative intrapleural pressure at the upper portions of the lungs would cause the air spaces in this region to have greater volumes than identical air spaces in the lower portions of the lungs at end-expiration. The larger air spaces in the upper parts would have a smaller change in volume per unit volume during inspiration; this could account for the smaller ventilation per unit volume in the upper parts of the lungs found by the radioactive xenon technique.

Although this explanation is attractive, the problem cannot be handled so simply, because the pressure–volume curve of an individual unit of the lung is nonlinear, and the compliance is therefore a function of the initial volume of the unit. The larger the initial volume, the less the compliance. Therefore, it might be expected that when a breath is taken from functional residual capacity, the difference in compliance between the lower and upper parts of the lungs would favor greater tidal volumes in the lower parts.

The problem is further complicated when the phenomenon of air trapping is considered. If intrapleural pressure is increased until residual volume is reached, the transpulmonary pressure of units in the dependent parts of the lungs might be sufficiently low to cause air trapping in these units. If a breath were then taken from residual volume, the trapped units in the lower

parts of the lungs would not be expected to take in air until the intrapleural pressure fell below a critical value. Under these conditions, a small breath taken from residual volume would go predominantly to the upper parts of the lungs, unlike a breath of the same size taken from functional residual capacity. Fowler (1964) found that inspired gas was indeed distributed predominantly to the upper parts of the lungs when a breath was taken from residual volume and to the lower parts of the lungs when the breath was taken from an initially high lung volume.

Recently, Milic-Emili et al. (1966) studied the expansion of different regions of the lungs at various lung volumes in seated normal men, using ^{133}Xe. They found that the volume per alveolus was always greater in upper than in lower zones. When the lung volume was increased from residual volume to about 20 percent of the vital capacity, the changes in volume per alveolus were greater in the upper than in the lower lung regions, whereas the opposite was true at higher lung volumes. In a further study the same group (Kaneko, 1966) was able to show that the same relationships held for the highest and lowest parts of the lungs regardless of the body position.

The effect of an increased positive acceleration would be expected to magnify the regional differences in ventilation. Bryan et al. (1966) found that increased gravitational force increases the difference in lung expansion between the upper and lower regions. A most interesting discovery of these workers was that if they extrapolated their findings at different $+ G_z$ to zero G, regional lung expansion and regional ventilation were found to be uniform throughout the lungs. Glaister (1965) has shown unequivocally that the dependent portions of the lungs show considerably more trapping during positive acceleration. On the basis of the washout of ^{133}Xe from the dependent part of the lung at $+ 3\ G_z$, he described a fast compartment with a half-time of 10 to 20 sec and a slow compartment of more than 2 min, the latter compartment presumably from trapped gas. When repeated with 100 percent oxygen, sufficient collapse of the lung occurred to reduce the vital capacity by 56 percent, and the slow compartment disappeared, presumably from the trapped gas's being rapidly absorbed, leaving only atelectatic areas. That the disappearance of the slow compartment was due to complete absorption of oxygen was shown by a fourfold increase in radioactivity of the systemic blood from shunt with oxygen breathing.

Atelectasis and Trapping

If the transpulmonary pressure in the alveolus falls below a critical level, gas is expelled from the alveolus, and it becomes

atelectatic. The critical transpulmonary pressure depends on the surface tension of the liquid - air interface of the alveolus which in turn depends on the nature of the material that accumulates at the interface. Clements (1962) has shown that in the normal lung a special substance, believed to be lipoprotein in nature, is present at the interface and acts to reduce the surface tension under conditions where the surface area is decreasing. This special substance, now called surfactant, reduces the critical transpulmonary pressure at which atelectasis occurs. If surfactant is absent or diminished in amount, the critical transpulmonary pressure is at a higher level.

Another effect of reduction in transpulmonary pressure is a decrease in the diameter of terminal bronchioles and probably of alveolar ducts also. It now appears quite likely that when the transpulmonary pressure of a terminal bronchiole or alveolar duct falls below a critical level, the bronchiole or duct closes. If the critical transpulmonary pressure of the bronchiole or alveolar duct is higher than the critical transpulmonary pressure of the alveoli peripheral to it, closure of the conducting airway occurs when gas is still present in the alveoli, thus producing trapping. If, on the other hand, the critical transpulmonary pressure of the alveoli is higher than the critical transpulmonary pressure of the conducting airways, atelectasis occurs first.

Apparently surfactant has little, if any, influence on the critical transpulmonary pressure of the conducting airways. Thus, if surfactant is present, low transpulmonary pressures produce trapping; if surfactant is absent or diminished, low transpulmonary pressures produce atelectasis (Faridy and Permutt, unpublished material). The critical transpulmonary pressure at which trapping occurs depends on the state of the conducting airways. Any narrowing, increased smooth muscle tone, or secretions within the lumina of conducting airways would be expected to increase the critical transpulmonary pressure at which trapping occurs.

The basic mechanism of producing atelectasis or trapping, then, is a reduction of transpulmonary pressure below a critical level. The effect of gravity is obviously of great importance because of the resulting gradient of intrapleural pressure. In the presence of gravity, the transpulmonary pressures are always lower in the more dependent than in the upper parts of the lungs. With increasing positive acceleration, the transpulmonary pressure becomes less and less. Sooner or later atelectasis or trapping must occur in the more dependent regions of the lungs. In normal subjects, where there should be no reason to suspect alterations in surfactant, one would expect trapping to occur; and the studies of Glaister, described above, certainly bear this out. It is possible, however, that fluid accumulation in the alveoli, which probably occurs in the more

dependent regions, could have some effect in altering surfactant or the surface properties of the lungs (Johnson et al., 1964), but thus far there has been no work to suggest that this is a significant factor in the production of atelectasis during positive acceleration.

Regardless of whether trapping or atelectasis occurs first, the end result is still atelectasis as the trapped gas diffuses into the blood perfusing the trapped alveoli. The rate at which atelectasis occurs from a trapped alveolus is highly dependent upon the type of gas trapped (Rahn and Farhi, 1963). If alveolar gas contains no nitrogen or other inert gas, as would be the case if the person were breathing pure oxygen, the rate of production of atelectasis following trapping would be increased manyfold. The studies of Rahn and Farhi (1963) show that breathing pure oxygen at reduced ambient pressure, as the Mercury and Gemini astronauts have done, increases the rate of production of atelectasis above that which occurs when breathing pure oxygen at 1 atm. Recent studies of Ernsting (1965) and DuBois et al. (1966) demonstrate the importance of even relatively small concentrations of nitrogen in preventing the occurrence of atelectasis. The study made by DuBois and co-workers is especially interesting because they showed that atelectasis occurs in some subjects breathing pure oxygen at 1 G, whether at sea-level or reduced pressures. They also presented evidence that air trapping was probably the causal mechanism.

DuBois et al. (1966) suggest that in the presence of bronchiolar obstruction the airway conductance, which has been shown to decrease with a decrease in transpulmonary pressure, may be virtually nonexistent in the most dependent part of the lungs. In subjects with bronchiolar obstruction, breathing pure oxygen at 1 G would produce atelectasis in the same manner as in normal subjects under positive acceleration. The significant effect of pure oxygen on the production of atelectasis under conditions of increased G favors the idea that trapping precedes atelectasis. In a recent study by Williams et al. (1966) where atelectasis was produced in dogs by decreasing surfactant, breathing pure oxygen had no effect on the rate of formation of atelectasis, because the atelectasis occurred in the absence of bronchiolar closure.

Trapping and atelectasis are unquestionably the cause of the decreased arterial oxygen saturation under conditions of positive acceleration (Barr, 1962; Wood et al., 1963). As far as the effect of desaturation of the arterial blood is concerned, it makes little difference whether atelectasis or trapping is present, for in either situation the alveoli are not ventilated, and blood passing through these regions is being effectively shunted from the pulmonary artery to the pulmonary veins. Although breathing 100 percent oxygen increases the tendency

to atelectasis, it should improve the arterial oxygen saturation; and that this is so has been demonstrated by Wood et al. (1963). If a subject were to be exposed to positive acceleration for only limited periods, it might be debatable whether it would be better to breathe pure oxygen or a gas mixture containing a significant concentration of nitrogen. If the major concern were the prevention of arterial oxygen desaturation, then breathing 100 percent oxygen would be preferable. Not only would the higher oxygen content in the blood from the non-shunting areas be beneficial, but also, a trapped alveolus containing only oxygen, carbon dioxide, and water vapor would not act as a shunt at all until it became atelectatic. On the other hand, if the prevention of atelectasis is considered of primary importance, then the presence of an inert gas is of considerable benefit.

It is possible that the presence of atelectasis is more serious than the limited degree of arterial oxygen desaturation that has been found. Atelectasis unquestionably produces symptoms, consisting of coughing and chest discomfort, that are accentuated by attempting to take a deep breath (Ernsting, 1965). DuBois et al. (1966) discuss the possibility that once atelectasis occurs, the pressure required to open gas-free alveoli might not be reached even during a deep inspiration, which could account for the persistence of atelectasis while the subject continues to breathe oxygen and for the delay in recovery even after he has returned to room air.

In the weightless state, all factors tending to produce atelectasis would be at a minimum. The probability remains that the breathing of pure oxygen for long periods in zero G would produce atelectasis in some individuals, especially those who might develop bronchiolar obstruction either during a respiratory infection or because of unsuspected pre-existing conditions of the lungs (DuBois et al., 1966). Also, the long-term effect of pure oxygen, even at reduced atmospheres, on surfactant is still unknown.

Research Problems

In this rather cursory review of the problems of manned space flight in respect to pulmonary circulation and distribution of blood and gas within the lungs, I see no major problems of which we are now aware that must be solved before prolonged trips can be undertaken. Although the risks from positive acceleration appear considerable, they have already been faced without any serious consequences, and I do not think that they will be increased with prolongation of space flight. In regard to distribution of blood and gas within the lungs, it seems that man will

be better off, at least on the basis of our current knowledge, in the weightless state than at 1 G. I suspect that the real problems to be faced in the future in the subject under review are at present unknown, and I suggest that the greatest dividends from money spent at this time will come from the support given to basic physiological investigation. Some of the studies that I would like to see emphasized are:

1. Basic mechanics of flow through collapsible tubes.
2. Factors controlling the distributions of intrapleural pressures, i.e., distribution of pressures at the surface of the lungs, heart, and great vessels within the thorax.
3. Distribution of forces across the heart chambers; studies on heart function under positive acceleration.
4. Measurement of pressures within the heart chambers under a variety of conditions at different G levels.
5. The effect of the Starling resistor phenomenon on the function of pulmonary capillaries with respect to fluid transudation, filtering function, and the passage of blood elements through the capillaries.
6. Use of macroaggregated albumin technique in transient weightlessness.
7. Extension to - G_x acceleration of the type of study carried out by Hoppin et al. (1967). If the reasons presented by these authors for the even distribution of pulmonary blood flow under + G_x are correct, one would expect an uneven distribution of blood flow under - G_x.
8. Measurements of the distribution of blood volume within the thorax and lungs. Better methods of measuring the distribution of blood volume throughout the lungs in different gravitational fields are required. We need to know how the pulmonary blood volume is partitioned between arteries, veins, and capillaries.
9. Better measurements of the distribution of blood volume between the systemic and pulmonary circulations in different gravitational fields. We need experiments that will shed light on the mechanisms involved in controlling the distribution. The capacitance of the pulmonary circulation is so small in relation to the systemic circulation that the major factors in this area are more likely to be found in the systemic circulation, but we do need to know more about the effect of perhaps even small volume changes within the vascular structures of the thorax on the capacitance of the systemic circulation through reflex and hormonal changes.

RENAL CIRCULATION

The unique juxtaglomerular complexes associated with renal afferent arterioles provide a means by which the renal circulation plays a part in regulation of the mechanical properties of blood vessels and in the regulation of plasma volume. The spiral vessels arising from the interlobular arteries and the vasa recta system supply blood to the papillary zone of the kidney. This site contains the tips of the loops of Henle and is the region of maximum osmotic concentration within the renal paryenchyma and tubules. The vasa recta system is importantly involved in the renal countercurrent multiplier mechanism, which is responsible for urine concentration, and participates in the renal tubular mechanism for absorption and excretion of water and electrolytes (Selkurt, 1963).

The juxtaglomerular complexes (Goormaghtigh, 1939; McManus, 1942; Selkurt, 1963) consist of two structural entities, the juxtaglomerular apparatus (JGA) and the macula densa. They are located at the vascular poles of the glomeruli. The JGA is a thickening of the media of the afferent arterioles (polkissen). The juxtaglomerular cells contain granules that are considered the most likely storage site for the enzyme renin (Hartroft et al., 1964; Robertson et al., 1966). The macula densa, a thickening portion of the distal convoluted tubule, is located near the vascular pole of the glomerulus and is in contact with the JGA. It is important to note that the site of active sodium reabsorption is located in the vicinity of the distal convoluted tubule. The macula densa has been suggested as the site of formation of renin (Bing and Kazimierczak, 1960) and is believed to be sensitive to changes in tubular sodium concentration (Selkurt, 1963; Vander and Miller, 1964) and perhaps to osmotic changes in this region. The JGA responds to changes in stretch (Tobian, 1960) or radius of the afferent arteriole by altering its rate of release of renin into the arterial blood. According to Tobian (1960), an inverse relationship exists between the degree of stretch of the arteriole wall and the rate of renin secretion. Renin secretion by the JGA in response to small changes in stretch of the afferent arteriole forms a vital step in the renin–angiotensin system.

This system may be defined as follows: The renin released from the JG cells into the blood flowing through the afferent arterioles and glomeruli reacts with angiotensinogen (renin substrate), an $alpha_2$ globulin fraction, to form angiotensin I, a decapeptide, which is vasoinactive (Skeggs et al., 1956, 1957; Helmer, 1965). This is accomplished as the result of the action of renin splitting the leucyl-leucyl bond in the renin substrate (Skeggs et al., 1957; Helmer, 1965). The angiotensin I is acted upon by converting enzyme (Skeggs et al., 1957) in the plasma

and is converted to the vasoactive octapeptide, angiotensin II.

According to Helmer (1965), the range of renin activity, expressed in Goldblatt units (G.U.) per liter, found in peripheral plasma of normal humans varied from 0.03 G.U. to 0.12 G.U./liter. Renin plasma concentration as high as 7.0 G.U./liter of plasma may be found in the peripheral plasma of patients with occlusive renal vascular disease, and the plasma renin concentration is usually markedly elevated in patients with malignant hypertension.

The change in stretch of the afferent arteriole wall discussed by Tobian (1960) properly refers to changes in afferent arteriolar radius and is subject to all those factors that affect the mechanical properties of the arteriole wall and the perfusion pressure. Chief among these are factors that influence the total peripheral resistance, activity of the sympathetic nerves supplying the renal vessels, and the effects of changes in renal tubular and interstitial sodium concentration, as sensed by the macula densa (Selkurt, 1963; Skinner et al., 1964; Vander and Miller, 1964; Brubacher and Vander, 1966).

The studies of Skinner et al. (1964) support the concept that changes in renal arterial pressure are inversely related to renin liberation by the JG cells. However, studies by Davis (1965), Brown et al. (1966), and Vander and Miller (1964) suggest that changes in plasma sodium concentration, as they affect renal tubular sodium concentration, may be of primary importance in the control of renin secretion. Sodium depletion and repletion in dogs with chronic hypertension following renal artery constriction have been shown to cause corresponding increases and decreases in plasma renin concentration (Brown et al., 1966). In addition, Vander and Miller (1964) have shown that renin secretion is independent of renal arterial perfusion over a fairly wide range of pressures under conditions where sodium excretion of the kidney is prevented from decreasing through use of osmotic and chlorathiazide-induced diuresis. These authors suggest that the macula densa functions as the principal regulator of renin secretion, perhaps by sensing changes in renal tubular sodium concentration.

The exact role of the vasa recta system has not been defined. It is believed, however, that the vascular "hairpin loops," consisting of the vasa rectae descending toward the papilla and the ascending vena rectae, may provide a system for accumulating high concentrations of albumin in this portion of the loops (Selkurt, 1963) and a countercurrent multiplier system for water. Certainly the vasa rectae play a role in removing the water from the medullary interstitium (Selkurt, 1963). The amount of water removed depends upon the presence or absence of the antidiuretic hormone-induced relative water permeability and of the sodium impermeability of the collecting ducts at any given time.

A great deal more work needs to be done in this area, however, before the role of the vasa rectae can be clearly defined.

Renal blood flow in man is normally about a liter per minute (20 percent of the cardiac output) and is normally maintained within narrow limits of this value by the kidney's autoregulatory power, which is mainly determined by the autonomous activity of the renal arterioles (Selkurt, 1963). As a result of this myogenic control, the renal circulation can maintain a constant renal blood flow over a fairly wide range of renal arterial pressures (60 to 140 mm Hg) even in the absence of regulation by nervous and external factors.

The kidneys are richly supplied with sympathetic vasoconstrictor nerves. They arise mainly from the twelfth thoracic to the second lumbar ganglia of the sympathetic nervous system in man (Selkurt, 1963). Apparently no parasympathetic vasomotor fibers supply the kidneys, and vasomotor tone is primarily maintained by changes in sympathetic vasoconstrictor activity. Moreover, only alpha adrenergic receptors appear to be present. Renal sympathetic nerve effects are blocked by dybenzylene, an alpha adrenergic blocking agent.

The renal circulation is highly responsive to central nervous system control (Kottke et al., 1945; Hoff et al., 1951; Shipley and Study, 1951; Kubicek et al., 1953; Celander, 1954; Pappenheimer, 1960), and marked renal vasoconstriction, associated with significant decreases in renal blood flow, may be induced psychogenically. The renal vasculature is very labile, and in emergencies, such as hemorrhage, shock, or severe emotional stress, renal blood flow is severely reduced and may remain so for a considerable period after the emergency is over. Hence, frequent repetition of these episodes may produce a severe, prolonged renal ischemia (Block et al., 1952) and result in varying degrees of renal damage. Experimental studies in dogs by Kubicek et al. (1953) suggest, but not conclusively, that renal hypertension may result from chronic renal sympathetic nerve stimulation.

Renal circulation is anatomically divided into three major components, represented by the three major histological divisions of the kidney: the cortex, the outer medulla and juxtamedullary cortex, and the inner medulla. According to studies in unanesthetized dogs (Thorburn et al., 1963) average blood flow rates per 100 g of total kidney for these three areas are: 474 ml/min for the cortex, 132 ml/min for the outer medulla, and 17 ml/min for the inner medulla. The distribution of blood flow between the outer cortex and the outer medulla and juxtamedullary cortex is controlled by renal sympathetic nerve activity. Increased sympathetic nerve activity decreases cortical blood flow and increases juxtamedulla cortical and outer medullary flow simultaneously, while the reverse occurs with decreased sympathetic activity. These changes in renal blood flow

distribution are associated with changes in renal sodium excretion. Patients with autonomic hypofunction and subjects treated with an adrenergic blocking agent such as guanethidine (Thorburn et al., 1963; Barger et al., 1966) have an increased rate of sodium excretion as compared with normal man. Unanesthetized dogs with valvular lesions and increased renal sympathetic tone, and dogs receiving intrarenal artery infusions of I-norepinephrine are unable to excrete a sodium chloride load as rapidly as normal dogs (Barger et al., 1966). The effects on sodium excretion are related to the shifts in distribution of renal blood flow between the cortex and the outer medulla, which are produced by changed renal sympathetic tone. Recent anatomic and autoradiographic studies of the renal circulation and the factors affecting the distribution of renal blood flow show that glomeruli in the outer third of the cortex do not receive their blood supply from the interlobular arteries but from previously undescribed superficial cortical arteries which arise from the arcuate arteries and extend to the subcapsular region. The branches of these vessels turn inward, so that blood flows in a direction opposite to that of the interlobular arteries. In dogs with increased sympathetic activity, it appears that blood flow through the superficial cortical arteries is the first to be reduced. It is striking that the region supplied by these vessels contains most of the renin in the kidneys. At this time one can only speculate on the significance of these new observations. Perhaps both views on the pathogenesis of sodium retention are correct; the decreased blood flow through the outer portion of the cortex may lead to decreased filtration of sodium, while increased blood flow through the outer medulla may lead to increased sodium reabsorption (Skinner et al., 1964; Barger et al., 1966).

Effects of Exercise, Tilting, and Postural Changes

A large number of studies have been made to determine the renal effects of exercise, tilting, and postural changes using renal clearance techniques and associated measurements such as arteriovenous oxygen difference. The technical difficulties involved in standard renal clearance studies and the varied methods used make it difficult, however, to evaluate the data derived from such research.

