V. COUNTERMEASURE SYSTEMS

A. Introduction

Countermeasures Systems (CS) compensate for the detrimental effects of the space environment on crewmembers. While EHLSS systems prevent the space environment from degrading the crews' health status by providing or emulating Earth-normal cabin conditions (e.g. normal temperature, pressure, gas concentration, shields to minimize radiation from reaching the crew, and artificial 1g transit vehicles), CS must compensate for the fact that the crewmember is directly exposed to a hazardous environment. There are three types of CS: (1) those that depend upon preflight selection criteria; (2) those that prevent adaptive responses to microgravity and other space flight environment factors and therefore are prescribed throughout the mission (e.g., intermittant artificial gravity); and (3) those that restore or correct a deficit that only becomes evident during transition to a new g field (e.g., landing on Mars or return to Earth) and would be administered just before and/or after the transition. Ideally, CS will prophylactically intervene to prevent illness, injury, and pathophysiology that would result in behavioral and performance degradation. Countermeasure Systems must provide acceptable mission performance and postflight recovery when: (1) EHLSS cannot provide nominally Earth-normal environmental conditions for crews because science or technology are not available, or where cost and schedule limitations prohibit them; or (2) EHLSS fail, but only for short periods. Critical questions[1] in life sciences that support a constrained research and development program for CS are detailed in Volume II.

B. Constrained Program — Countermeasures for Crew Exposure to Hypogravity

U.S. and Soviet flight experiments, ground-based research, and operational flight experience have identified detrimental effects on human health and performance in microgravity on short-duration missions, even though currently available countermeasures are used. Generally, undesirable effects become more severe with extended exposure duration. Duration of exposure and levels of gravity within transit vehicles and in planetary base habitats are directly related to specific mission scenarios. Likewise, the impact on crew physiology, mission performance, and postflight recovery are mission specific (Table V-1).

The requirements for countermeasures become more complex as NASA advances from Spacelabs to SSF to Moon and Mars missions of increasingly extended duration with multiple gravity levels (Table V-2).

Although improved capability is desirable, the Apollo Program demonstrated the ability for crews to successfully perform short-duration Moon mission tasks during microgravity transit EVA and surface (0.16g) EHA. Gravity thresholds for biological processes have not been determined. Therefore, the impact of extended duration exposure to 0.16g on the Moon surface is unknown. Consequently, the requirements for countermeasures in long-duration Moon bases cannot be fully defined.

Footnote 1. 11.5% of the criticality 1 and 2 questions support a constrained CS program (Volume II, Table 2).

TABLE V-1
PROTECTION AGAINST HYPOGRAVITY EFFECTS

MISSION SCENARIOS	SYSTEMS PROVIDING CAPABILITY		
	ENVIRONMENTAL HEALTH & LIFE SUPPORT	COUNTER-MEASURES*	MEDICAL CARE
(1) Transit Vehicles			
• Mars Missions	X*	X*	C
• Moon Missions			C
• EVA			C
(2) Planetary Surfaces			
• Base			
Mars	TBD	X	C
Moon	TBD	X	C
• EHA			
Mars			C
Moon			C

* — May include artificial gravity
X — Implies the potential for a solution
C — Contingency capability for limited and temporary intervention or treatment
TBD — Indicates uncertainty about system requirements at 0.16g and 0.38g

Data from U.S. and Soviet space flights dictate a critical requirement for improved countermeasures in microgravity transit vehicles. The known detrimental effects of microgravity, and the absence of biological threshold data or specific data on livingsystems under Mars (0.38g) gravitational conditions make it prudent to plan for countermeasures at a Mars base even in the shortest (<30 day) scenarios. Human centrifuges could be technologically and programmatically feasible as countermeasures for decreased gravity within planetary bases or a Mars transit vehicle. However, scientific evidence on the merit of intermittent gravity loading under these conditions is needed.

The microgravity countermeasures research plan encompasses activities necessary to establish the strategies for developing, testing, and validating the efficacy of procedures, tools, models, and systems necessary to maintain health and performance. This report addresses the most complex case (microgravity Mars transit and effects of 0.16g and 0.38g are assumed to be as serious as microgravity) and assumes that hypogravity countermeasures will be required during Mars transit and Moon and Mars surface activities.

The constrained countermeasures program against hypogravity effects contains critical issues from the following life sciences disciplines:

- Musculoskeletal
- Neuroscience
- Cardiopulmonary
- Regulatory Physiology
- Cell and Developmental.

Table V-2
Microgravity Countermeasure Requirements

Spacelabs	
Current Capabilities	≤16 days µg
SSF	
Orbiter*	30 day µg
Orbiter*	60 day µg
Orbiter*	90 day µg
Station	90 -? day µg
Moon	
Visit	
Orbiter crew:	< 20 days µg
Surface crew:	≈14 days 0.16g Plus several days µg
Outpost	
Orbiter crew:	? days µg
Surface crew:	40-180 days 0.16g Plus several days µg
Settlement	
Orbiter crew:	? days µg
Surface crew:	360-600 days 0.16g Plus several days µg
Mars Simulation	
Moon orbiter:	120-460 days µg
Mars (without artificial gravity)	
Visit	
Orbiter crew:	600-1000 days µg
Surface crew:	
Transit	? days µg
Surface	30-100 days 0.38g
Transit	? days µg
Outpost	
Orbiter crew:	≈1500 days µg
Surface crew:	
Transit	? days µg
Surface	≈600 days 038g
Transit	? days µg

