APPENDIX B

SKELETAL MUSCLE DISCIPLINE - SUPPORTING MATERIAL

B-1 - Microgravity: Muscle Structure, Function, and Motor Performance

I. Introduction

This appendix presents information concerning the effects of microgravity and/or states of muscle unloading on a) the intrinsic structural and functional properties of skeletal muscle; b) the performance of muscular activities associated with locomotion and other motor tasks both during and following exposure to space flight; and c) the status of countermeasures routinely used to either maintain or prevent observed deficits in musculoskeletal function. Data from both human and animal models from in-flight and ground-based experiments are used.

A. Principles Of Muscle Homeostasis

The skeletal muscle system of adult mammalian species, including humans, is quite stable in a 1G environment in terms of maintaining normal morphological and functional properties. Although muscle protein pools undergo continuous synthesis and degradation, the kinetic properties of these pathways are such that muscle mass and protein phenotype are very stable thereby insuring the maintenance of the key properties of strength, endurance, and locomotor/movement capacity. However, in the absence of a 1G stimulus, these homeostatic properties are altered such that the ratio of protein synthesis to degradation is reduced, and the ability to maintain of protein pools and phenotypes are compromised thereby reducing the capacity of the muscle system to function at 1G. Thus, the central objective of any countermeasure strategy during spaceflight is to maintain or closely preserve the neuromuscular properties that exists at 1G.

B. Principles Of Motor Control

Under normal environmental conditions, the ability of the central nervous system (CNS) to precisely control a wide assortment of movement patterns is remarkable given the variety of conditions under which this control must be managed. All physiological systems that play important roles in the control of movement seem to be affected in one or more ways by the space environment. The supraspinal and spinal pathways of the CNS must provide for both accurate and rapid coordination of a number of neuro-sensory and motor activities regardless of the environmental conditions, i.e., 1-G versus 0-G. In considering any countermeasure to minimize deadaptation to 1 G during spaceflight it is important to recognize that spaceflight results in: 1) changes in visual, vestibular, and proprioceptive function during movement; 2) changes in coordination of activity of flexor

and extensor musculature of the arms and legs in the control of body orientation and locomotion. For example, in microgravity, the relative loading of both the upper and lower extremities are markedly reduced thereby affecting both the velocity and extent of movement in performing both flexion and extension of the various joints. Further, the control of movement is shifted toward the upper extremities, hands, and fingers while relying on the lower extremities chiefly for adjusting the center of gravity.
3) Changes in the neural control of the level of motorneuron recruitment and the force generated by a given muscle or muscle group. This adjustment must be accomplished by modulating the number of motor units from each motor pool needed for a specific task in accordance with the size principle, i.e., smaller motor units recruited first and larger motor units recruited last and by frequencing modulation.

Associated with the changes in the motor activity during spaceflight, as noted above, is the occurrence of a range of detrimental effects on the functional and morphological properties of muscle. Changes in the metabolic and mechanical properties of the musculature can be attributed largely to the loss of and the alteration in the relative proportion of the proteins in skeletal muscle, particularly in the muscles that have an antigravity function at 1G. These adaptations could result in decrements in the performance of routine or specialized motor tasks both of which may be critical for survival in an altered gravitational field, i.e., during spaceflight and during the return to 1G. For example, the loss in extensor muscle mass will require a higher percentage of recruitment of the motor pools for any specific motor task. Thus, a faster rate of fatigue will occur in the activated muscles. Thus, it would appear to be an advantage to minimize muscle loss during spaceflight, at least in preparation for the return to 1G after spaceflight. New insights into the complexity and the interactive elements that contribute to the neuromuscular adaptations to space have been gained from studies of the role of exercise and/or growth factors as countermeasures of atrophy. The present section of the report illustrates the inevitable interactive effects of neural and muscular systems in adapting to space. Only modest progress has been made toward understanding the physiological and biochemical stimuli that induce the neuromuscular adaptations to space.