Exercise

In man, renal plasma flow decreases progressively as the strenuousness and amount of exercise increase. At peak exercise, renal plasma flow may be reduced to 45 percent of central values (Harpuder et al., 1957).

Tilting

Tilting man in stages from the horizontal to 70° in the head-up position progressively decreases renal plasma flow and the glomerular filtration rate, especially in the presence of adequate compensatory reflex mechanisms as evidenced by a well-maintained central blood pressure during the tilting (Goormaghtigh, 1939; McManus, 1942; Selkurt, 1963).

It has been pointed out, however, that in certain individuals, when the central arterial pressure is not well maintained with tilting, or when fainting is imminent, the renal blood flow may not show this progressive fall until after the subject is returned to the horizontal (Selkurt, 1963; Werko et al., 1949). This "opening up" of the renal circulation reflects poor reflex compensation to the tilt and the participation of the kidneys in a more widespread splanchnic vasodilation during syncope (Selkurt, 1963).

Weightlessness and Urinary Excretion of Salt and Water

Studies on human subjects undergoing prolonged bedrest indicate that initially, when the recumbent position is first assumed, urinary sodium excretion (meq/24 hr) increases and then shows a downward trend as bedrest continues. These subjects also experience profound water diuresis which is clearly evident as early as 8 to 10 days after bedrest begins. Prolonged bedrest is assumed to simulate the conditions imposed on astronauts by long-term weightlessness. In both cases there is believed to be a decrease in general sympathetic tone and (see below) decreased renal sympathetic nerve activity, which results primarily from the lack of the postural adjustments that normally occur with assuming the upright position in a 1-G environment. The lack of postural adjustments, or weightlessness, would cause an increase in afferent impulses to the central nervous system from the carotid sinus mechanoreceptors, as intrasinal pressure would be higher than normal (on the average by 25 mm Hg) due to the absence of the $+G_Z$ effect on carotid sinus pressure in upright man on Earth.

One might speculate that initially, owing to increased urinary sodium and water excretion, the stiffness of the carotid sinus wall would decrease and mechanoreceptor activity return toward normal. Further study is required to test these assumptions. However, there is evidence (Barger et al., 1966) to support the view that decreased renal sympathetic nerve activity results in increased urine flow rate and urinary excretion of sodium.

Possible Effects of Prolonged Space Flights

The major effects of weightlessness during prolonged space flights on the renal circulation are expected to result from the absence of reflex adjustments in renal blood flow that normally occur on Earth with postural changes. Astronauts exposed to long periods of weightlessness are likely to have chronic hypofunction of the sympathetic nervous system and, especially, decreased renal sympathetic nerve activity. Significant among the factors producing this effect would be the altered activity of the carotid sinus mechanoreceptors noted above. This view is supported by the fact that astronauts have had a tendency toward diuresis and increased renal salt and water excretion during space flight. More accurate studies of this phenomenon are needed. Presently, there are only a few data available in the literature on the effects on renal function of chronic low levels of renal sympathetic nerve activity. Even fewer studies have been reported on the converse situation.

Under space-flight conditions, changes in renal vasomotor tone are anticipated as a result of central nervous system responses to emotional stress and altered patterns of exercise. Changes in acceleration of the spacecraft, manipulations such as orbit adjustments, course-correction burns, spacecraft rotation, velocity-reduction burns—all these and more would be expected to incite reflex adjustments in renal circulation. In addition, changes in concentration of a variety of blood-borne humoral agents, such as angiotensin II, catecholamines and certain other hormones, and plasma electrolytes are likely to alter renal excretory function, renal blood flow, and renal endocrine function.

Proposed Research

It must be pointed out that it is exceedingly difficult to make concrete predictions about the possible effects of prolonged space flights lasting up to 1,000 days, since no adequate simulation studies that deal with the renal circulatory consequences of prolonged reduction in renal sympathetic nerve activity have yet been made. There is need for additional, intensive investigation in this area, both in experimental animals and in man. Experiments in dogs and primates could be designed around renal denervation, chronic adrenergic blockage, chronically produced increased renal sympathetic nerve activity, and generalized hyperfunction of the autonomic nervous system.

The study of animals with experimentally induced neurogenic hypertension as a result of "debuffering" (removal of the sinus nerves and aortic nerves) may be one approach to the experimental production of a chronic increase in sympathetic nerve activity (especially cardiac and renal).

It is suggested that research efforts be directed toward the development of provocative tests, in man and primates, designed to observe the response of the renin–angiotensin–aldosterone system and of renal blood flow to standardized acceleration (short-axis acceleration), preferably in the $+G_Z$ direction; and also, perhaps, to a standardized application of lower-body negative pressure during a control period prior to launch, during orbital space flights of varying lengths, and for a period after the flight.

The animal (primate) experiments could be designed to include a minimum, continuous monitoring of arterial pressures, renal blood flow (electromagnetic flowmeter), and other variables such as heart rate and ECG. Blood and urine samples should be taken at regular intervals, including control periods, to study changes in plasma aldosterone and renin concentration and in concentrations of electrolytes and catecholamines. Other animals could be implanted with depth electrodes at various sites in the central nervous system known to affect, when stimulated, the renal circulation. The programmed sequence of central nervous system stimulation together with simultaneous monitoring of the variables cited above would provide valuable information on central nervous system control of renal circulation in a zero-G environment. Studies of the effects of drugs, especially sympathomimetic and blocking agents, would also be of value and could be added to a later stage of the experimental program.

In conclusion, an adequate appraisal of the possible effects of prolonged space flight in respect to forcing functions such as weightlessness, acceleration, heat, emotional stress, and noise on the renal circulation appears to require both animal and human studies during weightlessness.

CIRCULATION IN MUSCLE, SKIN, AND BONE

Present concepts of the behavior of blood vessels in muscle, skin, and bone in man are based on inferences derived from experimental studies of blood flow through the limbs. These concepts are summarized below.

Nervous System Control

The resistance blood vessels in human skeletal muscles have a sympathetic nerve supply. When these nerves are activated by exercise, norepinephrine is released at the nerve terminals and the vessels constrict. With the cessation of exercise, a threefold increase in blood flow occurs. Although this increase is small per unit of muscle, since skeletal muscle constitutes almost 50 percent of the body weight the vascular bed in muscle ranks in

importance with the splanchnic area and the kidneys in the reflex control of systemic arterial blood pressure.

During muscular exercise, despite the increase in carotid sinus pressure, the vasoconstrictor nerves in muscle vessels are activated in proportion to the extent of the exercise. In exercising muscles, the action of these nerves is overcome by locally produced metabolites, and vasodilation ensues; the resultant increase in vessel tone in nonexercising muscles and other vascular beds conserves the increase in left ventricular output for the active muscles. The receptors and afferent pathways involved in this reflex are unknown at the present time.

During emotional stress, the muscle blood vessels dilate. Evidence to date indicates that this is caused by sympathetic cholinergic fibers and by a humoral agent, possibly epinephrine.

The resistance vessels in the skin are supplied by sympathetic noradrenergic fibers which primarily influence vessels in the distal parts of the limbs and in the ear. Reflex control of most other skin areas derives from sympathetic cholinergic fibers to the sweat glands with resultant formation of a vasodilator polypeptide, bradykinin. Nervous impulses to the skin vessels are controlled by changes in blood temperature acting on receptors in the brain and also by afferent impulses to the brain from receptors in the skin. The central receptors respond to changes in blood temperature of about 0.2°C. Resultant changes in blood flow are confined to the skin vessels. (The average increase in over-all skin blood flow during severe thermal stress has been estimated at 1.8 liters/min/m^2 of body surface.)

In addition to this thermoregulatory control, circulation to the skin is controlled by mechanoreceptors. Thus, when blood is transferred from the trunk to the legs, vasoconstriction may temporarily override thermoregulatory vasodilation.

The capacity vessels in the limbs act in unison with the total postcapillary systemic vascular bed. Active changes in wall tension are mediated by sympathetic noradrenergic fibers. Noradrenergic nerves to the resistance vessels in the muscle are active under comfortable environmental conditions, while those to the capacity vessels are not. Stimuli that may cause increased activity in the nerves to the capacity vessels include exercise, deep breathing, emotion, and exposure to cold. The resulting increase in wall tension augments the filling pressure of the ventricles and so contributes to the increase in cardiac output associated with these stimuli. Changes in intrathoracic blood volume or in carotid sinus pressure, which reflexly alter the tone of the resistance vessels in the limbs, do not alter the activity in the sympathetic fibers to the capacity vessels. In head-up tilt or radial acceleration, the reflex constriction of the resistance vessels, by controlling the rate of filling of the capacity

vessels, plays the predominant role in maintaining the systemic arterial blood pressure.

Blood-Borne Agents

Epinephrine constricts vessels in the skin and dilates those in the muscles, while norepinephrine constricts both. This difference is explained by the concept of alpha and beta receptors in the blood vessels. Activation of the alpha receptors causes an increase, and of the beta receptors a decrease, in wall tension. Blood vessels in muscle have both alpha and beta receptors, the latter predominating. Blood vessels in the skin have only alpha receptors. Epinephrine acts on both types of receptors, norepinephrine predominantly on alpha receptors. While the alpha receptors are activated normally via the sympathetic nerves, the beta receptors in muscle blood vessels are stimulated only by blood-borne catecholamines, especially epinephrine. The concentration of epinephrine in the blood increases with muscular exercise, under emotional stress, and possibly with hyperventilation. The response of vessels in the hands to norepinephrine and epinephrine is similar after ganglionic (as opposed to preganglionic) cervical sympathectomy.

Local Control

The threefold increase in muscle blood flow that follows sympathectomy is small compared with the more than tenfold increase caused by strong muscle contractions or by ischemia. The dilation with exercise is due to unknown chemical changes in the muscles acting directly or via a local axon reflex on the resistance vessels. Reactive hyperemia results primarily from the accumulation of chemical substances in the blood and, secondarily, from the reduction in vascular tone consequent on the decrease in transmural pressure during the period of circulatory arrest. With prolonged circulatory arrest, release of histamine accounts for part of the vasodilation which follows.

During contraction of voluntary muscle, the flow of blood to the muscle is a compromise between the dilator action of metabolites on the resistance vessels and the constricting effect of the mechanical compression by the contracting muscle on these vessels. Blood flow through the forearm is not completely occluded until the tension exceeds 70 percent of a maximal voluntary contraction. Strong, sustained, or rhythmic contractions of small muscle groups cause a much greater increase in heart rate and systemic arterial blood pressure than mild exercise of larger muscle groups with the same increase in body oxygen

consumption; this reflex increase in blood pressure is associated with increased cardiac output, increased peripheral vascular resistance, or a combination of both of these phenomena.

Resistance vessels in the limbs dilate slightly when subjected to an increase in transmural pressure of less than 50 mm Hg. With increases above 50 mm Hg, the vessels oppose the distending force by an active increase in wall tension. With greater distending pressures, the vessels dilate. This occurs in the upper limb at 150 to 200 mm Hg, but in the lower limbs greater increases in transmural pressures are required to overcome the active increase in wall tension. Since this increase in tension persists after sympathectomy and after degeneration of both somatic and sympathetic nerves, the mechanism is a local one; perhaps a direct response of the smooth muscle to stretch. These local adjustments of the circulation to changes in transmural pressure must contribute to the over-all control of the circulation; in the adjustment to gravity, vessels in the lower limbs seem to be especially adapted to oppose increases in wall tension.

After removal of the branchial plexus (with resultant somatic and sympathetic denervation and atrophy of the arm muscles), the hand and forearm vessels remain reactive when tested 10 months to 3 years later. When they are subjected to an increase in transmural pressure, their wall tension increases actively. With local heat up to 43° C, total blood flow through the denervated forearm is greater than that through the opposite normal forearm exposed to the same conditions. These results suggest that the smooth muscle of denervated blood vessels will not atrophy and will continue to respond actively to local and humoral factors, even after prolonged muscular inactivity and reduction in skeletal muscle mass.

Blood Flow in Bone

In studies of total blood flow through the limbs in man, the assumption is made that bone blood flow is small and that it changes little during experimental procedures that alter blood flow through skin and muscle. While it is clearly increased in Paget's disease and pulmonary osteoarthropathy, no normal values are available, and there are no data on the effects of nervous, humoral, or local influences.

In dogs, the total skeletal blood flow has been estimated at about 5 percent of the resting cardiac output. Direct measurements of blood flow in the femur gave values around 8 ml/min/100 gm. The blood volume of the femur was about 4 ml/100 gm as compared with 2 ml/100 gm in the muscle and 1 ml/100 gm in the skin. Over a six-week period, there was no evidence of

changes in flow in an immobilized and non-weight-bearing femur (Ray, personal communication).

Response to Forcing Functions and Provocative Tests

During prolonged space flight, the absence of gravity means that antigravity reflexes will not be stimulated, and thus the possibility exists that these reflexes may become less efficient. However, since other vascular reflexes operate over similar pathways and are easily evoked during space flight, the autonomic nervous system should continue to function effectively. Table 1 lists tests that alter sympathetic nerve activity and that can be conveniently applied preflight, in-flight, and postflight; these tests may prove to be adequate stimuli to the autonomic nervous system during prolonged space flight. The addition of apparatus to apply subatmospheric pressures to the lower limbs should maintain local responses of the vessels to increased transmural pressure and at the same time actuate the sympathetic nervous system.

Since control of body temperature involves complex reflex changes in skin blood flow, an increase and decrease in cabin

TABLE 1
Tests That Alter Sympathetic Nerve Activity and Their Effects on Resistance and Capacity Vessels[a]

Stimulus	Resistance Vessels	Capacity Vessels
Deep breath	↑	↑
Cold	↑	↑
Valsalva maneuver[b]	↑	↑
Coughing	↓	?
Emotional stress	↓	↑
Subatmospheric pressure to lower body	↑	—
Muscular exercise	↑	↑
Subatmospheric pressure to carotid sinus	↓	—

[a] ↑ = active increase, ↓ = active decrease, — = no change in wall tension mediated by sympathetic noradrenegic fibers.
[b] Increase of intrapulmonic pressure by forcible exhalation against the closed glottis.

temperature at intervals during prolonged space flight might be advantageous.

To predict accurately the effects of space flight on the circulation in muscle, skin, and bone, answers to the following questions should be obtained:

1. Do human veins react to changes in transmural pressure, i.e., do they, through a local mechanism, develop active tensions to oppose an increased distending force?
2. What is the role of the high-pressure strain receptors, i.e., carotid and aortic sinus, as compared with the low-pressure receptors, i.e., in the heart and pulmonary vessels, in cardiovascular reflex responses to gravitational changes?
3. Do primary changes develop in the cardiovascular system as a result of prolonged inactivity?
4. What are the receptor mechanisms concerned in fainting which trigger the bradycardia and the decrease in systemic vascular resistance?
5. What is the link between so-called volume receptors and cardiovascular receptors?

SPLANCHNIC CIRCULATION

The splanchnic circulation includes the circulation to the liver, spleen, gastrointestinal tract, and pancreas (Grayson and Mendel, 1965). It is customary to think of the splanchnic circulation as a whole, rather than deal with each of these organs separately, largely because the liver, spleen, and gastrointestinal tract are functionally linked and anatomically connected through the portal vein. Bradley (1963) has pointed out that "in even the lowest vertebrates the liver lies in the path of all the vessels draining the splanchnic viscera, thus potentially controlling the splanchnic venous out-flow." Katz and Rodbard (1939) characterized the splanchnic circulation in yet another way in their statement, "Consideration of the fact that the liver may hold as much as 35 percent of the total blood volume and that the preportal bed holds another 30 percent places proper emphasis upon the quantitative importance of this system. The hepatoportal system is thus truly 'the venesector and blood giver of the circulatory system'." Thus the hepatoportal system may be looked upon as a variable "capacity" system within the circulation.

The hepatoportal venous system drains the blood from the spleen, pancreas, and gastrointestinal tract. The volume of blood flowing into the liver by way of the portal vein is uniquely determined by (1) the factors that control the behavior of these vascular beds, (2) the resistance to portal outflow (largely af-

fected by the venules and sinusoids of the liver), and (3) hepatic arterial pressure.

The main controller of the splanchnic circulation is the central nervous system, which differentially adjusts the output of catecholamines to receptor sites in the splanchnic vasculature through changes in autonomic sympathetic nerve activity. Changes in splanchnic sympathetic nerve activity are a major factor in determining the degree of vasoconstriction and flow at any given time throughout the splanchnic circulation. Changes in concentration of certain substances in the circulating blood also affect splanchnic blood flow. These substances are principally histamine, glucose, insulin, glucogen, various products of metabolism, pituitrin, epinephrine, and norepinephrine. Histamine decreases splenic volume and reduces splenic blood flow but causes vasodilation and increases hepatic blood flow. Pituitrin causes splenic vascular constriction, while the epinephrines are vasoconstrictors to the entire splanchnic arterial circuit.

Factors Affecting Splenic Blood Flow

The major factors affecting the blood flow in the spleen are changes in sympathetic tone and in blood catecholamine, histamine, and pituitrin levels. The splenic circulation is sensitive to anoxia, and splenic volume and flow are mainly controlled by mechanoreceptor reflex mechanisms in the carotid sinus and aortic arch.

Pancreatic Blood Flow

Little is known about the factors that affect the pancreatic circulation (hence the broken lines around it in Figure 2). This gap in our knowledge of the splanchnic circulation is in need of study.

Factors Affecting Blood Flow in the Gastrointestinal Tract

The major control of gastrointestinal blood flow is provided by changes in autonomic sympathetic nerve activity and in the blood levels of certain substances. This basic control is modulated by at least nine variables, including changes in carotid body (chemoreceptor) activity, changes in pO_2, anoxia, external environmental temperature, intraintestinal temperature, intestinal motility, and reflex effects produced by pacinian corpuscle stimulation.

Factors Affecting Hepatic Blood Flow

Blood flows into the liver primarily through the portal vein. The control of liver blood flow depends, on the one hand, on factors that affect portal vein outflow, and on the other, by the perfusion pressure in the hepatic artery. Hepatic flow is modulated by

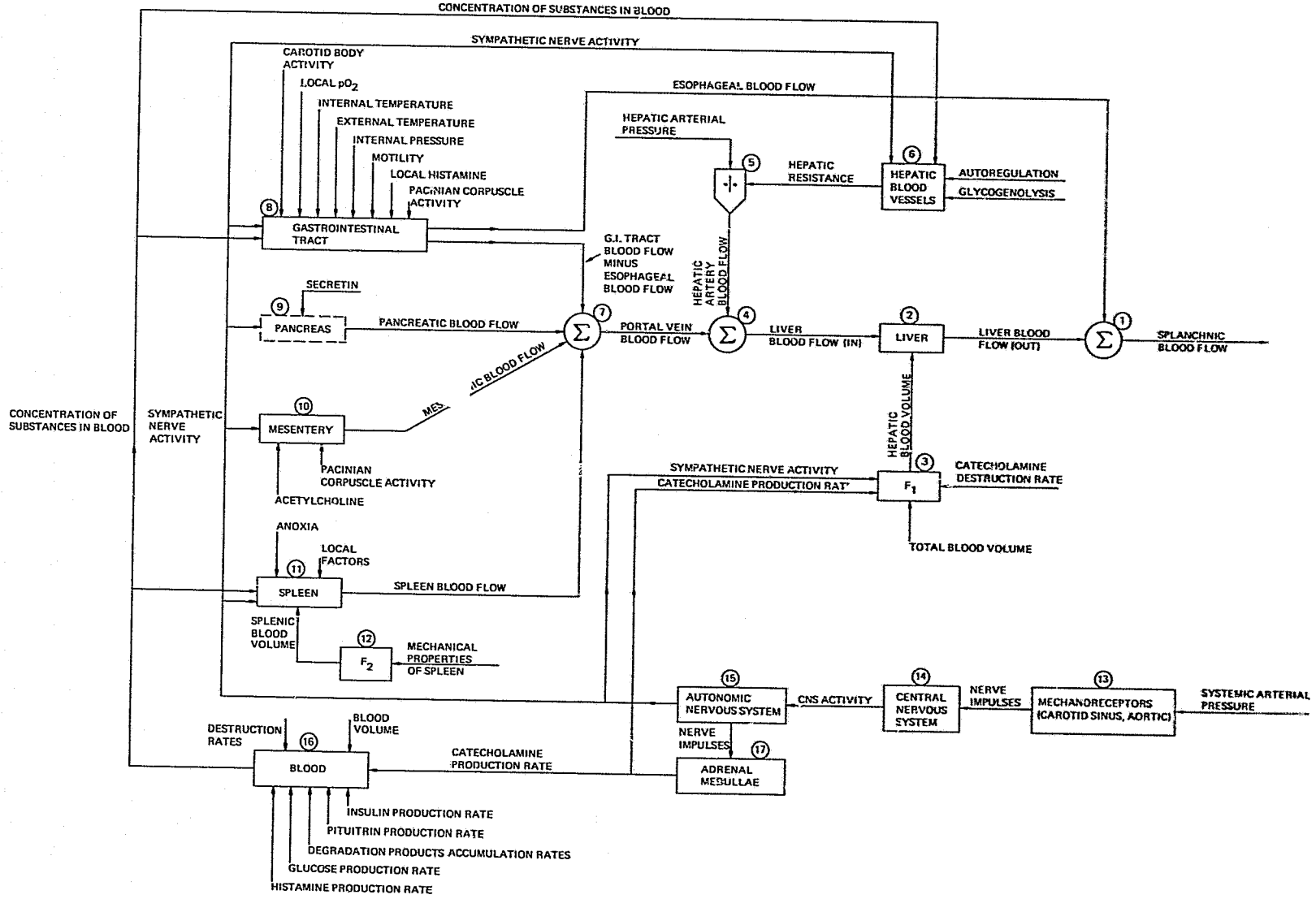

FIGURE 2. Factors regulating the splanchnic circulation.

changes in hepatic arterial pressure; in the rate of glycogenolysis; in the degree of sympathetic vasoconstrictor activity; in blood levels of glucose, insulin, glucogen, epinephrine, norepinephrine, histamine, and other substances; and by changes in systemic arterial pressure and intrinsic autoregulation. Liver blood volume is very labile and can be altered by changes in sympathetic nerve activity.