* Options being studied

Countermeasure procedures are currently being developed, utilized, and evaluated in both the U.S. and Russian space programs. The normal sequence of adaptive physiological events, normal variability between individuals, and the interaction among individual countermeasures confound evaluation of their effectiveness. Current countermeasures include:

- Pharmacological (anti-motion sickness, anti-orthostatic intolerance and anti-bone loss drugs)
- Exercise (treadmill, cycle ergometer and resistance exercise; isometric, isokinetic, isotonic and concentric protocols)
- Dietary (fluid loading, mineral and/or metabolic supplements)
- Environmental (lighting, oxygen pre-breathing)
- Mechanical (lower body negative pressure, gravity suit)
- Psychological (ground support, biofeedback)
- Special training (preflight adaptation trainer, skill maintenance).

Crews in Mars transit vehicles with EHLSS systems that may incorporate artificial gravity should experience near Earth-normal conditions. This may be helpful in transit and on return to Earth. Chronic exposure to coriolis forces necessary to create arificial gravity will have to be studied. The physiological response to transition between the vehicle providing artificial gravity and the Mars surface (0.38g) during arrival and departure are unknown. Extensive U.S and Soviet EVA experience suggests that microgravity effects for EVA or transition to Mars gravity from transit vehicles (with 1g artificial) will not require EHLSS or CS. But the deconditioning resulting from stopping the rotation (for 1g artificial) of the transit vehicle may affect performance during and after Mars landing. The physiological and behavioral consequences of repeated, planned or emergency EVAs from a 1g transit vehicle are also unknown.

1. Musculoskeletal

The extensive list of issues (Table V-3) related to musculoskeletal systems reflects: (1) extensive evidence of detrimental effects from U.S. and Soviet space flight; (2) the results of relatively robust flight and ground-based musculoskeletal research programs; and (3) evidence that, without countermeasures, crews are likely to suffer mission limiting (or terminating) injury or illness and/or irreversible damage from a long duration Mars mission.

Table V-3
Musculoskeletal

- • Determine regulation of muscle metabolism during normal activity and exercise, after acute and chronic unloaded states, and during recovery from unloading
- • • Determine the endocrine and nutritional requirements to maintain bone, muscle, and connective tissue, the interaction with mechanical loading and the effects induced by space flight
- • • Determine whether bone loss is reversible in terms of mass, ultra- and microstructural organization
  - -- Extent to which irreversible adaptations in bone architecture affect structural integrity
- • Identify bone and connective tissue markers or metabolism

• = Required for Mars
• • = Required for Moon and Mars

In muscle the primary effect of adaptations to space flight appears to be a loss of contractile protein in the muscle fibers. This translates to a loss in the cross-sectional area of muscle fibers which is proportional to the loss of force potential. The extent of loss remains undefined. The loss in cross-sectional area reflects a general loss of muscle mass. Although there are subsequent and even simultaneous adaptations in the type of contractile protein (e.g., types of myosin) expressed by some fibers, the principal adaptation of physiological significance seems to be the loss of contractile protein.

Connective tissue (bone and soft tissue) function is also affected by space flight. However, the precise effect and time course of changes in connective tissue is not as clearly defined as those in skeletal muscle. It is known that bone growth is inhibited in growing rats during space flight. In older rats bone length is unaffected by short flights (i.e., up to 2 weeks) but some structural remodeling may occur. The effects of space flight on other connective tissue, such as those which contribute to the extra fiber space in skeletal muscle and the tendonous component of muscle and ligaments of a joint remains undefined. Although much less is known about soft connective tissues, initial indications are that they are highly affected by unloading during rat tail suspension, human bedrest studies, and space flight.

The functional significance of these changes lies in the high probability that muscle atrophied because of space flight, if suddenly required to be active, may be particularly susceptible to injury at one or more attachment interfaces between the contractile elements of muscle and the connective tissue that transmits forces to the bones. To develop countermeasures for muscle atrophy, understanding of the mechanisms by which the space flight environment induces muscle atrophy must be significantly improved.

There is clear evidence that forces transmitted by or to musculoskeletal tissues play a modulatory role in the adaptation of bone to space flight and the effectiveness of countermeasures. It is equally clear that some hormones can influence both the kind of proteins expressed (e.g., slow or fast myosin) and the amount of protein. Further, it is becoming increasingly obvious that musculoskeletal tissues may be affected by growth factors. In establishing countermeasure strategies to maintain musculoskeletal homeostasis, it is important to consider that previous research has not been successful in fully preventing atrophy of this system using conditioning paradigms predicated on low force, high frequency activities (i.e., aerobic treadmill and cycling).

Research Requirements. Based on current information, one key goal is to develop countermeasures to the known adaptative changes in space flight that lead to impaired function. Specifically, efforts must be made to define the force patterns of specific types of muscles and bones during routine activities over the microgravity to 1g range to determine the role these forces play in maintaining structure and function of muscle, connective tissue, and bone.

Research efforts to define the role of growth factors in modulating musculoskeletal proteins during growth and development, and during adaptations to the space environment, are equally important. The primary goal for programmatic development of efficacious countermeasures for musculoskeletal function in prolonged spaceflight is to identify factors that influence musculoskeletal protein synthesis and degradation, and its assembly and disassembly as organized intercellular and extracellular and transmembrane functional units (e.g., sarcomeres). A fundamental scientific understanding, which includes the sequence of physiological and molecular events that lead to protein modulation, will provide the basis for selecting effective countermeasures for a variety of functionally unique musculoskeletal units (e.g., flexors vs. extensors, or arms vs. legs).

Since heavy resistance exercise (i.e., high force, low frequency) has been shown to induce muscle hypertrophy in both human and animal subjects, it is reasonable to more extensively explore high force, low frequency countermeasures. It is important to examine: 1) different activity paradigms in combination; 2) the combination of activity and pharmacological and hormonal interventions; and 3) the interaction of activity and intermittent exposure to gravitational loads.

Development of effective measures to prevent, limit, or counter bone loss will require research to: (1) identify the sites, time course, and magnitude of bone loss in microgravity, 0.16g and 0.38g; (2) understand the interactions with other body systems (e.g. endocrine), other space flight factors (e.g., nutrition and circulation rhythms), and countermeasures for other adaptations (e.g., mechanical loading and exercise countermeasure for hypogravity; (3) characterize bone recovery on planetary surfaces (0.16g, 0.38g and 1g); (4) quantify the risk of fractures; and (5) develop countermeasures. It is essential to understand the effects of space flight on the mechanisms which control changes in bones (e.g., balance of osteoblastic and osteoclastic activity, perfusion dynamics, changes in serum calcium balance) in both males and females. The impact of the space flight environment on bone fracture healing in unknown.

2. Cardiopulmonary

The potential for cardiovascular problems is well known from U.S. and Soviet space flights. Cardiovascular difficulties include orthostatic intolerance, headward shift of body fluids, reduction in aerobic capacity and musculoskeletal weakening associated with fluid and electrolyte changes (Table V-3). Various countermeasures for these problems have been implemented both in the United States and Russia, but none has been fully successful. Weakness and orthostatic intolerance pose potential operational hazards during transition to Moon, Mars, or Earth gravity fields, or emergencies during flight.

Table V-4
Cardiovascular

- • Determine relationship (and threshold) between electrical and mechanical (cardiac output and reserve) cardiovascular responses and exposure to various gravity levels (force, frequency and time interval)
- • • Determine most effective countermeasures to avert adverse cardiovascular effects for both long- and short-duration missions and how they should be applied

• = Required for Mars
• • = Required for Moon and Mars

Less is known about the stability of electrical activity of the heart. There is evidence of electrical instability (e.g., arrhythmias) during EVA and during Moon exploration. It is not known whether arrhythmia is part of the orthostatic intolerance syndrome, or more importantly, whether the stress of prolonged weightlessness, increases the occurrence of arrhythmias and reduces mechanical efficiency of the heart. The cardiovascular and pulmonary (e.g., ventilation and respiration) effects of crew exposure to toxins and radiation pose a completely unexplored threat.

Research Requirements. Integrated physiology research programs involving each body system function must address beneficial and detrimental adaptations. Careful study of neurovascular and cardiac responses must continue, and include histological and morphometric (e.g., electron microscopic) studies of small vessels and neural structures. Comprehensive investigations, on Earth and in microgravity, of intracellular and intercellular processes, including elucidation of myocardial cellular and molecular biology, is a promising approach to develop optimal countermeasures. Many of these issues could be clarified by low Earth orbit (e.g., Space Shuttle, SSF) experiments on animals.

3. Regulatory Physiology

Regulatory physiology is central to research programs involving any individual body system and must be incorporated into all investigations aimed at understanding adaptation processes and countermeasures.

The physiology of humans is composed of a totally integrated set of complex subsystems that: (1) adapt to changes in their internal and external environments; and (2) maintain critical physiological parameters (e.g., temperature, fluid and electrolyte levels) at relatively stable levels (i.e., homeostasis). Operational observations andspace flight experiments have demonstrated changes in a wide diversity of these physiological parameters and processes. We do not know which of these changes are simply adjustments to a new homeostatic equilibrium (analogous to changes that occur when humans change diets, altitudes, climates, etc., on Earth) appropriate for the hypogravity environment (i.e., what is "normal" in hypogravity) and therefore do not require countermeasures (in fact countermeasures during space flight could be detrimental). Nor do we know which are life or performance threatening changes that must be ameliorated. It is clear that hypogravity countermeasures must consist of integrated approaches that encompass the complete set of human subsystems, and they must be evaluated for beneficial and detrimental effects (Table V-4).

a. Endocrinology

The transmission of information in the body and its integration across subsystems depends on integrated central nervous system (CNS) and endocrine (neurohumoral, neuroendocrine) communication systems. Recent endocrinology studies of diffuse and extensive control mechanisms outside the CNS (e.g., kidney, gut) have demonstrated widespread regulatory effects. Endocrine and neuroendocrine secretions play an extensive modulatory role, and are the basis for developing and sustaining regulatory changes throughout the body.