Effects of Postural Changes on Splanchnic Blood Flow

During tilting, the most important factor determining splanchnic blood flow should be the result of change in mechanoreceptor activity. Decreases in arterial pressure within the carotid sinus and aortic arch would result in a reflex increase in sympathetic nerve impulses to the splanchnic vasculature, widespread splanchnic vasoconstriction, and a rise in splanchnic resistance. The effect of posture on liver blood flow in man has been studied by Culbertson and co-workers (1951). In their studies, tilting subjects 75° (head up) from the horizontal caused liver blood flow to fall from 845 ml/min/m^2 to 620 ml/min/m^2, while blood pressure fell from 149 mm Hg to 125 mm Hg. It was concluded that "in man there is a sympathetically mediated increase in splanchnic resistance when posture changes from the supine to the near vertical."

Possible Effects of Prolonged Space Flight

The major effect of prolonged space flights on the splanchnic circulation is expected to result from weightlessness and the consequent lack of reflex adjustments of the splanchnic vasculature that ordinarily occur on Earth as a result of postural changes. The diminished sympathetic activity will be the result of reduced mechanoreceptor activity.

An example of how the systems approach can be applied to the regulation of blood flow is shown in Figure 2, where the regulation of splanchnic blood flow is considered. Splanchnic blood flow is shown at the right of the diagram and is composed of the sum of the blood flow leaving the liver and the esophageal blood flow, as shown by block number 1 (Σ). Block number 2 (liver) shows that blood flow out of the liver is dependent upon the blood flow entering the liver and the hepatic blood volume. (During hepatic blood volume changes the flow out differs from the flow in.) Block number 3 (F_1) shows that hepatic blood volume is a function of the total blood volume, the sympathetic nerve innervation of the hepatic vessels, and the catecholamine production and destruction rates. (F_1 and F_2—see box number 12—refer to func-

tions or conditions that result from the combined action of several factors; in this case, the relationship between local blood volume and the factors named.) Block number 4 shows that the blood flow entering the liver is the sum of the hepatic artery blood flow and the portal vein blood flow. Hepatic artery blood flow is determined by the division of hepatic arterial pressure by hepatic resistance (block number 5). Block number 6 (hepatic blood vessels) shows that hepatic resistance is determined by autoregulation of the hepatic vessels, the rate glycogenolysis, sympathetic innervation of the vessels, and the concentrations of substances in the blood. Block number 7 shows that portal vein blood flow is determined by the sum of gastrointestinal blood flow (minus the esophageal flow), pancreatic blood flow, mesenteric blood flow, and spleen blood flow. Gastrointestinal tract blood flow, as shown by block number 8 (gastrointestinal tract), is composed of two components as shown and is determined by the concentration of substances in the blood, the sympathetic nerve innervation, the activity of the carotid body, the local pO_2, the internal temperature, the external temperature, the pressure within the G.I. tract, the motility of the tract, the local histamine concentration, and the pacinian corpuscle activity within the tract. Pancreatic blood flow is determined by the sympathetic nerve innervation of the pancreas and by the local secretin concentration as shown by block number 9 (pancreas). This block is shown in dashed lines to indicate that not enough is presently known about the factors affecting pancreatic blood flow. Block number 10 (mesentery) shows that mesenteric blood flow is determined by the sympathetic nerve innervation of the mesentery, the local acetylcholine concentration, and the local pacinian corpuscle activity. Spleen blood flow, as shown by block number 11 (spleen), is determined by the sympathetic innervation of the spleen, the concentration of substances in the blood, anoxia, various local factors, and the splenic blood volume. Splenic blood volume is a function of the mechanical properties of the spleen as shown by block number 12 (F_2).

Sympathetic nerve activity results from a chain of events beginning with block number 13 (mechanoreceptors). The nerve activity of these mechanoreceptors is determined by the systematic arterial pressure. This nerve activity acts on the central nervous system (block number 14) to result in central nervous system activity which activates the autonomic nervous system (block number 15) to result in sympathetic nerve activity.

The concentrations of substances in the blood are determined, as shown by block number 16 (blood), by the production and destruction rates of the substances along with the blood volume according to the following formula:

$$\text{concentration} = \frac{1}{\text{blood volume}} \int (\text{production rate} - \text{destruction rate}) dt.$$

These substances consist of histamine, glucose, metabolic degradation products, pituitrin, insulin, and catecholamines. The catecholamine production rate is determined by autonomic innervation of the adrenal medullae as shown by block number 17 (adrenal medullae).

System diagrams of the regulation of blood flow through other parts of the circulator system can be constructed in a similar manner.

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5

CONTROL AND REGULATION OF BLOOD VOLUME AND CARDIAC OUTPUT

CONTROL AND REGULATION OF BLOOD VOLUME

Blood volume is defined as the sum of the volume of cells and plasma inside the whole circulatory system or a specific portion of it. Total blood volume is integrally related to the functioning of the cardiovascular system, as are its control and regulation. This section summarizes present knowledge of the factors that control and regulate red cell mass and plasma volume.

Since analysis of this system depends on accurate measurement, advances can only be made by an understanding of the theory behind and limitations of methods of measurement in current use.

Considering the anatomical and rheological complexities of the cardiovascular system, and the fact that all components of the blood are to some degree present outside blood vessels, it is not surprising that the many methods that have been used to measure the total blood volume or the volumes of its components are subject to inaccuracy. All methods in current use are based on the observed dilution of a known amount of some suitable test substance introduced into the circulation. Proper use can be made of these methods only with an understanding of their limitations (Gregersen and Rawson, 1959).

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Measurement of Red Blood Cell Mass

The most widely used technique for measuring red cell mass employs the introduction into the vascular system of 5 to 10 ml of the subject's own erythrocytes labeled *in vitro* by exposure to about 5 to 50 μCi of sodium chromate-51 (Sterling and Gray, 1950). The chromium binds with the globin portion of the hemoglobin. Loss of the label from the red cells, probably by elution, is slow (about 1 percent per day), so that only one sample, taken after sufficient time has elapsed to permit complete mixing in the circulation, is required. The principal disadvantage of the method lies in the relatively long half-life of the isotope (26.5 days), which makes it difficult to repeat measurements at short intervals because of the high background radioactivity remaining from previous measurements. Normally, measurements repeated within a week or ten days require at least doubling the amount of isotope for each subsequent measurement. In these circumstances care must be taken not to exceed the safe radiation dosage level.

Inorganic phosphorus-32 has been used to measure red cell mass by incorporating it as a phosphate ion into the red cells' inorganic and organic phosphate pools by *in vitro* incubation (Reeve, 1952). The label is lost at a rate of 6 percent per hour in man by equilibration with body phosphate pools. To correct for loss during mixing, several samples must be taken to obtain a time–concentration curve. The method permits determinations to be carried out at shorter time intervals than is feasible with chromium-51.

Another technique for determining red cell mass is diisopropylfluorophosphate labeled with either ^{32}P or ^{14}C, but these isotopes have long half-lives. Compatible-donor red cells labeled *in vivo* by the incorporation of iron-59 may be used, but this method exposes human subjects to the risk of serum hepatitis and is subject to errors if occult immunological incompatibility exists between donor and recipient. The removal of red blood cells from the subject and the substitution of an equal volume of donor red cells carrying a serologically identifiable label can also be used. The concentration of donor cells in the recipient's red cell mass can be measured by differential agglutination. Here, again, there is the possibility of hepatitis and of serological incompatibility.

Regulation of Red Cell Mass

The principal direct stimulus to red cell production is a hormonal substance, erythropoietin, a glycoprotein formed in the tissues of the body in response to anoxia. Erythropoietin acts

on the bone marrow to increase the rate of red blood cell production. Erythropoietin is produced mainly in the kidney, possibly in the juxtaglomerular cells of the renal medulla. All the factors that influence erythropoietin production are not known, and progress is hampered by the relative insensitivity of the present bioassay technique for measuring the hormone. Tissue oxygenation appears to be its basic regulator, as shown by the increase in red blood cells in anemia and on exposure to high altitudes. As implied above, the bone marrow does not respond directly to hypoxia; hypoxia acts on the kidney either directly, causing increased production of erythropoietin, or indirectly, through neurohumoral mechanisms, as a consequence of its effects on the central nervous system. Bilateral nephrectomy in the dog and rat cause almost complete cessation of erythropoiesis; in the rabbit and in man, erythropoiesis is suppressed. Thus, a nephrectomized rabbit maintained by dialysis and subjected to hypoxia will show increased erythropoiesis. These observations may be interpreted either as evidence that a source of erythropoietin in addition to the kidney exists in some species, including man, or, alternatively, that some other mechanism sustains a basal level of erythropoiesis. In support of the latter view, erythropoietin appears to regulate the rate of red blood cell production above the basal level in much the same way that regulation of metabolic processes previously regulated by the thyroid hormone continues after total thyroidectomy.

A proliferative response in the erythroid marrow and increased production of reticulocytes is noticeable two to three days after the onset of an erythropoietic stimulus, such as exposure to a low-oxygen atmosphere. Maximal rates of red cell formation usually occur within five to seven days. Thereafter, cells continue to be produced for as long as the person remains in the low-oxygen atmosphere or until he has produced enough red blood cells to carry adequate amounts of oxygen to his tissues.

The time course of the decrease in erythropoietin production and red cell formation is less well known, and there is little information on the mechanism by which erythropoietin influences red cell proliferation.

Other hormones also affect the rate of red cell production in man. Deficiency of thyroid hormone results in a decrease in the red cell mass, and administration of androgens in pharmacological doses produces an increase. Growth hormone has been implicated in the process of red cell production. Corticosteroids may also influence erythropoiesis, but their role is unclear.

Rate of Red Blood Cell Production

The rate of red cell production is most commonly measured by determining the rate of incorporation into the red cell mass of

a tracer dose of ^{59}Fe. When the erythrocytes are normochronic and have normal iron kinetics, this rate is directly related to the number of new red cells produced. When hemolysis is present, the rate of radio-iron incorporation inadequately reflects total red cell production because the large pool of kinetic iron in which the tracer is diluted causes less of the tracer to be incorporated in each developing cell. The opposite error occurs in the case of iron depletion. By measuring plasma iron simultaneously with red cell iron, reasonable corrections for these abnormal states can be made.

Another technique used to estimate the rate of red cell production involves administration of a tracer dose of radioactive glycine and measuring the amount of radioactive carbon monoxide produced and of heme incorporation. This determines the "ineffective" hemoglobin production, i.e., hemoglobin that is degraded after synthesis. A disadvantage of this technique is that it assumes a relatively constant fraction of ineffective hemoglobin production at varying rates of erythropoiesis, an assumption that is wrong in at least some pathological states.

A simple measurement can be obtained by enumerating the percentages or absolute numbers of reticulocytes. Since the reticulocyte count can be influenced both by the absolute rate of delivery of new cells to the circulation and by the length of time these cells persist in the circulation in reticulated form, the technique gives only a relative measurement of the rate of red cell production.

Life Span of Red Blood Cells and Rate of Destruction

Normal human red cells have a life span of approximately 120 days. In the normal condition of hematopoietic–hemolytic equilibrium, red cells are destroyed only by senescence, and with time, survival of the population of erythrocytes is linear. Occasionally, red cells are destroyed prior to senescence as when the increased red cell mass of a chronically hypoxic subject is reduced after return to normal oxygen tension. The mechanism of destruction is not clear. Senescence appears to result from a gradual running down of energy-producing enzymes followed by loss of red cell membrane substance and a reduction in cell volume. Finally, osmotic hemolysis occurs, with phagocytosis of residual red cell ghosts probably largely in the spleen. There may be a diurnal variation in the rate of both red cell destruction and red cell production. Serum iron curves fall steadily during the waking hours and rise at night. This may reflect differential rates of red cell destruction with liberation of iron, differential rates of red cell utilization of iron for hemoglobin synthesis, or both.

The life span and rate of destruction of red cells are measured by using variations of the methods used to determine red

cell mass. Red blood cells can be labeled with about 50 to 100 μCi of chromium-51, and the rate of elimination of the isotope from the subject's red cell mass can be determined. Since, in addition to the biological loss of the label, the chromium label is not firmly attached to the cells but elutes from them at about 1 percent per day, there is a nonlinear curve of disappearance of the isotope. To correct for this, a variety of assumptions are required concerning the elution rate of the label and the constancy of the red cell mass. However, the simplicity and safety of the technique, if not repeated too often, usually make it the method of choice. However, the method will only permit the detection of marked deviations from the normal red cell life span.

Diisopropylfluorophosphate labeled with ^{14}C may provide a more satisfactory measurement of red cell life span if it can be shown that the label remains firmly bound to the red cell mass over the entire life-span of the cells. Cohorts of red cells may be labeled in vivo with small pulse labels of inorganic iron-59 or of nitrogen-15 administered as glycine. Cohort labels of this type do not yield precise end points, and those involving nitrogen-15 are unwieldy from the analytical point of view. Measurement of the rate of endogenous CO production is one of the most promising techniques for determination of red cell destruction. This technique is based on the fact that the methene bridge cleaved in the process of degrading the cyclic tetrapyrrole of hemoglobin is stoichimetrically converted to CO. Although the apparatus required for this measurement is cumbersome, further development of the technique seems promising. A disadvantage is the fact that the method integrates the hemoglobin being catabolized from ineffective erythropoiesis with the hemoglobin that reflects destruction of red cells from within the vascular compartment.

Red cell destruction rates can be determined indirectly by measurements of the fecal output of bile pigments. Under normal circumstances, where the amount of bile pigment introduced into the feces via the hemoglobin-synthesis shunt is small, reasonably accurate measurements of red cell destruction can be obtained. However, the methods are difficult, and in circumstances where the shunt of bile pigment from ineffective erythropoiesis is large, they yield values that are difficult to interpret.

Plasma Volume

Plasma volume has been measured principally by techniques that label plasma albumin. These include the use of the blue dye T-1824, iodine-131, and iodine-125. Multiple samples are usually taken following injection of the indicator. These substances all yield the same value for plasma volume, provided that the latter is calculated from the conventional extrapolation of the time–concentration curve on a semilog plot.

Total Blood Volume

Total blood volume is obtained most directly by measuring both red cell mass and plasma volume. By far the most published results on blood volume are derived from determinations of either plasma volume or red cell volume alone. From this and the whole-body hematocrit value, the total blood volume has been calculated. It should be noted that the hematocrit value is not identical with the volume percentage of red cells in the blood sample. In order to obtain the volume percentage from the hematocrit value, correction must be made for the plasma trapped in the "packed cell column." The validity of this method depends upon the accuracy of the estimation of whole-body hematocrit.

On the basis of comparative measurements of red cell mass and plasma volume, several investigators have shown that the ratio of whole-body hematocrit to venous hematocrit is from 0.91 to 0.93 in normal man. Various disturbances of the blood chemistry may change this ratio, so that the simultaenous measurement of red cell and plasma volume is to be preferred.

Changes in the volume of blood contained in human limbs can be made by plethysmography. Indicator–dilution techniques have been used to measure the volume of blood in the heart and lung and in the splanchnic area. The indicator is injected at one site in the circulation, and the resultant time–concentration curve of the indicator is recorded at a downstream site. The volume measured is that between the injection and sampling sites and includes the volume of all the blood vessels equidistant in time with the injection and sampling sites (Meier and Zierler, 1954).

Basis of Fluid Volume Control

Plasma volume consists of water, electrolytes, proteins, and other substances. One constituent used in determining its size can be the circulating plasma albumin. The primary source of albumin production appears to be the liver. In contrast with the red blood cells where the production rate can be increased about sixfold, production of this protein can be no more than doubled. There is little evidence of a reserve store of albumin for emergency use. The mechanisms controlling the synthesis of albumin are not entirely understood. Recent studies have suggested that the hepatic interstitial albumin content is important in regulating albumin synthesis. Albumin synthesis does not appear to be directly related to serum albumin levels. Changes in the colloid osmotic pressure of the hepatic interstitial fluid by albumin itself, by other circulating proteins, or by injection of substances such as dextran, have been demon-

strated to alter the rate of albumin synthesis. It has been suggested that the rate of albumin loss from the vascular pool is related to the total amount present and is a percentage of that value. It may be, therefore, that under normal circumstances albumin is added to the regular pool at a relatively constant rate and depleted from that pool at a percentage of the total value. This assumption would allow for a basic controlling mechanism which undoubtedly is superseded by more active ones when necessary.

In the course of capillary perfusion, bidirectional transfers of water and solute, and some exchange of proteins, occur across the capillary membrane between plasma and the interstitial fluid. Alterations in plasma volume are subordinated to alterations of total blood volume by shifts in the balance between filtration and reabsorption of fluid in the capillary bed. The rate of transcapillary exchange of fluid is so great that relatively enormous shifts in plasma volume can readily occur if there is a shift in the osmotic and hydrostatic forces which determine the steady state between the inter- and extravascular spaces.

There does not seem to be a common mechanism regulating both plasma volume and red cell mass simultaneously. Under most circumstances the mechanism controlling red blood cell volume appears to be predominant and overrides changes in plasma volume. In other words, red cell volume is regulated first; then plasma volume adjusts appropriately so that the total blood volume is maintained within a relatively narrow range. This mechanism may not be complete. For instance, when there is a severe loss of red cell mass there may be only partial compensation by plasma volume.

A block diagram summarizing the regulation of blood volume is shown in Figure 3. Total blood volume is the sum of red cell volume and plasma volume (block number 1). Block number 2 (plasma) shows that plasma volume depends on fluid shifts across the capillaries, the net rate of fluid exchange with the environment, and lymph flow. Block number 3 describes capillary dynamics. Fluid and protein shifts across the capillary wall are complex functions of capillary pressure, interstitial fluid pressure, plasma osmotic pressure, interstitial osmotic pressure, viscosity, temperature, and membrane factors. Block number 4 (interstitial fluid) shows that interstitial fluid volume is a function of fluid and protein shifts across the capillaries and fluid shifts across the cell wall. Block number 5 shows that the properties of the intracellular fluid are a function of fluid shifts across the cell wall and water metabolism.