Measurement of changes in hormonal synthesis, release, and target cell or organ response during space flight is essential to understanding adaptation to this new environment. Understanding the effect of space flight-induced changes in hormones on the brain is key to homeostatic regulation of physiological processes (e.g., body

Table V-5
Regulatory Physiology

- Determine effects of space flight on sleep cycles and regulation of circadian rhythms and their impact on physiological adaptation, response to stress and performance and develop countermeasure systems accordingly
- Determine how adaptive responses to space flight effect absorption, potency, toxicity and side effects of hormones and medications
- Determine effects of extended missions on kidney functions, especially filtration, reabsorption, secretion and excretion (e.g., fluid and electrolyte losses, kidney stones)
- Determine effects of prolonged space flight, EVA, and countermeasures on thirst, sweating, appetite and body temperature regulation
- Determine nature, time course, and severity of immune function changes in space flight and which factors are responsible
- Determine how space flight factors affect nutritional requirements and gastrointestinal function (e.g., absorption, motility, secretion)

• = Required for Mars

temperature, fluid balance, biological rhythms) and is central to understanding the role of gravity in: (1) the evolution and regulation of living systems, and (2) physiological and behavioral (e.g., emotional state, performance) changes that occur in humans during space flight.

Although data regarding the detailed responses of the neuroendocrine system to extended space flight are limited, it is clear that countermeasures to stabilize endocrine levels are required. Furthermore, pharmacological and behavioral manipulation of the endocrine system is an attractive avenue for introducing countermeasures for other space flight adaptations.

Research Requirements. The changes in hormone levels, receptor activity, and hormone action during space flight and re-exposure to a gravitational and other space flight environment must be understood and countermeasures for detrimental adaptations must be developed. Research to understand the effects of space flight induced endocrine system changes on the function of other homeostatic systems (e.g., cardiovascular, immune, musculoskeletal, and central nervous system) is key to understanding adaptations to space flight, and developing countermeasures for those systems.

b. Fluid and Electrolyte Balance

Mechanisms leading to the acute loss of fluid and electrolytes observed during the initial phase of adaptation to microgravity during U.S. and Soviet space flights are not fully understood. Mechanisms operative in regulation and maintenance of fluid and electrolyte balance during chronic exposure to microgravity are even less defined.

Regulation of body fluid and electrolyte balance is a fundamental homeostatic function. Severe dehydration or loss of electrolytes (especially sodium and potassium) can alter cardiac performance, skeletal muscle function, temperature regulation and cellular electrochemical gradients, potentially resulting in circulatory collapse. The regulation of fluid and electrolytes is essential to the ability to respond to physical and emotional stress. It is important to understand, as completely as possible, the fluid and electrolyte changes that occur during exposure to microgravity, as well as changes in hormones and other factors regulating those balances. A more complete analysis of renal function, including changes in blood urea nitrogen and occurence of kidney stones is required.

Research Requirements. Mechanical, dietary, behavioral, and chemical countermeasures will be evaluated for long-duration missions. Studies should include the magnitude, time course, and steady state levels of changes in key electrolytes within different body fluid compartments, throughout the process of adaptation to microgravity. The functional relationship between changes in fluid and electrolyte regulatory mechanisms and cardiovascular system deconditioning in microgravity should be studied. Ground models, such as antiorthostatic bedrest as a method of simulating microgravity for studying long-duration space flight induced alterations in fluid and electrolyte metabolism, and computer models, should be validated with humans in space. This is essential to enable screening of countermeasure systems for long-duration missions.

c. Hematology

Loss of red blood cell mass is a significant and consistant response to space flight. Further, it may represent a model of the effects of space flight on proliferative tissues. Despite substantial investigation in the United States and Soviet Union, the etiology, biological mechanisms, and potential operational significance of the loss of red blood cell mass have not been adequately defined. The loss undoubtably contributes to orthostatic intolerance and decreased postflight exercise capacity. While the primary cause appears to be the influence of microgravity itself, the etiology is probably multifactorial, including influences such as hypokinesis and hypodynamia, bone demineralization and remodeling, muscle atrophy, altered hemodynamics, modified oxygen demand or oxygen carrying capacity, and nutritional and metabolic disturbances which in turn may be due to microgravity. The influence of other environmental factors such as hyperoxia, hypobaria, ionizing radiation, toxic contaminants, and accelerative stresses of space flight remains to be established.

Research Requirements. Available information does not permit extrapolation of the course of red blood cell dynamics during space missions lasting a year or longer. Nor can the possibility be ruled out that the loss red blood cell mass could compromise the safety and effectiveness of crews in flights complicated by illness, injury, or life support equipment malfunction. Lack of information on mechanisms of red blood cell formation and release during space flight emphasizes the need to acquire more data. Moreover, uncertainties exist as to probable responses of the hematopoietic system during space missions lasting a year or longer. Therefore, reduction in red blood cell mass represents a contingent operational medical problem. Until the cause and mechanisms' of these changes are understood, appropriate countermeasures cannot be developed and validated. However, infusion of red blood cells or erythropoistin are potential solutions.

d. Immunology

Pre- and postflight measurements have demonstrated that space flight causes a suppression of the cell mediated immune system, which returns to preflight levels within approximately 30 days after return to Earth. Due to limited inflight data, we do not know: (1) inflight functional levels, or (2) the time course and magnitude of suppression. Therefore, we cannot predict whether functional levels could stabilize at a new depressed space flight homeostatic level or continue to decline. We cannot predict whether recovery will occur after extended duration missions. Furthermore, we do not know which space flight environmental factor causes the suppression, and we do not know the medical significance.

The immune system of higher animals protects the body from exogenous (e.g., infectious bacteria, fungi, and viruses) or endogenous (e.g., neoplastic) threats to survival. Surveillance and destruction of neoplastic or otherwise antigenically transformed cells before they can form a tumor and metastasize and spread cancer throughout the body will be particularly important in space because the relatively high radiation environment and potential for exposure to toxicants in closed cabins could increase the rate of mutation or tumorigenesis.

Research Requirements. The question of the time course, magnitude, and potential clinical significance of changes in immune competency must be addressed with a program of clinical and scientific investigations involving carefully designed and integrated ground-based and flight experiments. Space flight-related decrement(s) in immune function that would affect the identification and elimination of infectious organisms or surveillance of the internal environment for transformed cells must be identified. Their impact on crew health and safety must be assessed, and, if required, appropriate prophylactic or therapeutic measures developed. This is a particularly vulnerable area since state-of-the-art remedial procedures lag. It will be important to evaluate effects of space flight deconditioning and countermeasure procedures for beneficial as well as adverse effects on the immune system.

4. Neuroscience

Adaptation to space has a major impact on the motor system and on motor coordination because of the absence or reduction of gravity. Major neurological issues are shown in Table V-5. Antigravity muscles are unloaded continuously and antigravity reflexes, utilized in maintaining posture and locomotion on Earth, are inactive or modified. As a result, there is a loss of extensor reflexes in space. This may lead to the fetal posturing of legs that has been observed in space flight. Sensory information about limb position is not interpreted correctly in the absence of vision, and voluntary pointing accuracy and perception of static limb position are impaired. Upon return to Earth, there is postural imbalance and locomotor incoordination, including difficulty in walking and standing with eyes closed, and in executing quick turns. These symptoms occur even after relatively short missions where changes in muscle strength are minor. This indicates that such changes are largely due to lasting effects of adaptation of both central motor programs and the proprioceptive system. Anecdotal evidence from the Soviet space program of physical incoordination even several months after a mission, suggests that motor patterns may take a long time to readapt. The time required to fully readapt to preflight levels after very long periods of exposure to microgravity is unknown. A prolonged period of postural inactivation and impairment of locomotion would not be acceptable in the event of an emergency during the landing on Mars that demanded quick egress from the space vehicle. Moreover, it could also seriously impair the ability of astronauts to accomplish mission tasks, or even care for themselves, in the Mars gravitational environment. There are no known countermeasures other than readaptation during exercise in a 1g environment.

Table V-6
Neuroscience

• •	Determine sensory inputs and coordination of muscular function for generation of posture and locomotion before, during, and after flight
•	If an onboard centrifuge is used as a countermeasure, will repeated transition from 1-g to microgravity cause maladaption
• •	Determine optimal countermeasures for motor readaption to partial gravity or 1-g after adaptation to microgravity
•	Determine whether the decrease in afferent input to the vestibular. proprioceptive, and somatosensory systems that are associated with long-duration space flight result in permanent reflex deficits

• = Required for Mars
• • = Required for Moon and Mars

Research Requirements. Disabling motion sickness on return to a gravitational environment must be understood and alleviated. Studies of the motor system to understand and devise countermeasures to postural readaptation in space are required before a mission to Mars is possible. Important questions related to this objective include: (1) How are the sensory inputs and coordination of motor function organized for generation of posture and locomotion before, during, and after flight? (2) What adaptive processes modify motor control systems, including the occulomotor system? (3) What is the dynamic range of adaptation of motor responses in altered states of gravity? (4) What processes explain the altered perceptions of joint and body position in microgravity? (5) Will the decrease in afferent input to the vestibular, proprioceptive, and somato-sensory systems and the adaptation associated with long-duration flight result in permanent reflex deficits? (6) Are there morphological or structural changes in CNS and neuromuscular functions that form the basis for these deficits? and (7) If an onboard short-radius centrifuge is adopted as a physiological countermeasure, will humans be able to maintain a dual state of adaptation, and will they suffer from motion sickness when transitioning from microgravity to hypergravity?

5. Cell and Developmental

Cell and developmental studies provide the fundamental scientific knowledge and understanding of mechanisms necessary for development of effective countermeasures. Understanding the effect of the space environment on cellular and developmental processes (i.e., the generation, maintenance, differentiation, and turnover of tissue-specific cells) in adult humans is essential (Table V-6). These include erythropoietic stem cells (that produce red blood cells), osteogenic cells (that remodel bone), epithelial cells (that continually differentiate, function, and turnover) and the dynamic morphogenesis and differentiation of microvasculature. Cellular systems that have exhibited potentially serious alterations in space include: immune cell activation, muscle contractile activity and atrophy; mineralization-demineralization dynamics of bone and cartilage; secretory function of exocrine and endocrine epithelia; and cardiac myocyte electrical coordination. Changes in gene expression and altered mitotic activity (e.g., tumor formation) also fall into this category.