Hematocrit is a function of plasma volume and red cell volume as shown in block number 6, and hematocrit, in turn, determines viscosity (block number 7). Block number 8 shows that interstitial fluid pressure is a function of interstitial fluid volume,

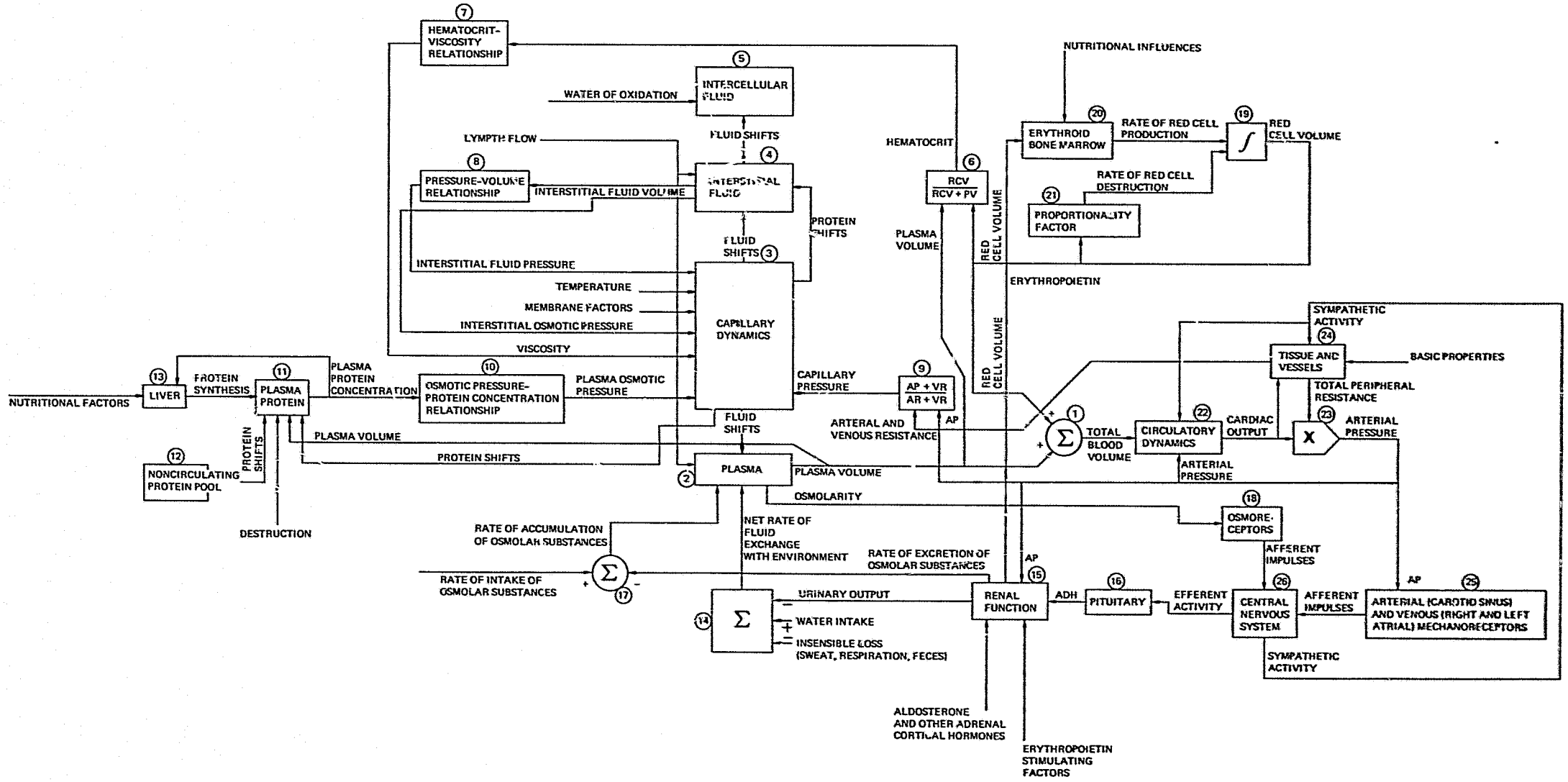

FIGURE 3. Regulation of blood volume.

while capillary pressure is a function of arterial pressure, arterial resistance, and venous resistance (block number 9).

Blocks 10 through 13 describe plasma protein dynamics. Block number 10 shows that plasma osmotic pressure is a function of plasma protein concentration which, in turn, depends on protein production and destruction rates, protein shifts to and from the interstitial fluid, protein shifts to and from the non-circulating protein pool (block number 12), and plasma volume. Protein synthesis by the liver (block number 13) depends on plasma protein concentration and nutritional factors.

The rate of fluid exchange with the environment is equal to water intake minus insensitive loss and urinary output as shown in block number 14. Urinary output, erythropoietin secretion, and the rate of excretion of osmolar substances all depend on renal function (block number 15). Urinary output is a function of arterial pressure, aldosterone and other adrenal cortical hormones, and ADH. The secretion of ADH by the pituitary (block number 16) is controlled by the central nervous system. The rate of excretion of osmolar substances is a complex function of all the variables that control urinary output. The net rate of accumulation of osmolar substances is equal to osmolar intake minus osmolar excretion as shown by block number 17. Osmolarity is determined by the total quantity of osmolar substances and plasma volume. The osmoreceptors (block number 18) monitor osmolarity for the central nervous system.

Red cell volume is the integral (block number 19) of the rate of red cell production minus the rate of red cell destruction. Block number 20 (bone marrow) shows that the rate of red cell production depends on erythropoietin and nutritional factors. Erythropoietin, in turn, depends on renal function (block number 15) and erythropoietin stimulating factors. Block number 21 shows that red cell destruction is a function of red cell volume.

Block number 22 suggests that cardiac output depends on blood volume, arterial pressure, and sympathetic activity. Cardiac output multiplied by the total peripheral resistance (block number 23) determines arterial pressure while total peripheral resistance, in turn, is determined by cardiac output, sympathetic activity, and the basic properties of the vessels as shown in block number 24. Arterial pressure is monitored by the mechanoreceptors (block number 25), and the resulting afferent impulses go to the central nervous system (block number 25).

The complete diagram suggests that blood volume is controlled by a very elaborate and complex set of mechanisms interacting with each other. The relative contribution of the various mechanisms to the over-all regulation of blood volume can best be evaluated by a quantitative study of the total system.

Stress Factors Affecting Red Cell Mass and Plasma Volume

Acceleration and Vibration Exposure to forward acceleration (5 G for 10 min) causes rapid hemoconcentration compatible with a decrease in plasma volume of nearly 400 ml in healthy humans (Wood et al., 1963). Little is known concerning the effects of vibration.

Weightlessness and Inactivity Essentially nothing is known of the effects of weightlessness on hematopoiesis or on control of plasma volume. Substantial research is needed to separate the effects of weightlessness from those due to other elements of the complex space-flight environment. This can best be done by simulating on Earth all other aspects of the space-flight environment and comparing the data with in-flight results.

Many studies on the effects of immobilization using bedrest or other means have indicated that plasma volume falls under these circumstances. The decrease may amount to 5 to 15 percent of total volume and may be related to alterations in the vascular system, such as nonutilization of the muscular-vascular bed that leads to readjustment in size of the blood volume. Although the decreases are well documented, the mechanisms causing them are not clearly understood.

It is possible that weightlessness and immobility may result in red cell destruction by affecting the microcirculation. If relatively large numbers of red cells are trapped for long periods in unperfused capillary beds, those cells may be injured irreversibly. Red cell sequestration can result in erythrocyte membrane injury, membrane loss, and ultimately hemolysis by the process of microfragmentation. These processes may interact with factors affecting the rheological properties of blood and factors causing rouleaux formation—a tendency of red cells to stick together in loose aggregates. At the present time, mechanisms that might cause red cell injury in space flight are hypothetical but deserve consideration. Conceivably, prolonged acceleration or severe vibration might have similar effects.

Weightlessness, immobility, acceleration, and vibration may also influence fluid exchange across the capillary bed and thus affect plasma volume.

Atmosphere Present preliminary data suggest that if even a mildly hyperoxic atmosphere is breathed over a long period, a downward adjustment of red cell mass may occur. This adjustment may involve two processes: (1) A physiological decrease in red cell mass because lower concentrations of hemoglobin and dissolved O_2 are needed to maintain adequate

tissue pO_2. Such a decrease, if it occurred during space flight, should be minor. (2) Activation of random red cell destruction induced by an oxidative injury to the red cell membrane, possibly by production of lipid peroxides or oxidation of other structural membrane components. The mechanisms of these effects and their impact on the red cell which result in hemolysis are unknown and present a major area for research. This effect of increased O_2 tension may interact with other stresses, which may, in fact, be required to activate the hemolytic process.

Present data also suggest that the increased rate of red cell destruction inferred from Gemini experience will be modest. If the regenerative capacity of the erythroid marrow is unimpaired (and there is no reason to predict impairment), a mild, compensated hemolytic state would have no practical significance. On prolonged missions, of the order of 1,000 days, the formation of biliary pigment calculi is conceivable. If only modestly increased rates of red cell destruction are encountered and the load of bile pigments is no more than doubled, the chance of calculi forming is slight.

Heat and Humidity Dehydration causes a reduction of plasma volume which is proportionally less than the total loss of body water. If plasma osmolarity increases, there may be some reduction of the mean red cell volume. Minor changes in blood volume, associated with changes in capacity of the vascular bed in the limbs, accompany changes in ambient temperature.

Radiation The radiation hazard to man in space cannot be predicted with accuracy at the present time since data on both the nature and amount of radiation to which astronauts may be exposed and its biological effects are very incomplete. The space environment itself should not alter the effects of energetic radiations as compared with the effects of exposures on Earth, although the possibility of increased injury to the hematopoietic system as a result of high oxygen tensions should be considered. With respect to blood volume, radiation injury from low and middle exposures is confined to red cell production, since direct cellular injury of erythrocytes occurs only at very high dosages. Specifically, red cell mass will decrease, or the capacity to increase erythropoiesis, in response to the need for more red cells after blood loss or hemolysis, will be lessened. With higher dosages, approaching minimal lethality, many other effects are encountered. Red cell mass and blood volume will be lost by internal and external hemorrhage. Effects on the capillary bed may be encountered, enhancing plasma loss. However, under these conditions, blood volume alterations affecting cardiovascular functions would be only one of many severe biological effects.

A different problem is presented if a relatively large, high-intensity exposure is delivered promptly, as from a solar flare. Here the timing of the exposure in relation to the mission time course may be of paramount importance. If the exposure is sub-lethal and occurs early in the mission, recovery may occur before the crew is required to enter a stressful phase of operation. On the other hand, if the exposure occurred 1 to 4 weeks prior to re-entry, for example, the effect could be extremely serious: the crew would be subjected to major accelerative forces at the time of maximal thrombocytopenia with attendant hemorrhage.

Multiple exposures to solar flares could exceed the radiation tolerance and result in fatalities. More data are needed on the responses of man to repeated large doses of whole-body radiation at different intervals. Similarly, additional data must be accumulated on the effects on man of low-dose, low dose-rate, and chronic exposures to the types of radiation expected in space. For obvious reasons, human data are meager and difficult to collect; it is probable that experiments on animals will provide the best available basis for planning.

Circadian Rhythms and Sleep There is some evidence that red cell production and destruction are phasic processes related to the normal work–rest cycle. As noted above, serum from levels show a regular diurnal variation. Nevertheless, no physiological abnormality in hematopoiesis has been recognized where circadian rhythms and sleep–activity cycles have been disturbed over long periods of time. At present, no adverse effects of this stress on blood volume can be reasonably predicted.

Nutrition and Water Balance Much of the weight loss resulting from decreased caloric intake is due to loss of water. As electrolytes are lost continually through the kidneys, the kidneys excrete equivalent quantities of water so that osmotic equilibria are maintained in the body. In long-term missions, insufficient protein or calorie intake could result in decreased albumin production, which could, in turn, be an important determinant of a reduced plasma volume or, if severe, hypoproteinemic edema. Evaluation of this risk in prolonged space flight is dependent upon the actual nutritional experience. It seems possible that abnormality of nutrition could occur in some crew members, but at present, no basis for reliable predictions can be made.

Red cell production is also dependent upon diet. Specifically, iron, folic acid, vitamin B_{12}, vitamin C, pyridoxine, and protein intakes must be adequate. No data exist to indicate altered needs for these nutrients in conditions of space flight, but the possibility must be entertained. Such effects would probably be manifest only over long periods—six months or greater. Similarly, the possibility that absorption processes may be subtly altered

in space flight should be considered, although no data suggesting problems of this type presently exist. The time course of such abnormalties will almost certainly be relatively long (months).

Infection and Inflammation Systemic or local infection, bacterial or viral, commonly exerts a suppressive effect on erythropoiesis and may limit the ability of the erythroid marrow to respond to stress. Inflammation of noninfectious etiology exerts a similar influence. Infection and inflammation both may inhibit albumin synthesis or raise the rate of catabolism. The problem of infection in a closed ecology in space flight is entirely unevaluated.

Toxicity A wide variety of materials have hemotoxic or hepatotoxic effects, and continued exposure may have cumulative effects. Some of these, including drugs, also induce idiosyncratic reactions, i.e., severe reactions disproportionate to the dose-response curve of normal subjects. Since these hazards cannot be entirely anticipated, and can be minimized only by careful review of all materials on board the craft, it is impossible to predict the time course of such changes on a prolonged flight.

Emotional Stress The emotional aspects of space flight, including the psychological effects of noise, are unlikely to affect the total volume of the vascular system.

Renal Dysfunction or Failure Erythropoiesis appears to depend upon an adequate mass of functioning renal tissue. Any effect, such as infection or infarction, that sharply reduces this mass can be expected to result in decreased red cell production and red cell mass. Effects on plasma volume of renal failure will relate to loss of the salt and water excretory and regulatory function of the kidney.

Hemolysis Hemolytic mechanisms of any type, congenital or acquired, can be expected to affect red cell mass in the same way that has been discussed above under Atmosphere. It may be important to screen astronaut candidates for certain congenital hemolytic states such as glucose-6-phosphate dehydogenase deficiency, other enzyme deficiency states, hemoglobinopathies, and hereditary spherocytosis.

Blood Loss Acute blood loss will produce the usual effects of hypovolemia on cardiac function. Chronic blood loss will express itself ultimately as iron depletion and iron deficiency anemia with reduction in the red cell mass and a compensatory rise in plasma volume. There is no reason now evident, save for accident or disease, to expect blood loss in space flight.

CONTROL AND REGULATION OF CARDIAC OUTPUT

Complex mechanical, humoral, and neural factors influence the performance of the heart by changing either its rate or its stroke volume. These factors adjust cardiac output so that arterial pressure and tissue perfusion are maintained at an optimal level. Stroke volume is regulated by the factors that affect the filling and emptying of the ventricular chambers. The venous system, through its control of venous return, plays a very important role in ventricular filling, as do atrial contraction and the respiratory cycle through their influence on intrathoracic and intra-abdominal pressures. The most important determinant of stroke volume is the contraction of the ventricular myocardium, which is regulated by humoral, neural, and mechanical factors. The effectiveness of the myocardial contraction in ejecting blood is determined by the load against which it must work—the arterial pressure.

Cardiac output is a direct function of heart rate so long as stroke volume remains constant. The increase in cardiac output resulting from exercise is due primarily to an increase in heart rate. With increased sympathetic activity that is usually responsible for an increase in heart rate there is a decrease in the duration of systole permitting a greater period for diastole filling.

The vascular system and blood volume interact closely with the heart in determining cardiac output. These interrelations, and the direct influence of mechanical, humoral, and neural controls on the regulation of cardiac output are depicted schematically in Figure 4. Cardiac output is equal to heart rate multiplied by stroke volume as shown by block number 1. The stroke volume, in turn, depends on the contractile force of the heart muscle, end diastolic volume, and arterial pressure as shown by block number 2. Block number 3 shows that contractile force is a function of coronary blood flow, sympathetic activity, arterial pressure (homeometric autoregulation), total metabolic substances, heart mass, and muscle fiber length (and velocity). Block number 5 (cardiac anatomy) shows that fiber length and compliance of the heart depend on the basic anatomy of the heart, heart mass (which is a function of body size), and end diastolic volume (this variable implies instantaneous volume where applicable).

Filling dynamics are described by block number 6. End diastolic volume depends on filling pressure, compliance, respiratory effects (from block number 7) and strain (from block number 8). Venous return relationships (block number 9) show that filling pressure is a function of blood volume, vascular compliance, resistance to venous return, and venous

BLOOD CONCENTRATION OF VASOACTIVE SUBSTANCES (INCLUDED IN TOTAL METABOLIC SUBSTANCES)
CATECHOLAMINES
ALDOSTERONE AND OTHER STEROIDS
ANGIOTENSIN
Na^+, K^+, Ca^{++}, Mg^{++}, H^+
O_2, CO_2
FATS, CARBOHYDRATES, PROTEINS
PITRESSIN
SEROTONIN

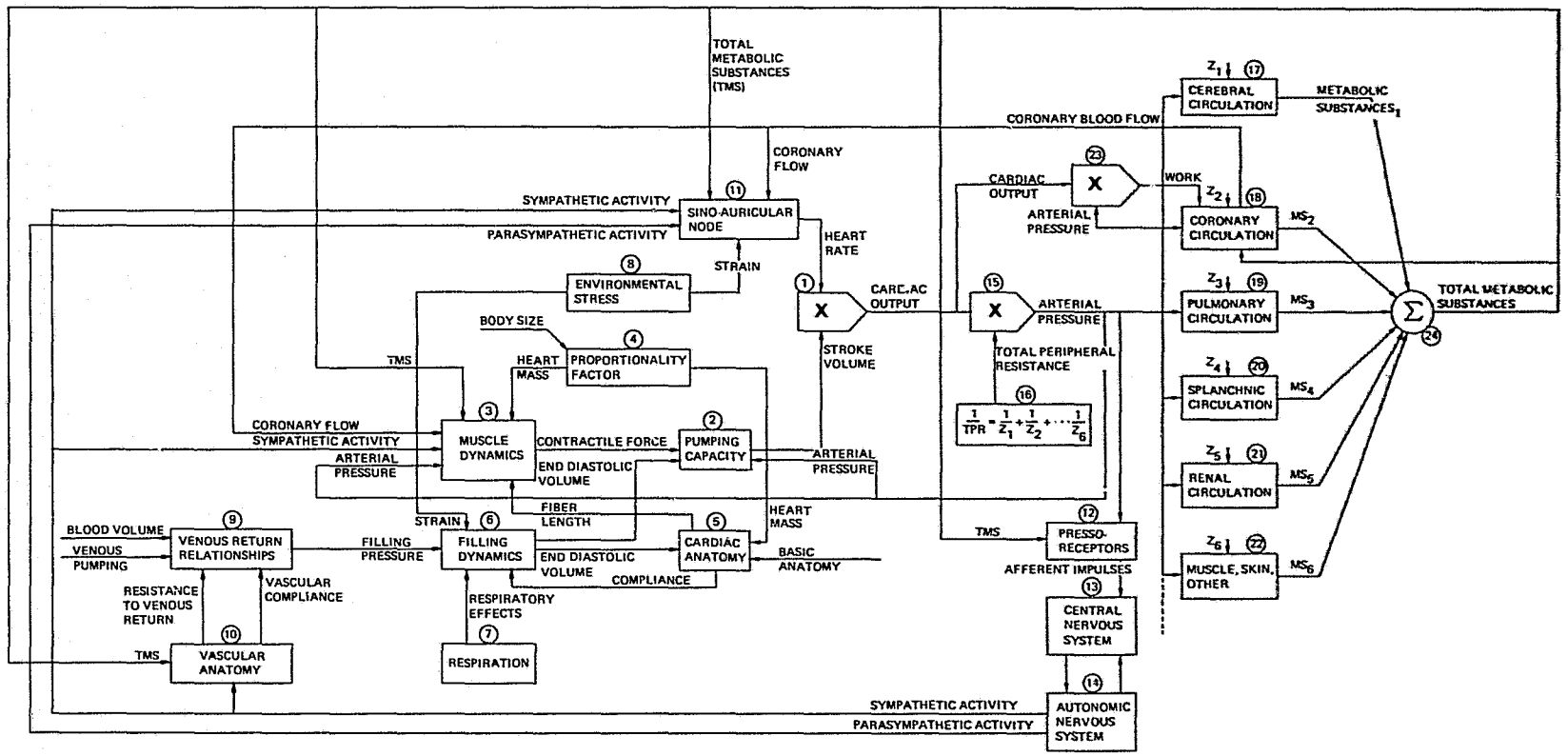

FIGURE 4. Regulation of cardiac output.

pumping. Vascular anatomy (block number 10) shows that vascular compliance and resistance to venous return depend on sympathetic activity and total metabolic substances. Total metabolic substances (including the vasoactive substances listed at the upper right corner of the diagram) are supplied by the various tissue beds of the body. This will be discussed later.

The sino-auricular node (block number 11) determines heart rate as a function of parasympathetic and sympathetic activity, coronary blood flow, total metabolic substances, and strain. Parasympathetic and sympathetic activity depend on arterial pressure and total metabolic substances as shown by block number 12 (pressoreceptors), block number 13 (central nervous system), and block number 14 (autonomic nervous system).

Arterial pressure is equal to cardiac output (from block number 1) multiplied by total peripheral resistance as shown by block number 15. Total peripheral resistance is a function of the parallel summation of the impedances of all the tissue beds in the body as shown by block number 16. The tissue beds of the body are represented schematically by blocks 17 through 22. The metabolic substances produced by the individual tissue beds are a function of arterial pressure, impedance to blood flow, and the unique characteristics and functions of each bed.

Coronary circulation (block number 18) is affected by the amount of work done by the heart, and work, in turn, is approximated by cardiac output multiplied by arterial pressure as shown by block number 23.