Table V-7
Cell and Developmental

- •• Determine microgravity adaptation and other space flight effects on musculoskeletal system responses including:
  - -- Biomechanical unloading
  - -- Fluid distribution, composition and pressure
  - -- Impacts on fluid homeostasis
- •• Determine interactive effects of radiation and microgravity
- •• How do neoplasms common to chronological aging relate to limitation of cell lifespan and susceptibility to abnormal growth regulation under altered gravitational fields?

• = Required for Mars
•• = Required for Moon and Mars

Research Requirements. The key issues that need to be addressed are: What are the effects of reduced gravity or other space flight environmental factors on gene expression, cell division, cell differentiation, cell and tissue interactions, signal generation and reception, signal transduction and target response, endocytosis and secretory activity? It is essential that a variety of cell types (*in vivo* and *in vitro)* be analyzed for microgravitational effects to elucidate mechanisms and develop countermeasures that inhibit or reverse deleterious effects.

6. Artificial Gravity

It is highly probable that imposing some level and pattern of artificial gravitational force on humans over a period of months and years would be an effective countermeasure. However, there is little information available on the physiological effects of intermittent g loading or the effects of different levels of g loading. It would seem prudent to identify how variable levels of gravity can be used to normalize physiological processes. This program should identify the gravity levels that are necessary to maintain affected tissue and physiological systems, determine how these loads should be applied (e.g., continuous vs. intermittent), and provide protocols to minimize or eliminate undesirable side effects. Artificial gravity countermeasures should be integrated with other countermeasures such as exercise, hydration, and sensory-motor training. Additionally, these studies will contribute to our fundamental understanding of the effects of gravitational and coriolis forces on physiological systems.Artificial gravity may be necessary if other countermeasures are not sufficient for long-duration Mars missions. It is possible that artificial gravity countermeasures could reduce the cost and logistics burden while enhancing crew performance on Mars missions. The payoff for artificial gravity countermeasures or a continuous 1g environment on the transit vehicle will be larger if physiological adaptation to Mars gravity (0.38g) is significantly less than that experienced in microgravity, thereby allowing simpler countermeasures throughout the mission.

C. Constrained Program — Countermeasures for Crew Exposure to Space Flight Factors

Living systems have an exquisitely refined capability to integrate sensory input (e.g., visual, thermal, light, nutrient levels, gravity), coordinate global subsystem responses (e.g., circulatory, musculoskeletal), and produce a unified whole body response (e.g., redirect blood flow to body surfaces, sweat and increase water intake to adjust temperature). Furthermore, responses to inflight environmental factors could exacerbate the effects of microgravity (e.g., sleep disturbances and orthostatic intolerance). Therefore, it is artificial to separate the inflight effects of hypogravity from other space flight effects. However, the separation is pragmatically necessary, both for this plan and to design interpretable experiments. Countermeasure systems for these should be readily identifiable. The following life sciences disciplines address critical issues that primarily respond to space environmental factors (Table V-7), but include some aspects of hypogravity response:

- Behavior and Performance
- Environmental Health
- Regulatory Physiology.

Table V-8
Spacecraft Cabin Environmental Factors

Pressure
Temperature
Gas composition
Microbiology and Toxicology (quality/quantity)
Lighting (intensity, quality, duration)
Food (quality, diversity, quantity)
Restricted habitability and personnel hygiene standards
Confinement and isolation
Potentially sustained stressful situations

1. Behavior, Performance and Human Factors

Most of the research in this area is required for a Mars mission, of even the shortest possible duration. The overall issue is effective functioning of a crew enclosed in a confined environment in microgravity and subjected to continuous operational and environmental stress (Table V-8). Problems of morale, hostility, and breakdowns of communication have been documented with increasing frequency as the duration of the interaction increased, even in ground-based operations. Problems are compounded by the stresses of space, for example: (1) deconditioning in microgravity; (2) closed environmental life support systems; (3) unpredictable risk of radiation exposure beyond the magnetosphere; and (4) limited (low Earth orbit and Moon) or extremely long- duration (Mars) escape or abort capability.

Although data are limited, both the U.S. and Soviet space programs have documented behavioral problems, including fatigue, irritability, depression, anxiety, mood fluctuations, boredom, tension, social withdrawal, and motivational changes. Instances of hostility between flight crewmembers, and space and ground crews have been reported. Data from short-duration (10-day) space flights demonstrate

Table V-9
Behavior, Performance, and Human Factors

- •• Determine criteria for evaluating individual and crew performance/productivity
- •• Determine effects of prolonged space flight on behavior and group dynamics (including differences such as age, sex, culture)
- •• Determine critical characteristics of leader influence on productivity and stability among crewmembers
  - -- Define optimal crew command structure for Moon and Mars missions
- •• Establish protocols for training effective ground and space crews in such areas as enhanced communication, crew coordination, interpersonal dynamics, and problem solving
- •• Determine requirements for optimal integration failtomated systems with human capability to maximize productivity and reliability.