Block number 24 sums the metabolic substances from each tissue bed to yield the quantity called total metabolic substances.

Resistance to Cardiac Emptying

The ease with which blood can flow through the vascular tree influences both venous return and cardiac output. The role played by vascular resistance as an influence on venous return, and hence on ventricular filling, has been reviewed in Chapter 1 under "Mechanical Properties of Blood Vessels"; its influence on cardiac emptying is mediated both through a direct effect on the pressure load against which the myocardium must work and indirectly through changes in neurogenic control of the heart initiated by changes in arterial pressure.

When vascular resistance increases and the heart is called on to work against a greater pressure load, it undergoes a sequence of adaptive changes. Systolic ejection is less complete, causing first an increase in end systolic volume, then an increase in end diastolic volume. Ventricular emptying is thereby improved by the mechanism of heterometric autoregulation. The decreased load secondarily induces the true inotropic

change referred to as homometric autoregulation. By these two adaptive mechanisms the heart is able by autoregulation to maintain a normal output in the presence of large changes in vascular resistance.

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PART III
STRESS FACTORS IN MANNED SPACE FLIGHT

6

STRESS FACTORS IN MANNED SPACE FLIGHT

INTRODUCTION

This section discusses the principal stress factors associated with prolonged manned space flight that are likely to influence the cardiovascular system. These factors are environmental, physiological, or psychological stresses that induce a shift in level of function, an adaptive change in response, or a physical change, in the physiological system. Examples of the likely or possible effects of the stresses on the elements of the circulatory system are given. Knowledge obtained from actual or simulated space flights is summarized. Figure 5 presents a qualitative estimate of the magnitude of some of the stresses with respect to time in a postulated Mars mission.

GRAVITATION, ACCELERATION, AND VIBRATION

Definitions

Motion Change of position and/or orientation of a body with respect to a given reference frame. The instantaneous state of

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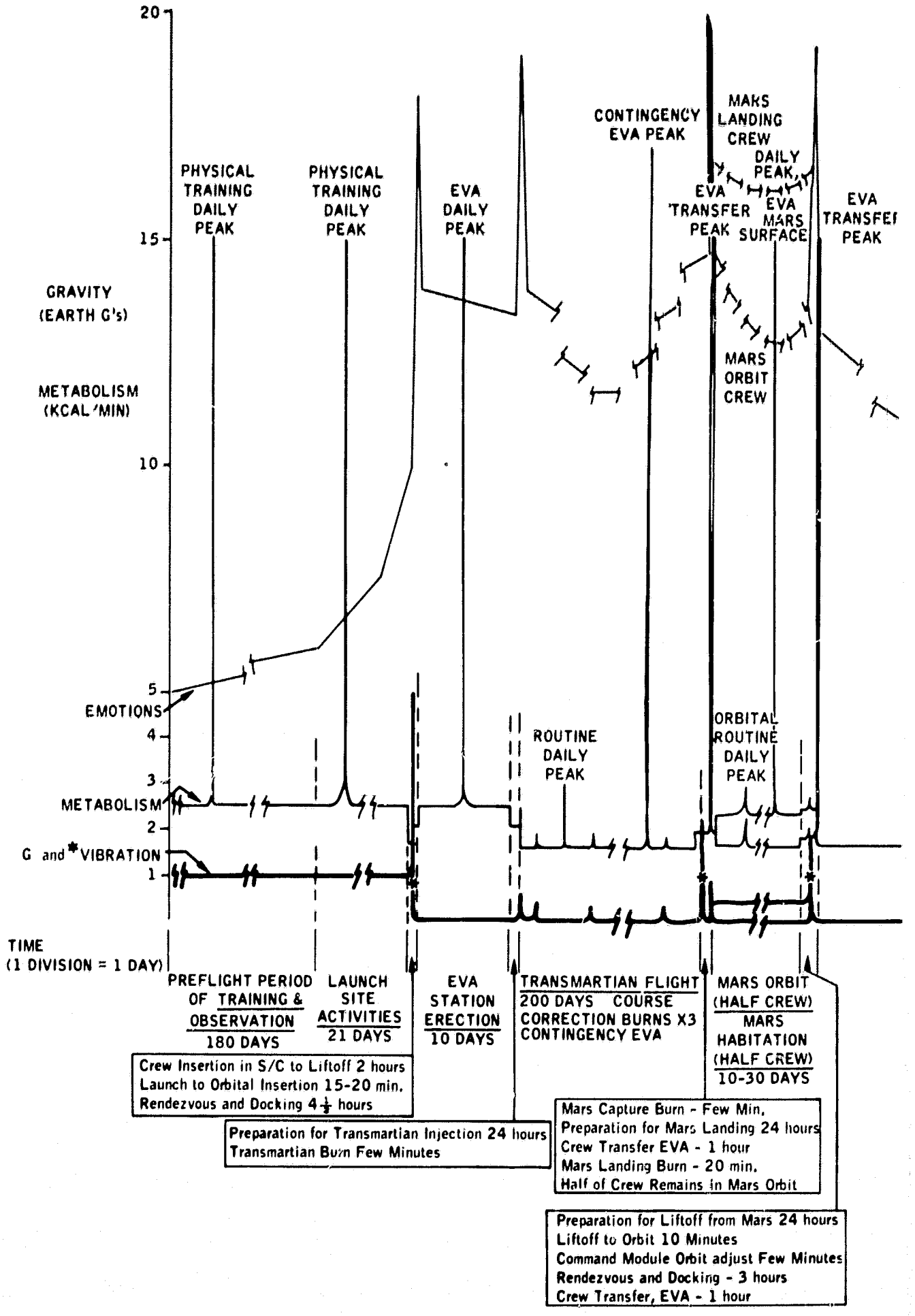
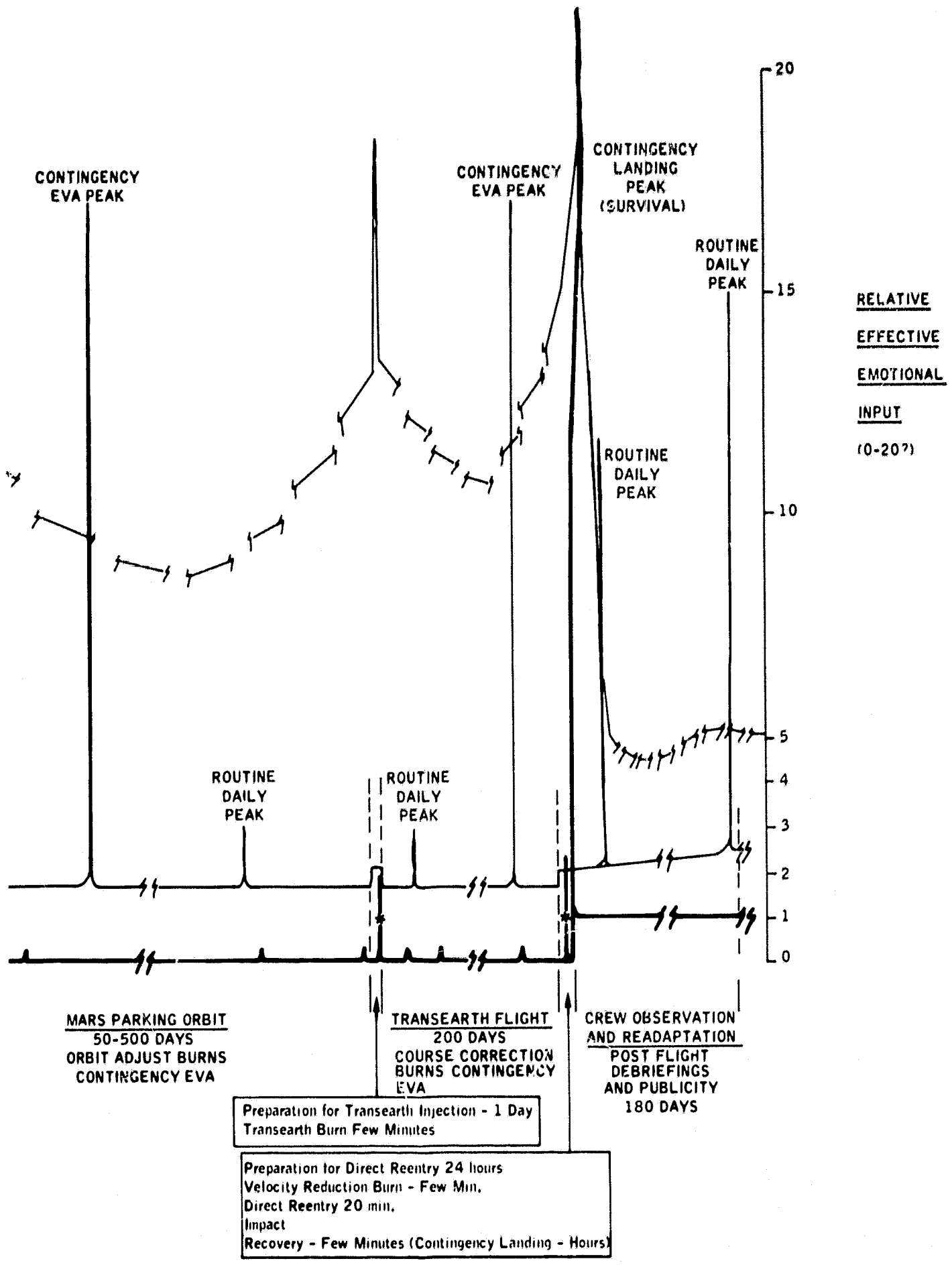


FIGURE 5

Postulated manned space flight to Mars with qualitative estimates of the magnitude of some of the stresses to be encountered during the various phases of the mission.


CONTINGENCY EVA PEAK
CONTINGENCY EVA PEAK
CONTINGENCY LANDING PEAK (SURVIVAL)
ROUTINE DAILY PEAK
ROUTINE DAILY PEAK
ROUTINE DAILY PEAK
ROUTINE DAILY PEAK
20
15
10
5
4
3
2
1
0
RELATIVE EFFECTIVE EMOTIONAL INPUT (0-20?)
MARS PARKING ORBIT
50-500 DAYS
ORBIT ADJUST BURNS
CONTINGENCY EVA
TRANSEARTH FLIGHT
200 DAYS
COURSE CORRECTION BURNS CONTINGENCY EVA
CREW OBSERVATION AND READAPTATION
POST FLIGHT DEBRIEFINGS AND PUBLICITY
180 DAYS
Preparation for Transearth Injection - 1 Day
Transearth Burn Few Minutes
Preparation for Direct Reentry 24 hours
Velocity Reduction Burn - Few Min.
Direct Reentry 20 min.
Impact
Recovery - Few Minutes (Contingency Landing - Hours)

motion of a rigid body with respect to a given reference frame can be described by the velocity vector of any of its points, say P_0, and the angular velocity vector. The velocity of a point is the time rate of change of the position vector in the given reference frame. The angular velocity is the time rate of change of the orientation of the body. We can express the velocity of an arbitrary point P, $\vec{v}(P)$, in terms of the velocity of the point P_0 and the angular velocity $\vec{\omega}$ as follows:

$$\vec{v}(P) = \vec{v}(P_0) + \vec{\omega} \times \vec{r}_{P_0P} ,$$

where $\vec{r}_{P_0P}$ is the position vector of P with respect to P_0 and $\vec{v}(P_0)$ is the velocity of the point P_0. The angular velocity is a free vector given by

$$\omega = \frac{\frac{d}{dt}\vec{c}_1 \times \frac{d}{dt}\vec{c}_2}{\frac{d}{dt}\vec{c}_1 \times \vec{c}_2} ,$$

where $\vec{c}_1$ and $\vec{c}_2$ are two nonparallel vectors fixed to the body.

Acceleration If the velocity vector of a point changes with time, that point is undergoing an acceleration. The acceleration of a point P with respect to a given reference frame is defined as the time rate of change of its velocity vector:

$$\vec{a}\,(P) = \frac{d}{dt}\,\vec{v}\,(P).$$

If we know the acceleration of a point P_0 of a rigid body and the time rate of change of the angular velocity of the body, we can determine the acceleration of an arbitrary point P with the aid of the following relation:

$$\vec{a}\,(P) = \vec{a}\,(P_0) + \vec{\alpha} \times \vec{r}_{P_0P} + \vec{\omega} \times (\vec{\omega} \times \vec{r}_{P_0P}),$$

where

$\vec{a}\,(P_0)$ = acceleration of the point P_0,

$\vec{\alpha} = \frac{d}{dt}\vec{\omega}$ = angular acceleration.

Centripetal Acceleration When the motion of a body is of the nature of a rotation about a fixed axis that may or may not pass through the body, then every point of the body moves on a circle which lies in a plane perpendicular to the axis of rotation. In such a case, the acceleration of each point is usually decomposed into a component tangential to the circular path and a radial component that is directed toward the center of rotation. The tangential component of the acceleration

$$a_t = R\frac{d\omega}{dt} \text{ (R = radius of the circle),}$$

is also referred to as the azimuthal acceleration, while the radial component

$$a_\rho = R\omega^2$$

is called centripetal acceleration.

Coriolis and Centrifugal Forces Newton's second law can be formulated also for the motion of a particle relative to a noninertial reference frame (a reference frame that is itself moving in a nonuniform fashion and/or is rotating) if we supplement the real forces acting on the particle by two fictitious forces—the so-called centrifugal force and the Coriolis force. The centrifugal force $\vec{Z}$ is defined as

$$\vec{Z} = - m\vec{a}_f,$$

where m is the mass of the particle and $\vec{a}_f$ is the acceleration of following or drag acceleration, i.e., the acceleration the particle would have if it were fixed to the moving reference frame. The Coriolis force is defined as

$$\vec{C} = - 2m\vec{u} \times \vec{v}_r,$$

where $\vec{u}$ is the angular velocity of the moving reference frame with respect to an inertial reference frame and $\vec{v}_r$ is the velocity of the particle relative to the moving reference frame. For the motion of the particle with respect to the moving reference frame we can then write

$$m\vec{a}_r = \vec{F} + \vec{Z} + \vec{C},$$

where $\vec{a}_r$ is the acceleration of the particle relative to the moving reference frame and $\vec{F}$ is resultant of the real forces acting on the particle.

The Coriolis effect, or phenomenon (an ill-conceived term), refers to the vestibular disorientation and motion-sickness syndrome most commonly induced by head motion in an altered gravitational or accelerative field. It has been attributed to the effect of Coriolis acceleration on the semicircular canal system.

Gravity That force which is produced by mass attraction between bodies. When a mass is subjected to gravitation, the resulting force (acting vectorially) is its weight. Although the forces due to inertia and gravitation are not identical, no distinction is made in studying their effects.

g A symbol for the acceleration produced by the gravitational field of the Earth, approximately 981 cm/sec^2 (standard).

G (dimensionless) The symbol for the ratio of gravitational or accelerative force divided by the force of the Earth's gravity.

It is used often to connote an accelerative force (i.e., G-stress, G-tolerance) and as an inertial resultant of accelerative forces (i.e., a force of 3 G).

Often symbols and descriptors are used to denote the direction of gravitational and inertial forces in relation to the reactive displacement of body organs and tissues. Figure 6 presents and explains this nomenclature.

G-Seconds The product of acceleration and the time of exposure. Used often as index of stress and tolerance.

Vibration A periodic or random motion of a mechanical system about equilibrium configurations. It is usually defined by the frequency and amplitude of displacement. The direction of the acceleration vector induced by the vibration in relation to the human body may be described by the G_x, G_y, G_z coordinate system as defined for linear acceleration in Figure 6.

Impact Rapid changes in the momenta of bodies.

Tolerance The capacity to endure the effects of the mechanical forces under consideration. Tolerance limits may be drawn on the basis of performance decrements, subjective criteria, physiological responses, or injury.

Characteristics of the Stress Factors and Conditions of Test and Subject

To understand the physiological effects that may result from exposure to gravitational or accelerative forces, it is necessary to know in detail the determinants of the physical stresses, the environmental and operational conditions, and the condition of the subject.

A. Parameters and variables of stress: Pattern or profile of exposure

1. Rate of on-set and off-set of stress
2. Magnitude(s) of stress reached
3. Duration of maximal level(s) of stress
4. Total duration of stress
5. Direction of primary or resultant stress with respect to body axis
6. Frequency of oscillations (for vibration)

B. Environmental and Operational Conditions

1. Body support, restraint system and its coupling to the body

2. Body position; angles of the head, legs, and back
3. Performance requirements
4. Protective devices and countermeasures
5. Interactions with other environmental stresses

C. Condition of the Subject

1. Age
2. Physical condition and health
3. Emotional factors
4. Motivation
5. Previous acceleration training and experience (possible cumulative effects)
6. Physical characteristics of the body that may modify transmission of forces
7. Diurnal cycle
8. Instrumentation of subject

D. Normal ranges of tolerance

Sample G-Force Profile of Prolonged Space Flight

Most of these variables that pertain to prolonged space missions cannot be precisely predicted at this time. However, based on available engineering and physiological information, general descriptions of the anticipated gravitational and inertial stresses and their physiological consequences can be tentatively made.

Figure 5 displays in graphic form the profile of estimated time–activity relationships for a model Mars mission, which can serve as a basis for discussion of the environmental stresses. The time periods described are only rough approximations.

Preflight Period of Training and Observation (6 months) During this time, the crew members will be under normal gravity conditions ($+G_Z$ standing; $+G_X$, predominantly, when recumbent), except for possible brief exposures to centrifugation for training purposes.

Entrance into Spacecraft to Lift-off (2 hours) The only stress expected at this time is emotional.

Launch to Orbital Insertion (15-20 minutes) Over approximately 15 min of accelerative stress, crew members will be exposed to a complicated lift-off profile likely to involve three pulses to transient peak levels as high as $+6\ G_X$. Interactions with emotions, vibration, and noise, and a major adjustment in atmospheric conditions are certain.

Rendezvous and Docking (4-1/2 hours)

Vehicle Erection (10 days)

Preparation for Transplanetary Ejection (1 day) Throughout these periods of weightlessness, crew members will undergo brief G-stresses which should prove insignificant physiologically. The carry-over or "memory" effects of lifelong gravitational and recent accelerative experience will have a persisting, but probably dwindling, effect of uncertain magnitude and duration.

Trans-Martian burn (few minutes) Levels of +0.3–0.35 G_x are expected here; G-levels up to 5.0 G are possible, but the probable peak level will remain 1 G.

Trans-Martian Flight (200 days)

EVA Contingencies (4 hours each)

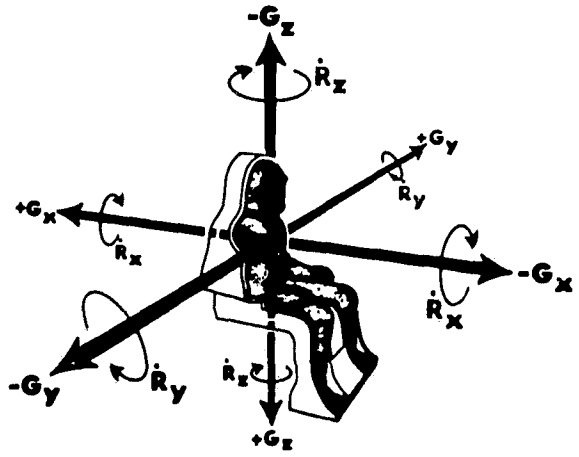
Course-Correction Burns (3-4 minutes each) Through this sustained interval of weightlessness there will be only brief and minor G-experience. Acceleration stress may be provided to prevent the anticipated loss of adaptation to gravitational and accelerative force-fields. Present plans call for a constant or frequent generation of 0.3 G_z if space-vehicle rotation is used for this purpose, and intermittent short-term exposure to +1 to -2 G_z (at the heart) if an on-board centrifuge is used.

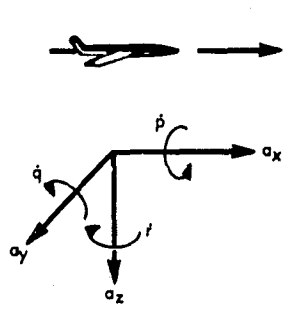
Mars Capture Burn (few minutes) A peak of +2 G_x is estimated for this velocity reduction maneuver, followed by

Preparation for Mars Landing (1 day) When no inertial stresses are anticipated, and

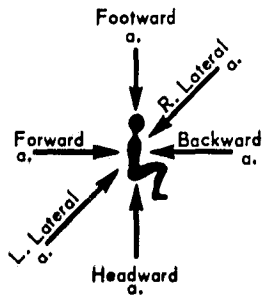
EVA Crew Transfer to MEM (Mars Excursion Module) (1 hour) When only brief, minor G-forces will be produced.

Mars Landing Burn (20 minutes) Three crew members will remain on-board the command module in Martian orbit exposed
150 to continued weightlessness except perhaps for induced, mild $+G_z$ exposures. The remaining three crew members who will descend to Mars may be exposed to up to 0.6 G in the z axis if the lunar-landing configuration is carried over. Major interactions will occur at this point with emotions, vibration, and noise; an unknown $+G_z$ impact force will occur on landing.





SYSTEM 1



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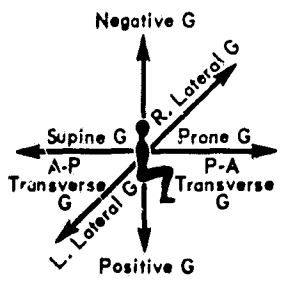
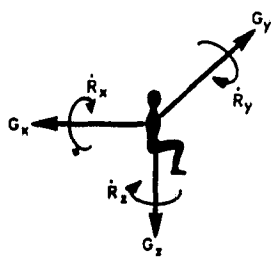


SYSTEM 3



SYSTEM 4

	Direction of Acceleration		Inertial Resultant of Body Acceleration		
Linear Motion	Aircraft Vector (System 1)	Acceleration Descriptive (System 2)	Physiological Descriptive (System 3)	Physiological Displacement (System 4)	Vernacular Descriptive (System 5)
Forward	$+a_x$	Forward accel.	Transverse A-P G* Supine G Chest to back G	$+G_x$	Eyeballs in
Backward	$-a_x$	Backward accel.	Transverse P-A G Prone G Back to chest G	$-G_x$	Eyeballs out
Upward	$-a_z$	Headward accel.	Positive G	$+G_z$	Eyeballs down
Downward	$+a_z$	Footward accel. (tailward)	Negative G	$-G_z$	Eyeballs up
To right	$+a_y$	R. lateral accel. (rightward)	Left lateral G	$+G_y$	Eyeballs left
To left	$-a_y$	L. lateral accel. (leftward)	Right lateral G	$-G_y$	Eyeballs right
Angular Motion					
Roll right	$+\dot{p}$	cartwheel	Roll	$-\dot{R}_x$	
Roll left	$-\dot{p}$	cartwheel		$+\dot{R}_x$	
Pitch up	$+\dot{q}$	somersault	Pitch	$-\dot{R}_y$	
Pitch down	$-\dot{q}$	somersault		$+\dot{R}_y$	
Yaw right	$+\dot{r}$	pirouette	Yaw	$+\dot{R}_z$	
Yaw left	$-\dot{r}$	pirouette		$-\dot{R}_z$	

* A-P and P-A refer to Anterior-Posterior and Posterior-Anterior

FIGURE 6

Acceleration terminology. The symbols and vectors are based on the direction a body organ (e.g., the heart) would be displaced by acceleration. The lower table, and in particular System 4, which is based on displacement of body fluids, explains the most commonly employed terms. Source: Bioastronautics Data Book (NASA SP-3006, Washington, D.C., p. 32, 1964), adapted from C. F. Gell, "Table of Equivalents for Acceleration Terminology Recommended by the Committee on Acceleration of the AGARD Aerospace Medical Panel" (Aerospace Med., 32, 425, 1961).

Mars Habitation (30 days)

Preparation for Lift-off from Mars (1 day) Members of the landing crew will be living under +0.3 G_Z and +0.3 G_X; emotional stresses, strenuous physical activity, and frequent change in atmospheric conditions will be the interacting stresses.

Lift-off to Martian Orbit (10 minutes) +0.3 to -0.6 G is the programmed peak accelerative force; body orientation has not been determined. Emotions, vibration, and noise will interact significantly.

Command Module Orbit Adjust (few minutes)

Rendezvous and Docking (3 hours)

Crew Transfer EVA to Command Module Only insignificant G-forces are expected.

Mars Parking Orbit (50–500 days)

Preparation for Trans-Earth Injection (1 day) Only induced accelerative stresses are anticipated.

Trans-Earth Burn (few minutes) G-forces are expected to reach +3 to -3.5 G_X, but may go as high as +6 G very briefly.

Trans-Earth Flight (200 days)

EVA Contingency (4 hours)

Course-Correction Burns (3–4 minutes each)

Preparation for Re-entry (1 day) Only mild, short-lived G-forces will interrupt this extended interval of weightlessness, unless induced acceleration is provided.

Velocity Reduction Burn (few minutes) G-forces may reach a peak of +0.6 G_X.

Re-entry (20 minutes) A direct, uninterrupted trajectory achieving +10 G_X at peak is presently planned, although the probable over-all G-stress of 1,100 G-sec may require a more complex re-entry profile ("skip") which will permit a somewhat lower

G-load to be distributed over a longer period. This severe inertial stress will be aggravated by the other re-entry stresses: emotions, vibration, vehicle roll-rate, landing impact, noise, and, perhaps, heat.

The loss of adaptation to inertial forces (deconditioning) which is expected following prolonged weightlessness (if preventive measures are not used or are ineffective) may seriously lower tolerance to the aggregate of stresses and require countermeasures.

Recovery Period (few minutes; contingency landing, hours) Re-exposure to the Earth's gravitational field may prove stressful if deconditioning proves to be an important factor and may be a special problem if landing occurs in a contingency area demanding maximal performance for a prolonged period in a hostile environment.

Crew Observation and Re-adaptation (180 days) Gradual re-adjustment to the Earth's environment. Consideration might be given to the use of intermittent centrifugation to hasten readaptation to gravity.

Physiological Effects of Gravitation and Acceleration

The most important primary physiological effect of sustained, distributed forces (force-fields) induced by gravitation and acceleration is the production of hydrostatic gradients, the physiological consequences of which can be affected by changes in body position. The hydrostatic heads induce changes in local vascular pressures and in local extravascular fluid pressures that are defined by the extent of confluency.

A second major effect of these force-fields is the displacement of mobile structures due to: (1) the flexibility of body parts and their support which causes: substantial displacements of body organs (e.g., liver, heart, kidneys); tethering of tissues and blood and lymphatic vessels, producing changes in vascular compliance and geometry and tissue distortion (e.g., lung compression due to displacement of the diaphragm caused by accelerative forces in the $+G_x$ direction); traction and compression of nervous tissue. (2) Density differences causing otolith motion. Of theoretical importance is the sedimentation of the components of intravascular fluids which may produce sensing errors due to changes in effective concentrations and sedimentation of intracellular components.

A third major physiological effect is weight-bearing, producing external and internal compression, traction, and shearing forces which cause: (1) changed skeletal loading; (2) local

tissue distortion produced by reactive forces exerted by external supports and restraints; (3) changes in compliance and pressure of perivascular tissues.

A fourth major effect is the altered thermal convection in gases and liquids which may alter thermal transfer at the skin.

Each of these effects can induce or alter neural and metabolic activity. Tables 2 and 3 depict the important cardiovascular consequences of these responses when G-forces are in the $+G_X$ and $+G_Z$ direction.

Mention should be made here of the high-gradient $+G_Z$ forces induced by centrifugation of subjects on a short-radius spin table. Such a device has been proposed as an on-board operational method for the prevention of deconditioning. The limited research carried on with this device has demonstrated that the cardiovascular effects of such a stress are, in general, qualitatively similar to exposures to distributed inertial forces, but tolerance is greater to the high-gradient force.

Physiological Effects of Vibration

The most important primary physiological effect of vibration is the production of hydrodynamic forces which may cause: (1) stimulation of vascular mechanoreceptors; (2) induction of resonance; (3) standing waves; (4) phasic changes in central and peripheral intravascular pressures, which may alter cardiac filling and output, and peripheral blood and lymph flow; (5) phasic effects on resistance vessels due to periodic pressure variation at the arterioles and venules, inducing myogenic responses (Bayliss effect), and causing variations in capillary pressure; (6) possible intermittent closure of vessels with consequent ischemia or congestion.

The displacement of mobile structures due to flexibility of body parts and their supports is a second effect which may cause: (1) movements and possible damage of body organs and tissues; (2) tethering of tissues and blood and lymphatic vessels; (3) tractions and compression of nervous tissue; (4) frictional heating.

A third major physiological effect is the loading of body structures which causes: (1) changed skeletal loading; (2) movements and possible damage of tissue, due to reactive forces exerted by external support and restraints; (3) changes in compliance and pressure of perivascular tissues and thoracic structures, primarily adjacent to supports and restraints (passive "pumping" of peripheral vessels, the heart, and the lungs).

Each of these effects can induce or alter neural and metabolic activity. Significant vibration stress is unlikely to occur in spaceflight, except in conjunction with linear acceleration forces.

TABLE 2
Cardiovascular Effects of $+G_x$ Acceleration

BPa, Arterial blood pressure
BV, Blood volume
CBV, Central blood volume
CO, Cardiac output
HR, Heart rate
PA, Pulmonary artery
pCO_2, Partial pressure of carbon dioxide
pO_2, Partial pressure of oxygen
RA, Right atrium
R_z, Peripheral vascular resistance
SV, Stroke volume
V_A/Q, Ventilation perfusion ratio
VO_2, Volume oxygen uptake

Primary Effects	Important Physiological Responses			Major Cardiovascular Consequences
Increased Hydrostatic Gradients	↓ BPa in Head and Neck	→ ↓ Perfusion Pressure (Brain) → Unconsciousness (Rare)	→	↑ HR, SV, CO, R_z, BPa
		→ Carotid Sinus Mechanoreceptors	→	
	↑ BPa at Heart and Dorsal to Heart → Aortic Mechanoreceptors		→	↓ HR, SV, CO, R_z, BPa
	↑ BP in RA and PA → Stimulation of Low-Pressure Mechanoreceptors		→	↑ HR
	Pool Blood in Vessels and Tissues of Dorsal Tissues	→ ↓ Effective BV and Venous Return	→	↑ HR ↓ CBV, SV, CO
Displacement of Mobile Structures	↓ V_A/Q → pO_2	→ Tissue Hypoxia	→	↑ HR, CO
		→ Stimulation of Chemoreceptors	→	↑ HR, CO
	Hypoventilation → pO_2	→ ↑ Minute Volume		
	Displacement and Distortion of Heart and Great Vessels; Chest Pain Limits Voluntary Tolerance			

TABLE 3
Cardiovascular Effects of $+G_z$ Acceleration (Abbreviations are the Same as in Table 2)

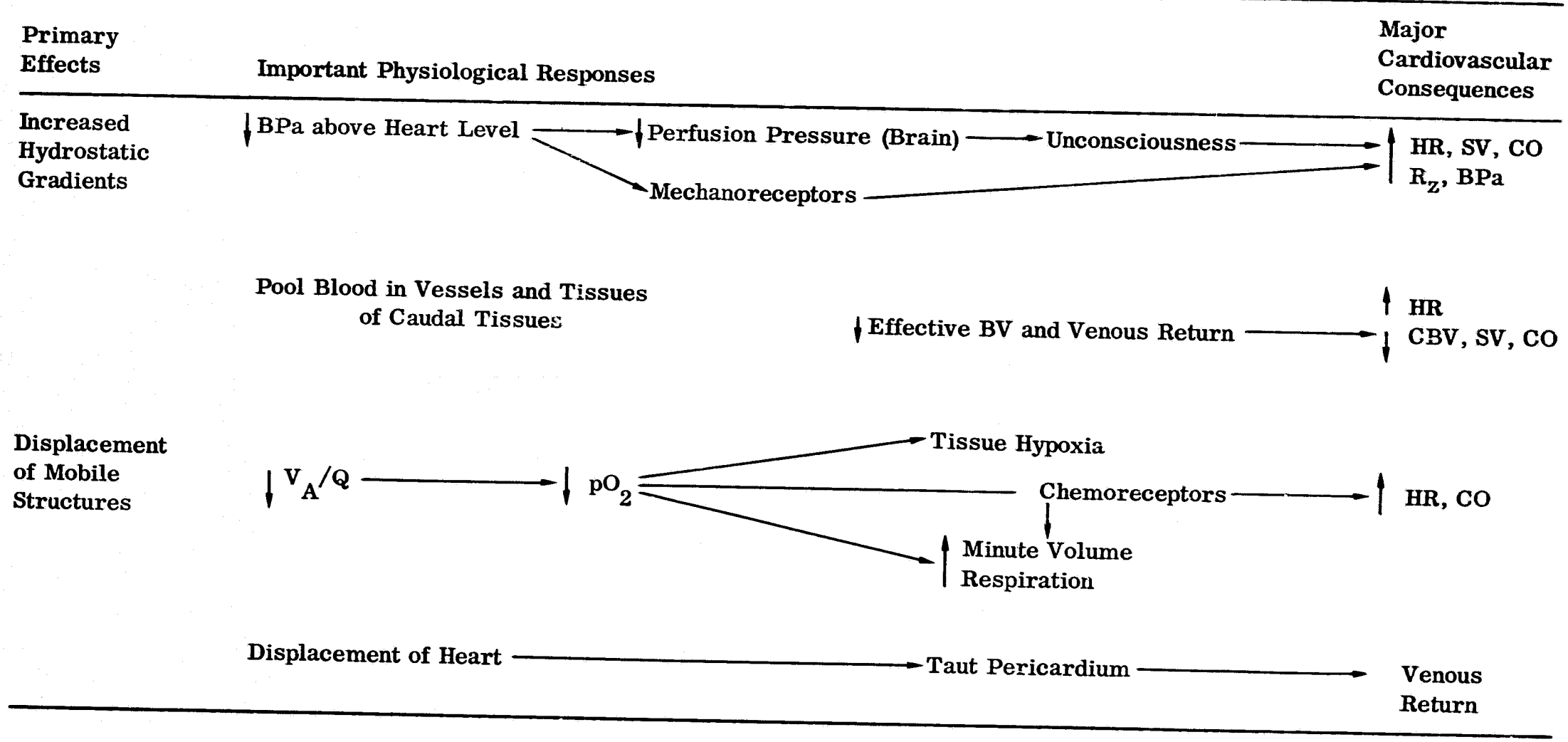


TABLE 4
Cardiovascular Effects of $\pm G_X$ Vibration (Abbreviations are the Same as in Table 2)

Primary Effects	Important Physiological Responses	Major Cardiovascular Consequences
Induced Hydrodynamic Forces and Standing Waves	Stimulation of Mechanoreceptors	↑ HR, SV, CO ↑ R_Z, BPa
Displacement of Mobile Structures	"Pumping" of Lungs ⟶ Hyperventilation ⟶ ↓ pCO_2 ⟶	↑ HR, CO
	↑ Muscle Tension and Metabolism ⟶ ↑ VO_2 ⟶	↑ HR, CO, BPa
	↑ Body Temperature due to Frictional Heating ⟶	↑ HR, CO
Loading of Body Structures by Acclerative Forces	Passive Vascular "Pumping" ⟶ ↑ Venous Return ⟶	↑ HR, CO
	Chest Wall Pain Limits Voluntary Tolerance	

Table 4 depicts the important cardiovascular consequences of these physiological responses.

Physiological Effects of Impact

Because studies of the effects of impact forces have been few and limited in scope, and because the variables of the impacting and the impacted body and restraint systems are so complex, there is little information on the cardiovascular consequences of impact. It is clear that many of the effects of the inertial force involved are similar to those of vibration but often greater in magnitude, although shorter-lived.

No attempt is made here to discuss the forces of angular and Coriolis acceleration, or jerk, jostle, and tumbling, or the extreme complexities of mixed accelerative forces.

Countermeasures to Gravitational and Accelerative Forces

Although limiting the amount and duration of G-stress remains the surest protection, significant improvement in tolerance can often by achieved by: (1) orientation of the body in relation to the force-field ($+G_x$ is the most tolerable orientation, followed by $-G_x$ and $+G_y$ and $+G_z$); (2) respiratory maneuvers; (3) mechanical supports, such as the use of G-suits, elastic leotards, and water immersion; (4) optimizing general health and physical conditions; (5) drugs, a few of which allegedly improve G-tolerance.

Combined Stress

It seems clear that none of the stresses involved in prolonged space flight can be considered independent operationally, for interactions among them will always occur. Very little is known about these interactions and their importance. The frequent association of the several types of gravitation and inertial forces has been mentioned above. Interaction with emotional stresses must be accepted as certain, frequent, and significant. Concomitant exposures to thermal stresses and unusual atmospheric variations seem possible and potentially serious, and the imposition of inertial forces on the subject conditioned to weightlessness is a cause for concern.

WEIGHTLESSNESS AND INACTIVITY

Definitions

Weightlessness A condition in which a mass possesses no weight, as in the absence of gravitational or accelerative forces, or when the vector sum of opposing forces or fields is zero.

Zero gravity The true absence of gravitational force. Often used synonymously with weightlessness, the term zero gravity is usually used to denote the physical state, while weightlessness is often reserved for describing the psychophysiological condition of the individual.

Physical activity Any performance of function or motion of the musculoskeletal system and its supports.

Weightlessness and Physical Activity during Extended Space Flight

The previous section described the anticipated exposures to gravitational and inertial forces during a model prolonged space flight. Except for these relatively brief periods, members of such a mission will be exposed continuously to weightlessness unless gravity is induced artificially. At the present time, experience of weightlessness during space flight and with the simulating environments of bedrest, inactivity, and water immersion suggest that the physiological adaptations accompanying weightlessness may take place in the first several days of exposure and remain unchanging after that time. However, contingency plans call for the development of systems to induce gravity artificially by means of an on-board centrifuge or by means of rotating the space vehicle itself, and the development of gravity-simulation devices, such as the application of negative pressure to the lower body. If deconditioning proves important, serious consideration must be given to the development of pharmacological means to attempt to prevent this space-adapted state and to sustain the cardiovascular system during periods of environmental stress.

During prolonged periods of weightlessness in the confinement of the space vehicle, ordinary physical activity will be diminished. Extensive programs of physical exercise will be required to maintain good physical conditioning and to prevent the physiological consequences of inactivity. During extravehicular activities and during planetary explorations, physical activity will greatly increase and will provide a major cardiovascular

stress. Physical fatigue may become the limiting factor in the execution of these activities.

Physiological Effects of Weightlessness

The most important physiological effect of weightlessness is the absence of hydrostatic gradients, which will particularly affect the cardiovascular system with its long, confluent columns of blood. The major physiological responses are: (1) diminished peripheral pooling of blood; (2) increased ventilation–perfusion ratio in the lungs; (3) also anticipated, but unproved, is initial increase in blood volume and central blood volume due to enhanced absorption of fluid across the capillary membrane. Such an increase causes distention of the central mechanoreceptors for volume (Gauer-Henry reflex), inducing a diuresis and fall in plasma volume to lower than normal values. These subnormal values have been observed to persist for varying periods of time during weightlessness simulation; the reasons for the persistence of this change are not clear; (4) lack of normal stimulation of vascular and nonvascular mechanoreceptors with altered output from the sympathetic nervous system and altered secretion of regulatory hormonal substances; (5) chronic circulatory adaptation to weightlessness with a loss of responsiveness to gravitational and inertial forces (deconditioning).

A second physiological effect is the lack of normal displacement of mobile structures or their constant abnormal displacement. The consequent physiological responses are unknown and unpredictable at present. A third effect is the lack of weight-bearing which causes: (1) diminished muscular activity and oxygen consumption which will bring about changes in cardiovascular function; (2) effects of disuse on metabolic and neuroendocrine functions, which could also affect the cardiovascular system. A fourth effect is the lack of thermal convection in gases and liquids.

Countermeasures to Weightlessness

Two manners of dealing with the possible effects of weightlessness are preventive measures, or treatment of deconditioning during or after exposure to stress. Preventive measures include:

160 Induced Acceleration (a) On-board, short-radius centrifuge to provide periodic, prolonged, low-intensity $+G_z$ acceleration. This device will be costly in terms of weight, space, power complexity, and astronaut time (since no other work can be carried on during centrifugation). Very little is known about the physiological response to the high G-gradient induced with

this device. Animal studies suggest that important, cumulative effects may develop when exposures are frequent. (b) Rotation of the space vehicle to provide very prolonged or constant low-intensity (less than 1.0-G_z acceleration). Simulation studies in a rotating room have demonstrated potentially serious adaptation problems (particularly vestibular) at onset and offset of rotation. This method is also demanding from the engineering viewpoint, but performance is apparently not hampered significantly. Its effectiveness in preserving cardiovascular adaptation to a 1.0-G_z environment is uncertain. (c) Vibration (or head-foot trampoline), although a promising technique has not been adequately studied and presents significant engineering and operational problems.