• = Required for Mars
•• = Required for Moon and Mars

Although data are limited, both the U.S. and Soviet space programs have documented behavioral problems, including fatigue, irritability, depression, anxiety, mood fluctuations, boredom, tension, social withdrawal, and motivational changes. Instances of hostility between flight crewmembers, and space and ground crews have been reported. Data from short-duration (10-day) space flights demonstrate deleterious effects on physical performance, particularly disturbances in sensory-motor systems, visual function (e.g., illusions) and proprioception. Some reflexes are slightly impaired early in flight but recover after adaptation. Postflight data show similar visual function impairments, including illusions and mass discrimination deficiencies. Explanations of these phenomena include changes due to learning of new perceptual and motor skills and/or effects of spatial disorientation and space motion sickness. The evidence from short-duration space missions indicates that behavioral capabilities can be maintained during space flight despite small decreases in work capacity early in flight. There is no database for long-duration missions.

Investigations of sleep patterns and performance have been conducted on several short-duration missions. Poor sleep quality and fatigue have been reported and approximately 30% of U.S. Shuttle astronauts have requested sleep medication in flight, though none had a history of usage on Earth.

The psychosocial dynamics of small groups of humans living in confined and isolated environments for prolonged periods are not well understood, even for ground operations. Critical issues focus on interactive crew behavior and performance. Selection criteria for crew composition and structure, and training protocols are key areas. They must consider the individual in the context of the group including suitability of skill mix and interpersonal attributes. Selection criteria that address leadership, and its impact on order, morale and group cohesion are critical.

Research Requirements. The most critical research elements include: how the individual will perform; how the group will continue to function effectively; monitoring and compensation strategies for environmental stresses; optimal integration of automation and human capabilities; and crew selection criteria. Behavior and performance countermeasures include: performance evaluation criteria; monitoring and control strategies for performance-related stress effects; mission stage-specific assessments of physical and cognitive performance capabilities; crew selection criteria related to group productivity and stability; protocols for enhanced communications; and development of special EVA performance requirements. Research elements related to performance and group functioning include: microgravity and other space environment factors effects on fundamental behavioral processes such as perception, sensation, learning, and motor skills; physiological changes and reliable correlates of performance; circadian rhythms, sleep patterns and work/rest schedules; and individual and team motivation and coping strategies for environmental stressors. Supporting research includes workloads, schedules, interactions with ground support teams, nonintrusive performance data collection, and modeling of complex performance.

A carefully integrated sequence of events, programmed to facilitate crew selection, should remain sufficiently resilient and elastic to incorporate modifications as the state-of-the-science advances. The process should include: (1) psychological testing to "select out" and "select in" candidates on the basis of personal and group interviews and psychological tests followed by group situations to determine compatibility; (2) simulation training of candidate crews in a high fidelity Mars transfer vehicle mock-up (a confinement period of three to four months will be required to gain experience and data on crew compatibility and performance); and (3) SSF testing for a three to four month exposure to test crew compatibility and performance in microgravity and to provide information for designing the Mars transit vehicle and base.

2. Environmental Health

The major environmental health issue for countermeasures involves adaptative responses of the body to altered pressure, varying concentrations of gases and contaminants (Table V-9). Problems associated with reduced pressure include decompression sickness and physiological problems associated with environmental gas concentrations, including hyperoxia and hypercapnia. Physiolgical monitoring equipment is required to study the effects of alterations in the environment on cardiovascular, regulatory, neurosensory, musculoskeletal, behavioral (performance), and other systems. Countermeasure systems will include surveillance, detection, warning, and remediation.

Table V-10
Environmental Health

•• Determine effects of prolonged exposure to microgravity and other space flight environmental factors

•• = Required for Moon and Mars

Research Requirements. Ground-based research should include studies on decompression sickness, mechanisms leading to countermeasures that facilitate safe EVA, optimal suit pressures, and gas compositions. Ground-based research and flight investigations should address the interaction of hyperoxia, hypercapnia, hypoxia, hypobaria, decompression sickness, ambient pressure, and microgravity. Ground-based research also includes the development of protocols for training to cope with decompression sickness and other adverse physiological responses. Research to develop models to predict physiological response to varying environmental conditions is also needed.

3. Regulatory Physiology

a. Circadian Rhythms/Sleep

Circadian rhythms (i.e., characteristics of living systems that cycle with a relatively fixed and predictable period of about 24 hours) are a fundamental property of most organisms. Circadian rhythmic variations are observed in almost all biochemical, cellular, physiological, and behavioral systems. These rhythms are generated by internal (i.e., endogenous) biological clocks that are normally entrained or synchronized to 24-hour changes in the physical environment by external signals (e.g., light-dark cycle). Extensive biochemical, molecular and cellular studies are ongoing to elucidate the biological mechanisms by which circadian rhythms are generated and entrained.

Biological rhythms are a common feature of regulatory systems, and the proper timing of circadian rhythms is vital for optimal health of organisms. Recent studies of humans focus on the importance of circadian rhythms and sleep for normal mental and physical health, and on methods to influence them for optimizing performance in a variety of work environments. Understanding and managing circadian rhythms in the absence of the normal 24-hour cycle of Earth signals is critical for crew health and performance.

Research Requirements. Countermeasures would include the design of lighting systems, imposed work/rest schedules, time-of-day scheduling of activities such as EVA and exercise, and use of pharmacological agents.

b. Metabolism/Nutrition

Metabolic status and nutritional requirements of humans are affected by changes in physiological state. Responses to weightlessness, limited food choices, and exposure to radiation during space flight could affect human metabolism and nutritional requirements, which in turn affect physiological systems. Thus, metabolic regulation and nutritional balance are integral parts of maintaining health and performance in space. In addition, long-duration effects of space flight on gastrointestinal (including liver) and kidney function and absorption of nutrients are unknown.