Lower-Body Negative Pressure The application of negative pressure to the lower body has been used to simulate gravity and has been shown to prevent the loss of gravity-adaptation during prolonged bedrest. Because of its advantages from the viewpoint of weight, space, power complexity, and astronaut time, the device may provide a useful alternative to the centrifuge. Similar physiological effects could probably be obtained by only leg suction. If so, the technique would be preferable to the application of negative pressure to the entire lower body since less apparatus is required and the astronaut would not be immobilized during treatment.

Cycled Venous Occlusion Cuffs on the Extremities This regimen has proved useful in preserving orthostatic tolerance on the tilt table following water immersion, although its success has been inconsistent; the size of the occlusion cuffs and their location, cycling frequency, and pressure are variables which have not been adequately studied.

Intermittent Positive-Pressure Breathing This is a potentially useful method which has not been adequately evaluated.

Drugs and Hormones The biochemical and pharamacological changes associated with adaptation to weightlessness are unknown so that there is no basis on which to prepare a rational treatment.

Vigorous Physical Activity Probably of limited use in preventing the effects of chronic weightlessness.

In regard to treatment of deconditioning before and during exposures to environmental stresses, simulation studies suggest that even when deconditioning has occurred, the cardiovascular system can be re-adapted to the 1-G state by using the measures described above. Also, there is some experimental evidence to

suggest that the restitution of blood volume to a normal or supernormal state will prevent, at least partially, the orthostatic intolerance of weightlessness simulation. Other methods of treatment include mechanical devices, including anti-G suits, elastic leotards, and immersion in water; respiratory maneuvers; and drugs and hormones. Although little information is available concerning the effects of vasoactive substances or hormones on cardiovascular responsivity during stress following weightlessness, there is reason to believe that these drugs and hormones may be useful.

Effects of Physical Activity

The first physiological effect is the production of hydrodynamic forces due to motion (acceleration transients) and to muscular contractions, which cause stimulation of vascular mechanoreceptors as a result of pressure fluctuations. A second physiological effect is changes in the relative position of body parts causing: (1) tethering of tissues and vessels producing tissue distortion and changes in vascular compliance and geometry; (2) traction and compression of nervous tissue.

A third effect is loading of body structures due to forces generated actively or reactively causing: local changes in vascular lumina (active or passive muscle "pumping") and changes in resistance to blood flow; transient changes in local tissue pressure; changed skeletal loading; effects due to reactive forces exerted by external supports and restraints, such as changes in compliance and pressure of perivascular tissues; increased oxygen consumption, production of metabolic products, and heat.

Countermeasures to Inactivity

The cardiovascular effects of diminished physical activity are due to alteration or absence of the changes described above. Circulatory demands are diminished; the circulation is more stable; orthostatic intolerance reflects an abnormal response to inertial forces. There is every reason to believe that proper, programmed physical activity and exercise will be adequate to prevent the circulatory effects of inactivity.

Combined Stress

Since weightlessness cannot be simulated adequately in the laboratory, there have been few studies of the interaction of weightlessness with environmental stresses. From simulation

experiments, it seems very likely that the space-adapted astronaut would be less tolerant of gravitation, acceleration, vibration, and heat and would have a restricted exercise capability.

ATMOSPHERE

Volume II of this Study (Respiration) describes in detail the atmospheric changes that may be anticipated during extended space missions and discusses the physiological implications of these changes. This section will present only those factors that may affect the circulatory system.

Potential atmospheric compositions being considered are:

Pb (mm Hg)	$\%O_2$	% Inert Gas	P_AO_2[a]	P_aO_2[b]
760	20.9	$79N_2$	103	90–100
380	44.0	$56N_2$	100	90–100
380	44.0	$56N_2$	100	90–100
258	70.0	$30N_2$	103	90–100
258	70.0	30He	103	90–100
258	100.0	—	171	130–140
187	100.0	—	100	90–100

(a) Alveolar oxygen tension.
(b) Arterial oxygen tension.

Effect of Total Pressure

The range of total pressures being considered for spacecraft atmospheres is 760 mm Hg (14.7 psi) to 187 mm Hg (3.5 psi). Several direct results of decreased molecular abundance (decreased gas density) as a function of decreased total pressure have been identified. An increased rate of evaporative water loss at altitude has been reported. This effect has been ascribed to the increased mean-free diffusion path which allows the water to move from the skin more easily. Decreased gas density also causes a decrease in convective heat transfer at low barometric pressures. As a result, problems of heat transfer in man may arise if cabin air movement is not adequate. This effect would be magnified during exercise and by the increased rate of evaporative water loss at decreased pressure.

The rate of absorptive atelectasis is greatly increased at decreased pressure. Atelectatic areas in the lung result in shunting, producing arterial oxygen desaturation. Superimposed accelerative forces will compound the problem by producing a combination of compression and absorptive atelectasis. These

effects will be magnified by the increased compressibility of gases at decreased pressures allowing more alveoli to come to closing volume and pressure.

Effects of Atmospheric Composition

Major Gas Constituents

Oxygen Arterial oxygen tension (P_aO_2) during space missions may range from 90 to 135 mm Hg in steady-state conditions. During high G-loads the P_aO_2 can be expected to drop to 25 to 40 mm Hg, but the drop should be transient. Although short periods (up to 4 hr) of prebreathing oxygen at sea level (pO_2 = 670 mm Hg) have no known cardiovascular effects, the effects of the high arterial oxygen tensions that ensue (620 to 630 mm Hg) should be carefully studied. Normal ranges of arterial oxygen tension have no effect on the circulatory system, but if the atmosphere providing the P_aO_2 is pure oxygen, atelectasis is possible. A P_aO_2 of greater than 100 mm Hg may have undesirable effects on the hematopoietic system. The data in this area are incomplete but indicate a hematological effect by causing a decrease in red cell mass. Transient decreases in P_aO_2 can be expected during G-loadings as an effect of pooling of the blood and atelectasis resulting in increased shunting.

Carbon Dioxide The inspired carbon dioxide in the space cabin will be less than 8 mm Hg. This moderate P_{CO_2} will result in a very slight increase in ventilation but have no effect on P_aCO_2. Carbon dioxide could become a problem in the case of failure of the CO_2 "scrubbers." The response will depend on the final level of CO_2 reached and will be typical of respiratory acidosis.

Inert Gases The use of nitrogen or helium as the inert component of a two-gas cabin atmosphere is currently being considered; neon has not been excluded. Nitrogen has the disadvantage, probably slight, of making the bends (bubble formation in the blood vessels) possible in the event of rapid decompression. Initial decompression at lift-off would be the most likely period for this to occur. The use of helium in a 7-psia atmosphere has the minor disadvantages that (a) the convective cooling capacity of the helium atmosphere is high and requires that cabin temperature be maintained 1 to 2°F higher, and (b) a helium atmosphere at this pressure slightly distorts the voice communications. However, transmissions are still quite understandable.

Minor Gas Constituents

Trace contaminants from the outgassing of space-cabin materials and from man himself will be present in the atmosphere. The current list of known contaminants from these materials contains several hundred compounds. In a leak-free system many of them could reach toxic levels. Unfortunately, toxic levels for man have not been identified for most compounds for chronic exposure, and, therefore, the actual magnitude of this problem cannot be assessed. Carbon monoxide and ozone are two important trace contaminants which have received most investigation.

Particulate Matter

Weightlessness increases the health hazard of particulate matter, since dust does not tend to settle as it does under normal gravity. Any floating particulate matter could be inspired into the lung, block an airway, and result in absorptive atelectasis with shunting of the blood as noted above. Food particles and even mucus can thus represent serious problems.

Atmospheric Considerations for a Model Mars Mission

The comments that follow are based on several assumptions: a cabin atmosphere of 50% oxygen–50% nitrogen at a total pressure of 7 psia, and the currently used 3.7 psia 100% oxygen full-pressure suits for extravehicular activities. It should be pointed out that advances in engineering technology may solve some of the problems raised, particularly if a 7-psia pressure suit becomes a reality.

Prelaunch It will be necessary to maintain the crews in semi-isolation to reduce the possibility of contact with airborne infectious organisms.

Just prior to launch, a 2- to 3-hr pure oxygen prebreathing period would be advisable to provide protection against the bends, particularly if early extravehicular activities are contemplated.

Launch A cabin atmosphere of 14.7 psi will probably be established on the pad prior to launch. At lift-off, the total pressure will be rapidly reduced to 7 psia. This initial decompression should not result in bends. However, the accelerative forces will result in some pulmonary atelectasis and arterial oxygen desaturation. It may be of some advantage to start the launch with an O_2 concentration higher than 50% to maintain arterial oxygen saturation at a higher level. The presence of the inert gas in the alveoli

will tend to hold them open and permit them to re-expand more easily.

Extravehicular Activity During each period of extravehicular activity, the astronaut must decompress from 7 psia to 3.7 psia. The presence of nitrogen dissolved in the blood presents the possibility of bends which will be at least the same, and may be increased, with each repeated period of extravehicular activity. Total ventilation and cooling capacity would be a problem with this suit atmosphere. Water-cooled garments may solve the cooling problem. However, very high metabolic rates may lead to relatively high ispired CO_2 tensions if ventilation through the helmet fails to keep pace. The development of a 5-psia or 7-psia pressure suit would eliminate these problems.

Trans-Martian Flight The atmosphere of 7 psia, 50% O_2–50% N_2 should offer no problems. The presence of nitrogen in the atmosphere will reduce the probability of pulmonary atelectasis and aural atelectasis. In addition, thermal control of the atmosphere should not be a major factor. If normal inspired CO_2 tensions are maintained, a small increase in pulmonary ventilation may result, but arterial tensions will not increase. Failure of CO_2 scrubbing systems could lead to increased CO_2 tensions. The magnitude of the problem will depend upon the CO_2 tension reached and the duration of the exposure before repairs can be made.

Trace contaminants may result in a variety of physiological effects depending on the particular compounds evolved. At present only endogenous CO production appears to be a major problem. Suitable scrubbing systems could be devised to handle most contaminants, e.g., catalytic burners for CO. In addition, material selection criteria could be established to minimize outgassing.

Re-entry During re-entry, accelerative forces will interact as indicated for launch. It may be advisable to enrich the atmosphere with additional oxygen during this period in an attempt to maintain arterial saturation. However, some inert gas should be maintained in the atmosphere.

HEAT

Introduction

At rest in a comfortable environment, heat produced by metabolism is dissipated from the body surfaces by radiative and

convective heat transfer and by evaporation of insensible moisture from the skin and respiratory tract (Gagge et al., 1938).

An increase in heat conductance of body tissues, resulting from an increase in blood flow to the skin, is indicated by a greater heat transfer per degree temperature difference between core and skin. Under extreme heat stress, cutaneous blood flow may increase by a factor of 4 to 6 over the level observed under resting, comfortable environmental conditions (Robinson, 1949). Sweat rate and heart rate are both used as indices of thermal load. The ratio of cutaneous blood flow to cardiac output has been suggested as a single index of strain. Since there have been no simultaneous measurements of cardiac output and cutaneous blood flow in human subjects under heat stress, no direct validation of this ratio as a predictor for the cardiac output has been obtained (Hatch, 1963). This large demand for cutaneous blood flow by thermoregulatory mechanisms imposes a severe strain on cardiac output which can be met only by diverting blood flow from other areas. In case of strenuous exertion, competitive demands for oxygen by active muscles may lead to insufficiency of the circulatory system (heat exhaustion) or failure of the thermoregulatory system (heat hyperpyrexia and heat stroke) (Leithead and Lind, 1964). It is recommended that average skin temperature be used as the variable to be plotted against time with relevance to heat loads of projected activity and internal heat in a model Mars mission.

Heat Stress during Flight

Coefficients for convective and evaporative heat transfer depend on the physical properties of the atmosphere—specifically, viscosity, density, thermal conductivity, and specific heat. The increased diffusivity of water vapor at subbaric pressures will increase the rate of evaporation but not the final equilibrium. There are no fundamental differences in the biophysical mechanics of heat transfer in the weightless state, except the absence of natural convection. Using the theory of heat transfer, Roth (1966) and Epperson et al. (1966) have derived convective heat transfer coefficients for helium–oxygen and nitrogen–oxygen mixtures at different atmospheric pressures. As predicted from theory, convective heat loss is demonstrably greater in a helium–oxygen atmosphere than in a nitrogen–oxygen atmosphere at the same pressure (Epperson et al., 1966). By the same token, comfort can be attained in the former by merely raising temperature or reducing velocity of the helium atmosphere.

Under resting conditions, mean skin temperature is a reliable

index of thermal comfort (Gagge et al., 1938; Yaglou, 1949). In the zone of vasomotor regulation of body temperature, heat transfer by radiation and convection, plus heat loss by insensible evaporation of moisture, maintains heat balance without recourse either to sweating or to shivering. Inputs from the thermoreceptors for warmth and cold are essentially in balance, so that the subject feels neither warmth nor chilliness but rather thermal neutrality. Skin temperature at thermal neutrality is approximately 92°F (33°C). This would be the mean skin temperature observed, for example, in subjects at rest or performing light work while exposed to conditions described by the comfort zone of the Effective Temperature (E.T.) scale (Yaglou, 1949).

The E.T. scale cannot, however, be used as a guide in design of thermal environments in space cabins because it was derived empirically in air at ground level. Any other mixture of gases, or air at any other ambient pressure, would require a different E.T. scale, not only for each gas mixture but for each condition of atmospheric pressure as well.

Parker and co-workers (see Roth, 1966) have proposed lines of equivalent skin temperature for man seated at rest in atmospheres of N_2-O_2 and $He-O_2$ at various atmospheric pressures and velocities. Once the gas mixture and ambient pressure for the cabin atmosphere of post-Apollo flights have been selected, it would seem a relatively straightforward procedure to conduct simulation tests to validate the thermal comfort conditions of the proposed atmosphere by adjusting atmospheric temperature, velocity, vapor pressure, and wall temperature in the experimental enclosure, until mean skin temperature of resting occupants stabilized at about 92°F.

The range of physical activity which could be tolerated under these conditions without active sweating would be limited. Removal of clothing, however, would provide a means of reducing effective insulation and thus allow the astronaut to increase his energy expenditure without recourse to sensible sweating.

In-Suit Operations

Immediately before and during lift-off, during flight emergencies, and in extravehicular activities, the astronaut will rely on the cooling capacity of the pressurized suit. Newly developed liquid-cooled suits (Waligora and Michel, 1966) provide a means not only for maintaining a comfortable mean skin temperature of 92° (33°C) at rest, but also possess sufficient heat capacity to effectively prevent sweating at increased work rates. The thermoregulatory center in the hypothalamus which normally initiates sweating in response to a rise in core or skin temperature can be inhibited if the rise in skin temperature is actively restrained

and forced downward despite a rise in core temperature above the set-point for sweating (Benzinger et al., 1963).

The rise in internal temperature resulting from activity, combined with a controlled lowering of skin temperature by the liquid cooler, establishes a greater core-to-skin temperature gradient, thereby facilitating heat transfer with less increase in cutaneous blood flow. Thus, in a subject having a nominal metabolic rate of 1 met, there is a heat transfer from skin (M_S) of 38 kcal/m^2/hr. If we assume a core temperature of 37°C and a comfortable mean skin temperature of 33°C, conductance can be expressed as follows:

$$\text{conductance} = \frac{M_s}{t} = \frac{38}{37 - 33} = 9.5 \text{ kcal/m}^2\text{/hr.}$$

An increase in metabolic rate to twice the resting value would double the rate of heat loss through the skin. Assuming that core and skin temperature did not change, the conductance factor would increase to 19, requiring that blood flow to the skin also be doubled. If, however, skin temperature is forced downward to 29°, conductance would not increase, since

$$C = \frac{M_s}{\Delta t} \text{ or } \frac{76}{37 - 29} = 9.5 \text{ kcal/m}^2\text{/hr.}$$

Thus by reducing skin temperature by 4°C, work output can be doubled without any increase in cutaneous blood flow.

At work rates four times resting metabolic rate, the same depression of skin temperature would result in a conductance of

$$C = \frac{M_s}{\Delta t} = \frac{4 \times 38}{37 - 29} = 19 \text{ kcal/m}^2\text{/hr.}$$

Hence, instead of a conductance of 38, as would be predicted without the increased core-to-skin thermal gradient, the blood flow to the skin would increase by only a factor of 2, being equivalent to the expected increase, as seen earlier, when resting metabolic rate is doubled. Of course, there will be an incremental rise in core temperature for each increase in metabolic rate. This increase in core-to-skin gradient will to some extent reduce the conductance values used as examples in the discussion above.

The heat pulse would be insignificant. The vehicle is outside the dense atmosphere before high velocities are reached.

Re-entry

Aerodynamic heating of the surface structure of the cabin during lift-off and re-entry gives rise to a heat pulse within the enclosed compartment. In the event that air conditioning fails, occupants would be exposed to transient intense heating by radiant heat from the cabin walls and, to a lesser extent, by convection from the heated atmosphere. Tests exposing subjects to conditions of wall and air temperature simulating such heat pulses have established time–intensity limits for transient heating of unprotected and covered skin above which pain becomes intolerable (Webb, 1964). These limits varied from approximately 210°C for 3 min for nude skin to 260°C for 8 min when the skin was protected by aluminized clothing. The rate of rise of wall temperature in these tests was 55°C/min. At lower rates of rise in wall temperature, skin temperature will remain below the pain threshold. In this case, transient heating of the body as a whole will impose limits to tolerance.

During re-entry, the inner wall temperature of the Mercury vehicles rose at a rate of 28°C/min to a peak of 138°C with a total exposure time to intense heat of approximately 12 min. Kaufman (1963) studied tolerance time of subjects exposed in a chamber in which wall temperatures rose at this rate, with time to peak temperature as the controlled variable. Limit for maximum peak temperature and total time of exposure was approximately 205°C for 17 min.

Murray (1966), in recent studies of cardiovascular responses to transient heating, exposed subjects to two conditions; in the first, a peak temperature of 150°C was reached, and in the second, 205°C. In both cases the rate of rise in wall temperature was the same as in Kaufman's tests (28°C/min). Total exposure time in each was 20 min. Subjects exposed to a peak of 205°C for 20 min revealed clinical and physiological evidence of being close to their limits of tolerance. Earlier studies on pilots by Blockley et al. (1954) indicated that at tolerance limits the rate of heat storage which established tolerance time could be expressed as follows:

rate of heat storage (kcal/hr) × tolerance time = 77 kcal.

Data on estimated rise in mean body temperature in Murray's experiments are in reasonably close agreement with this relationship.

Postflight

If the space vehicle lands in an unplanned area, astronauts may be exposed to such extreme climates as the humid heat of the

jungle, dry heat of the desert, or the frigid temperatures of winter, polar climates or high altitudes. Deconditioning from prolonged weightlessness may reduce their ability to adapt to these hostile environments, and survival will depend on their utilizing available supplies and equipment for thermal protection while awaiting rescue. Water is obviously the basic essential, with food as a secondary requirement. Restoration of physical capacities at Earth's gravity may require a program of graduated exercises.

RADIATION*

Stress Profile

The main sources of radiation to be encountered in space are galactic cosmic radiation, geomagnetically trapped radiation (the Van Allen belts), and solar particle radiation.

Galactic cosmic radiation is composed of protons (about 85 percent), alpha particles (about 13 percent), and the remaining few percent are heavier nuclei ranging up to Z = 10. The energy spectrum of these particles extends up into the GeV (billion-electron-volt) range. However, the fluxes are low and range from 2.5 during the maximum solar activity to 4.5 particles/cm^2/sec during solar minimum. The dose rate to be expected during a solar maximum behind minimum shielding (1 g/cm^2) is 0.6 mrad/hr or 14.4 mrad/day. (The daily dose would be somewhat greater during periods of solar minimum.) The values just quoted are considered typical for free-space conditions during times of maximum solar activity. It is estimated that the whole-body dose rate during solar maximum might run between 5 to 10 rad/year, with a possible increase by a factor of 4 or more during minimum solar activity.

According to Soviet calculations, the daily dose created by galactic cosmic radiation in space without shielding would be 21.5 mrad.

The effects of galactic radiation are difficult to assess. Although the dose rates are low and therefore the over-all doses to be received are also low, this does not necessarily indicate the full contribution to radiation injury.

*A detailed study of this subject, Radiobiological Factors in Manned Space Flight (Wright H. Langham, editor, NAS-NRC Publ. 1487, National Academy of Sciences–National Research Council, Washington, D.C., 1967), has recently been completed by the Space Radiation Study Panel of the Space Science Board's Life Sciences Committee. The reader is directed to this source of detailed information.