The therapeutic effect of drugs depends on the rate at which they are absorbed, metabolized, and eliminated; and on their distribution within the body. Changes in gastrointestinal, hepatic, or renal function or in circulatory dynamics may modify drug pharmacodynamics.

Long-term exposure to microgravity may change metabolic and energy requirements. Therefore, metabolic efficiency and steady state energy expenditure in space during nominal activities, exercise, and EVA should be determined. If there are changes, physiological factors must be elucidated and countermeasures must be developed.

Research Requirements. Countermeasures, discussed in other parts of this report, are being considered for bone demineralization, cardiopulmanary function, muscle atrophy, fluid shifts, electrolyte imbalances, etc. All of these are affected by metabolic and nutritional status. Therefore, nutritional countermeasures are an integral component of other countermeasure systems. For example, exercise is a primary countermeasure against muscle atrophy, and may be useful in minimizing bone demineralization, and provision of special amino acid combinations could aid in preventing muscle atrophy.

c. Temperature Regulation

Temperature regulation is an example of a highly complex, integrated regulatory system that maintains homeostasis in the face of wide variations in environmental conditions. In humans, except for an occasional episode of fever or exercise-induced hyperthermia, body temperature rarely varies more than two degrees centigrade from baseline throughout an individual's lifetime. A normally functioning thermoregulatory system is vital for the health of the individual. For example, thermoregulation is drastically impaired by body fluid alterations during dehydration. Sustained high fever can cause severe damage and even death. Even transient exposure to high or low temperature leads to discomfort and radically impairs sleep and performance.

Alteration of core body temperature observed on COSMOS and Spacelab flights led to numerous thermoregulation studies which document the effect of space flight. Anecdotal data from U.S. and Soviet space studies suggest that there may also be a shift in the thermal comfort zone. Current evidence suggests changes in the capability to homeostatically respond to altered thermal environments (i.e., ambient temperature) or loads (i.e., exercise or EVA). Other components of the space flight environment (e.g., light, pressure, and gas composition) may also alter this system.

Determination of whether a countermeasure system is necessary and establishment of design requirements await further understanding of the effects of space flight on thermoregulation. However, cooling garments have already been used for EVA, and environmental health and hydration strategies may provide simple countermeasures for extended duration missions.

D. Robust Program

The robust program for CS would include development of artificial gravity countermeasures capability as a parallel program with other microgravity countermeasures. The engineering requirements to deliver artificial gravity (e.g., tethers, rotating space craft, short-armed or long-radius centrifuges) would be developed in conjunction with EHLSS applications.

Artificial gravity is the only alternative for a Mars mission, if countermeasures currently being investigated in low Earth orbit are not sufficient for long duration missions. An artificial gravity countermeasure program would begin with investigation of the effects of intermittent g at various g-loads, rotation rates, and frequencies with and without activity as a universal or partial CS. It would include intensive, highly focused studies on the effects of 0.16g and 0.38g. Some studies of intermittent g and the effects of continuously rotating environments can be conducted on the ground using simulators and models. Most of this research will require small variable g centrifuges for a variety of diminutive model organisms and the Centrifuge Facility on SSF. Facilities on the Moon will enhance this research.

Slow rotating rooms will be used to examine the chronic physiological effects of continuous rotation on humans in 1g. The robust program would include a human variable gravity research facility in space to support basic investigations of the efficacy of fractional gravity in attenuating the effects of prolonged exposure to microgravity conditions. This facility would investigate human performance in a prolonged microgravity condition, habitability-related problems of working and living in a partial or intermittent gravity environment, effects of variable-rotation rate, level of artificial gravity required, and effect of duration, performance and productivity. It would evolve to become a full scale prototype used to simulate different scenarios and phases of Moon and Mars exploration missions.

A robust program will include advanced computer models and simulators for all components of the constrained countermeasures program. It will accelerate inclusion of artificial intelligence capabilities and will include enhancements in the basic science studies focusing on the mechanisms which underpin countermeasures development.

The robust program will investigate the extensive knowledge base resulting from experiments on estivation and hibernation in animals both to: 1) understand how modifications in body systems compensate for inactivity, which may provide totally new insights for countermeasures, and (2) to understand how changes in the environment and internal control systems initiate and control reduced metabolic activity, which may provide an initial pathway toward the benefits which would derive from a suspended animation-like capability for long-duration space missions.

E. Requirements for Moon Exploration Missions

Because of the relatively short Moon recovery time and mission duration, Countermeasure Systems can evolutionarily build in complexity from SSF capabilities until they incorporate a full scale operational test of Mars mission capabilities. The boxed lists in the previous discussion identify issues that are not required for Moon missions. The identified differences in life sciences research and technology programs for Moon and Mars missions are due to differences in mission durations and rescue times. Development of countermeasures for Mars missions will require extensive data on long-term effects of hypogravity and other space flight environmental factors, and better understanding of the underlying mechanisms in the musculoskeletal, cardiovascular, regulatory physiology, neuroscience, cell and developmental, and behavior, performance and human factors areas.