Radiation trapped in the Earth's magnetic field is composed of protons and electrons. It is concentrated in two separate zones, the inner consisting predominantly of protons and the outer of electrons. The distinctive feature of the inner zone is its relative stability with time, whereas the outer zone has large and rapid time variations. The inner zone reaches a maximum at 1.5 Earth radii (3,185 km) with an integral flux of slightly more than 10,000 protons/cm^2/sec of 40-MeV minimum energy. The electrons in the outer zone range in energy from about 50 keV to a few MeV, and the soft protons have energy of less than 1 MeV. Presumably it would take the spacecraft about 15 min to go through the high-intensity zone of the inner belt. With minimum shielding (1 g/cm^2), the dose rate inside the space vehicle would equal about 5 rad/hr. The electrons of the inner radiation belt will be deflected by the shielding, and the exposures would be caused predominantly by bremsstrahlung. Therefore the total dose received in traversing the inner Van Allen belt could be of the order of 2.0 to 2.5 rad.

Solar flares and solar-particle events are periodic emissions of high-energy particles from the Sun occurring roughly in correspondence with over-all cycles of solar activity. The particles emitted tend to be predominantly protons; in some events, alpha particles and heavy nuclei have been present. The solar flares are classed according to their optical brightness, ranging from 1 to 4. The generation of protons with dangerous radiation usually follows flares of class 3 to 3+.

For future manned flights, solar-particle events are the most hazardous and may be the most difficult of all natural radiations to cope with, because it is not possible at present to predict when a solar flare will occur nor what its energy characteristics will be. At this time it can be said that an astronaut behind shielding of 3 g/cm^2 during the height of a solar flare could be exposed to doses from 10 to several hundred rads.

Cardiovascular Responses to Radiation

Tissues that divide rapidly and manifest little differentiation are generally the most radiosensitive. Among the most radiosensitive are those that produce the formed elements of the blood—namely, the bone marrow and lymph nodes. Much research has been done in the past to determine the effects of high-intensity radiation on the blood-forming tissues, and there is considerable information in the literature on the subject. Little research has been performed using protracted, low-intensity exposures. Since much of the radiation received during long-term space flights may be of this latter type, more data on its effects are needed. The following paragraphs summarize

the principal effects on high-intensity radiation on the blood elements.

Following total-body exposures in excess of 100 to 200 rad, a slow, progressive drop in the red blood cell, hematocrit, and hemoglobin counts occurs, reaching a minimum 30 to 40 days after exposure. Values may return to normal in about 60 days. Doses in the vicinity of 400 rad or greater may be required to produce a 50 percent drop in red blood cell counts.

Thrombocyte levels in circulatory blood also drop as a result of radiation exposure. They remain stationary or show an initial rise during the first 8 to 10 days. After the 10th day, the platelets drop progressively to a minimum between 20 to 30 days after exposure. They return to above normal values between the 40th and 50th day.

The white blood cells are among the most sensitive indicators of high-intensity radiation exposure. Following radiation exposure, the leucocyte count may actually increase, especially with higher doses, in the first 3 days following exposure, after which it drops to a first minimum on about the 5th to 7th day. It then levels off or tends to increase again until the 14th to 16th day when it drops to an even lower minimum. Recovery then begins and appears to be more rapid following doses in excess of 250 to 300 rad. With doses below 250 rad, the leucocyte count appears to rise less rapidly and may remain in the low normal range for many weeks or even months after exposure.

The lymphocyte count is dose-dependent and starts dropping almost immediately after radiation exposure, reaching a minimum in about 3 to 5 days, and remaining at about that level until well into the 4th week. During the 4th week, recovery begins, and normal values are approached in about 6 to 9 weeks depending on the dose.

In the context of long-term planetary missions, a synergistic effect might be produced if a solar-flare radiation dose were superimposed on protracted, low-level galactic radiation exposure. Space radiation might also affect the cardiovascular system by causing acute but transient changes in both vascular and tissue permeability. The time course of the onset of such changes in both animals and man varies from minutes to days after exposure, and the dose levels to evoke these changes may start as low as 50 rad. In general, permeability changes will be greater, start sooner, and last longer with increasing dose. The mechanism by which radiation causes vascular permeability changes is obscure. Direct damage to vascular endothelium is a possibility. It has been suggested that acute alterations in permeability are associated with some direct physiological mechanism, and some evidence exists implicating venous vasoactive substances.

HIGH MAGNETIC FIELDS

Electromagnetic propulsion systems, the proposed use of high magnetic fields to shield against external ionizing radiation, and other on-board magnetic devices may expose astronauts during prolonged space missions to high magnetic fields.

Studies using perfused and nonperfused turtle hearts exposed to magnetic fields ranging from 3.4 to 15.6 kOe (or to 14,000 G) showed a decrease in the force of ventricular contraction and a varying degree of arrhythmia, suggestive of tetanus. Both the electrical and mechanical manifestations exhibited temporal latency with respect to the onset and cessation of the magnetic field. These changes may be due to alterations in ion transport mechanisms at the membrane level. Using squirrel monkeys exposed to magnetic fields of 70 kOe, an increase of the amplitude of the T wave of the electrocardiogram and an increase in amplitude and frequency of brain waves have been observed.

Young mice exposed to magnetic field strengths varying between 2,500 Oe and 13,000 Oe, develop lesion of the adrenal cortex, in which the fascicular cords are deranged. Since the adrenal cortex functions under the influence of the anterior pituitary gland by way of ACTH hormone, it seems justified to postulate that the organ affected by exposure to high magnetic fields is not the adrenal gland itself, but the hypothalamo-hypophyseal axis. It would appear, therefore, that high magnetic fields may produce significant biological effects, such as alterations in cardiovascular function and histological changes in the adrenal gland. Further detailed studies are necessary and are recommended.

CIRCADIAN RHYTHMS AND SLEEP

Circadian rhythms are cyclic changes in physiological functions with a period of approximately 24 hr. They are observed in virtually all living organisms, including man, under steady-state conditions. Circadian rhythms partially determine the response of the cardiovascular or other systems to such inputs as heat, acceleration and vibration, weightlessness, and isolation. The exact points of interaction between the circadian rhythm and the mechanisms controlling heart rate, peripheral conductance, and blood constituents are not known. Circadian periodicity is endogenous in origin, since the rhythms persist when conditions that normally vary—chiefly light, temperature, and sound—are

held constant. Under such conditions the cycles may no longer follow a period of exactly 24 hr but tend to become slightly longer or shorter than one day; hence the term circadian from circa and dies (Halberg, 1960). These so-called free-running rhythms again become entrained to the 24-hr diurnal cycle by restoring the subject to a natural environment. It is assumed that during prolonged space flight the astronauts' activity would be programmed to combine the work-recreation/rest cycle with a light/dark cycle sufficient to entrain the rhythms.

Circadian rhythms have been observed in essentially all major phyla, ranging from protozoa to plants, animals, and man. The subject has been extensively reviewed in the Cold Springs Harbor Symposium (see especially Hauty et al., 1960) and in the Annals of the New York Academy of Sciences (98, No. 4, 1962). Studies of human circadian rhythms and their significance are discussed by Halberg (1960) and by Aschoff (1965, 1967). Circadian rhythms have been demonstrated in heart rate, cutaneous blood flow, and the formed elements of the blood. Physiological functions, which display the circadian pattern in man, also include cycles in work-recreation/rest, body temperature, renal excretion of water and urinary constituents, hormone levels, and sensory motor performance.

A common experience illustrating the significance of circadian rhythms to human efficiency is that of the person who is rapidly transported by high-speed jet aircraft to a longitude differing by several hours from the traveler's customary time zone. A phase shift results between the physiological rhythms and the external environmental cycle. Adjustment to a normal phase relationship may require several days, during which time disturbances in mental and physical well-being are noted.

In the absence of natural environmental cycles (zeitgebers) which serve to synchronize the circadian rhythms to a period of exactly 24 hr, control of the sleep–wakefulness cycle to a period longer or shorter than 24 hr may lead to successful entrainment of circadian rhythms if the difference is no more than 2 or 3 hr (Kleitman, 1939). If longer than this, entrainment fails and rhythms become free-running. There is much individual variability in the ease of adjusting to artificial daily cycles, although subjects can usually adapt quite readily to artificial cycles of sleep and wakefulness which are multiples or submultiples of 24 hr, such as the usual shipboard watch of 4 hr on duty and 4 hr off (Aschoff, 1965).

The evidence strongly suggests, therefore, that all living organisms have a biological oscillator with a fundamental frequency of approximately 24 hr. This requires that a time dimension be added to the usual concept of homeostatis. Circadian periodicity of physiologic functions appears to have developed through the same evolutionary processes as other

adaptations but represents an adaptation to the diurnal changes in the environment. These rhythms are adaptive in the sense that they "adjust the organism continuously and in advance to the circumstances which are to be expected in the near future" (Aschoff, 1965). Within the terms of reference of this discussion, the significance of circadian periodicity is the clear implication that "the organism is a different biochemical and physical system at different times of the day" (Aschoff, 1965). This has been amply demonstrated in experimental studies which reveal that the capacity of animals to withstand severe stress such as lethal doses of alcohol, inoculation with bacterial toxin, and whole-body x radiation follows a similar circadian cycle (see Aschoff, 1965). It remains to be demonstrated whether resistance to stress varies in a similar fashion in man. For example, it may be that a disruption of rhythm indicates an alteration in the control system. Specifically, an increase of 10 to 15 beats per minute in heart rate from morning to evening alters the factor of safety represented in the range between the existing and the maximum heart rate.

Recent studies have shown marked individual differences in circadian rhythmicity of heart rate in two Gemini astronauts during a four-day space flight. One astronaut displayed a definite circadian rhythm in heart rate, whereas the other did not. There was no control, however, and no correlation was made with performance (Lipscomb et al., 1966). The same authors have described individual differences in body temperature and urinary output in healthy young subjects in simulation experiments on the ground. Failure to take into account circadian rhythmicity in cardiocirculatory measurements introduces an error in comparative data.

Sleep Patterns and the Cardiovascular System

No definitive relationships have been established between sleep patterns and the cardiovascular system. Indeed, the vagueness is more general as evidenced by the conclusions of Masterson (1965): "There is no evidence allowing us to say that sleep deficits have a deleterious effect on life expectancy or general well-being. The questions remain unanswered, as does the other imponderable; how much benefit occurs from deep compared with that from light sleep for the same time."

Although it is accepted as common knowledge that heart rate, peripheral pulse, and blood pressure change with sleep, there is a lack of definition of the relation between the depth or stage of sleep and the circulatory state. It is not clear that the relation between cardiovascular patterns and sleep is dependent on circadian cardiovascular changes.

Sleep may modulate central nervous control of the cardiovascular system in a manner similar to the central alteration of the CO_2 response in the respiratory system. The assessment of the effects on the cardiovascular system of the broad changes of consciousness (central nervous system activiation) from wakefulness to deep sleep, and the transient shifts associated with drowsiness and fatigue requires the development of a reliable system to monitor both electrophysiological phenomena and the state of the circulatory system.

NUTRITION AND WATER BALANCE*

Effects of Nutrition on the Cardiovascular System

Nutrition plays a major role in the maintenance of physiological and psychological homeostasis. Its effects on the cardiovascular system tend to be long-term and cumulative rather than immediate or sharp. A proper protein content in the blood is essential for the maintenance of the circulatory system; a slightly negative or positive nitrogen balance is not so important. The advent of partially or completely synthetic diets, likely to be used in prolonged space flight, may, with their limited variety and their mineral components, introduce problems heretofore unknown with respect to cardiac or smooth muscle, blood proteins, formed elements, and capillary integrity. Particularly where free amino acids, special lipids, and needed trace substances are synthetically compounded, possible effects on the pathophysiology and morphology of the cardiovascular system must be carefully investigated. It is conceivable that closed ecological systems, by retaining trace contaminants and by lacking essential elements may eventually affect food properties and produce harmful circulatory effects. Nutritional effects on the status of myocardium arteriolar reactivity and capillary activity should also be examined.

Individual variations in nutritional requirements may assume importance in prolonged space flight. Requirements for essential amino acids vary by as much as a factor of 2, and vitamin requirements by a factor of 3. Thus items supplied in amounts suitable for some individuals would be excessive for others. Also, preference for some items in a synthetic diet could give

*The subject of nutrition in manned space flight was treated in depth at the Conference on Nutrition and Related Problems, sponspored by the National Aeronautics and Space Administration and the National Academy of Sciences and held at the University of South Florida, April 27–30, 1964. The proceedings were published in 1964 as NASA SP-70.

rise to consumption above the prescribed levels and cause undesired cardiovascular effects.

Habits of eating or diet items that lead to abnormal changes or periodic large fluctuations in the lipids in the blood may also, over long periods of time, accelerate arteriosclerosis and cause difficulties in the cardiovascular tree.

The determination of nutritional requirements will necessarily be related to the programs of physical activity designed to maintain cardiovascular conditioning.

Water and Electrolyte Balance

Alterations in water balance and the consequent control system called into play have an interaction with the cardiovascular system. The cardiovascular system meets changes in fluid requirements by a reduction in its over-all volume primarily on the venous side of the system. The humoral factors that regulate water and electrolyte balance also have influence on the cardiovascular system. Perhaps the most important example of this is renin which, when converted to angiotension, serves as a peripheral vascular constrictor but also is a stimulus for secretion of aldosterone. Over-all changes in water, electrolyte, and colloid content of the extravascular fluid are reflected in a subtle way in the balance between hydrostatic and colloid osmotic pressures at the capillary.

Sodium, potassium, and calcium levels of blood are known to influence the heart with respect both to the conduction system and its contraction system. The influence of sodium and potassium on arteriolar tone and capillary activity are discussed in Chapter 3 under Vascular Reactivity. Calcium and sodium are necessary for normal membrane permeability.

Questions concerning water balance have already arisen in past manned space flights. All the Soviet and American astronauts have experienced extensive weight loss. Their water intake has been limited, due partly perhaps to the inaccessability of the water supply and the difficulty in drinking but also, according to anecdotal information, to lack of thirst. An imbalance of intake and output in the first few days of space flight may well be a natural reaction to a readjustment of the fluid volume. However, this must be clearly shown to be the case, because if it is frank dehydration, it will reflect in the functioning of the cardiovascular system.

While none of the nutritional, water, or electrolyte problems appear now to have serious effects on the cardiovascular system, difficulties may arise as new and novel ways are developed to meet nutritional requirements for longer space flights.

It is also clear that more definitive data must be collected

on the actual changes in blood volume, blood cell, and blood protein that occur during flight to establish whether fluid volume changes as a natural reaction to the weightlessness or whether it changes because of altered patterns of fluid intake and output. At the present time, the data are equivocal on these points.

CARDIOVASCULAR RESPONSES IN SPACE FLIGHT AND SIMULATION STUDIES

Various parameters of the cardiovascular system have been monitored during Soviet and American manned space flights and during experiments designed to simulate stress factors in space. Circulatory responses are charted qualitatively in Table 5 to illustrate the changes that have occurred as a function of time. The time base used in this table conforms with that in Figure 5 and suggests the extent of present knowledge of cardiovascular responses to the space environment as compared with knowledge needed for a Mars mission.

Some specific comments on these physiological responses and on the circumstances in which the investigations have been carried out may be helpful in reviewing the chart.

Manned Space Flights

Blood pressure elevations observed in Gemini astronauts prior to launch and in the preretrofire and re-entry phases have been systolic only and were associated with moderate to rather marked increases of heart rate. Precise data and time relationships are not readily available.

Body weight losses have been observed in all American and Soviet flight crewmen. Attempts to evaluate the time course of the loss of weight by plotting total flight duration against the fraction of the preflight weight lost are frustrated by several facts: (1) the flights have been performed in four different types of vehicles and in different configurations of the same vehicle; (2) at least nine different types of space clothing, including seven different space suits and two types of "shirtsleeve" garments, have been worn; (3) the crewmen have had widely varying activities, physical and mental, and very different intakes of food and water; (4) individual variations in preflight and in-flight physiological responses and in personal habits are well-documented; (5) large and unknown amounts of water have been drunk prior to re-entry, and after landing before weighing could be accomplished; (6) scaled calibration is not certain for some of the

TABLE 5
Cardiovascular Responses in Space Flight and Simulation Studies

MANNED SPACE FLIGHT	PREFLIGHT TRAINING 6MO	LAUNCH SITE 3 WK.	PREFLIGHT EXAM 2 HR.	ON PAD 2-5 HOURS
BLOOD VOLUME				
TOTAL BLOOD VOLUME		—		
PLASMA VOLUME		—		
RED CELL MASS		—		
PERIPHERAL HEMATOCRIT		—		
HEMOGLOBIN-RED CELL CT.		—		
RED CELL KINETICS		—		
BODY WEIGHT		—		
HEART & VESSELS		—		
HEART RATE	—	—	— ↑	— ↑
BLOOD PRESSURE	—	—	— ↑ SYS	— ↑ SYS
ECG (INTERVALS, ETC.)	—	—	—	—
TILT RESPONSE	—	—		
EXERCISE RESPONSE	—	—		

BED REST & WATER IMMERSION	CONTROL	PRELIMINARY OBSERVATION AND/OR PHYSICAL TRAINING 1-6 MONTHS	TRAINED
BLOOD VOLUME			
TOTAL BLOOD VOLUME	—		↑
PLASMA VOLUME	—		↑
RED CELL MASS	—		↑
PERIPHERAL HEMATOCRIT	—		↑
HEMOGLOBIN-RED COUNT	—		↑
RED CELL KINETICS	—		
BODY WEIGHT	—		— ↓↑
LEAN BODY MASS	—		↑
PLASMA ALBUMIN	—		↑
HEART			
HEART RATE	—		↓
BLOOD PRESSURE, MEAN	—		—
CENTRAL VENOUS PRESS.	—		—
CARDIAC OUTPUT	—		↑
STROKE VOLUME	—		↑
CENTRAL BLOOD VOLUME	—		
HEART SIZE	—		↑
VESSELS			
BLOOD CORTISOL	—		(—)
URINE 17-OH STEROIDS	—		(—)
URINE CATECHOLS	—		(↑)
BLOOD ELECTROLYTES	—		—
PROVOCATIVE TESTS			
TILT/LBNP	—		↑
EXERCISE	—		↑
VALSALVA	—		(↑?)
HEAT	—		↑
ACCELERATION	—		(↑?)

LAUNCH 15-20 MIN	WEIGHTLESS FLIGHT UP TO 14 DAYS	PRE RETRO FIRE 3-24 HR	REENTRY RECOVERY 1/2-3 HR	POST FLIGHT IMMED. 0-24 HR.	POST FLIGHT EARLY 24-72 HR.	LATE 20-180 DAYS
				— ↓		
				— ↓ ↑		
				— ↓		
—				↑	↓	—
				↑	↓	—
				— ↓		
				↓	— ↓	—
↑	— ↓	↑	↑	— ↑		
	—	— ↑ SYS	— ↑ SYS	—	—	—
—	—	—	—	—	—	—
				↓	— ↓	—
	--- (MILD EXER.)			↓		

WATER IMMERS, 24 HRS.	BED REST - SUPINE IMMOBILIZATION, ETC. 3-24 DAYS	POST DECONDITIONING OBSERVATION AND/OR PHYSICAL TRAINING IMMEDIATE 0-24 HRS.	1/2 - 6 MO.	RE-TRAINED
↓		↓		—
↓(—)		↓		—
		— (↓?)		—
↑(—)		— ↑		—
↑(—)		— ↑		—
		—		—
↓(—)		— ↓ ↑		—
		↓		—
↑		↓		—
— ↓		— ↑		—
— ↓		↓		—
—		↓		—
—		— (↓)		—
—		↓		—
		— ↓		—
		↓		—
		—		
		—		
↓		(↓)		
—		—		—
↓		↓		—
↓		↓		—
		(↓?)		—
↓				
(— ?)		(— ?)		—

FOR FURTHER INFORMATION ON MARTIAN FLIGHT, SEE OTHER CHARTS

data points. Factors such as these make it most difficult to determine the time course of responses to any of the space-flight conditions or to predict the point in time at which a stable adaptation to the flight environment may be expected to occur.

Simulation Studies

Several factors seriously hamper the interpretation of the results of simulation studies. Among the more notable examples are: (1) variations in design and control of experimental conditions; (2) selection of different populations of subjects, especially in relation to age and physical fitness; (3) varying duration of bedrest; (4) use of different test procedures and measurements; (5) the imposition of tests and procedures during the bedrest which may in some cases have affected the subjects' response; (6) the imposition of a wide variety of countermeasures in attempts to modify the effects of the bedrest.

Again, as in the flight results, it is difficult to determine the time dependency of most of the observed changes. For example, the few attempts that have been made to measure plasma volume repeatedly during bedrest have been inconclusive, probably because of errors introduced by the multiple tracer injections and blood samplings required. Because of the differences in subjects and experimental conditions, the attempt to plot quantitative change against time of exposure to the deconditioning environment yields inconclusive results for most of the variables of interest.

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