II. Effects Of Microgravity And Simulation Models On Skeletal Muscle Function

A. Observations on Animals (Rodents):

This section summarizes research concerning the effects of altered loading states on the morphological, functional, and molecular properties of mammalian skeletal muscle. The discussion examines both ground based models (i.e., hindlimb suspension) and spaceflight missions (Cosmos Missions and Space Life Sciences 1 and 2) involving adult rodents whereby the amount of weight bearing chronically imposed on the muscle(s) is markedly decreased thereby inducing a change in the amount and type of protein that is expressed in the targeted muscles. In each of these settings, a number of adaptations occur. These include:

1) Atrophy of both slow-twitch and fast-twitch fibers comprising ankle and knee extensor muscles used for both weight bearing and locomotion.

2) A change in contractile protein isoform expression in a select population of fibers reflecting a faster phenotype for controlling both cross bridge and calcium cycling processes, i.e., the primary pathways for energy consumption in performing mechanical activity.

3) Corresponding changes in the functional properties of the muscle manifesting a speeding of shortening and relaxation properties.
4) A reduction in both the absolute and relative force and power generating properties of antigravity and locomotor muscles.

5) A shift in the force frequency patterns of antigravity muscles whereby a greater frequency of electrical stimulation (i.e., action potential frequency) is needed to generate submaximal levels of force output.

6) A shift in the intrinsic substrate utilization profile of the muscle whereby the capacity to oxidize long chain fatty acids is reduced relative to that of carbohydrate.

7) An increase in enzyme levels supporting the pathways of glycogenolysis and glycolysis.

8) Corresponding increases in the fatigability of muscle groups most likely due to both a reduction in the balance for energy supply to energy demand within a given motor unit and a demand for the expanded recruitment of faster motor units with less resistance to fatigue.

9) A reduction in the oxidative properties of large dorsal root ganglia cells and in small motoneurons, which could impact the function of both sensory and motoneurons.

B. Observations on Humans

Based on over 40 years of experiments from the Russian space program as well as the U.S. space program, including the Apollo and numerous space shuttle flights, a number of observations have been made which demonstrate a wide range of effects on the motor performance of humans. Some of these effects are:

1) Loss of skeletal muscle mass, particularly in those muscles groups that function at 1G to maintain extension against normal gravitational loads, often referred to as antigravity muscles.

2) Reduction in the ability to exert maximum torque at varying velocities of movement, but particularly at the lower velocities of movement.

3) Reduction in size of slow and fast muscle fibers

4) Increase in the proportion of fast myosin in some fibers within two weeks of exposure to spaceflight.

5) Diminished ability to maintain a stable standing posture.

6) An imbalance of the relative bias of activation of flexor and extensor muscle groups, with greater bias toward flexion at 0G.

7) Reduced threshold of the stretch reflex combined with reduce sensitivity to stretch, i.e. less gain in responsiveness at a given level of stretch.

8) Modified sensitivity to cutaneous vibrations to the sole of the foot.

9) Increased susceptibility to fatigue during a given motor task upon return from 0G to 1G.

10) Altered perception of postural position at 0G and upon return to 1G.

III. Functional Significance of Adaptations to Spaceflight

A. Effects On The Control Of Movement

Perhaps the condition in spaceflight in which control of movement is most critical for crew safety is during extravehicular activity (EVA). There are several reasons for the danger associated with EVA. Other than the dangers of solar flares and the remote chance of collision with meteorites, the engineering of the EVA suit, the procedures for pressurizing the suit and the specialized tools needed in EVA can have a high impact on the success of space missions. The space suit, of course, must be pressurized to a level sufficient to avoid the "bends". This situation presents a very significant challenge to engineers primarily because of the required mobility of the arms and head. For the legs, joint mobility is less important but this control is still a factor in the maneuvering of one’s center of gravity. The mobility problem with the upper limbs is that the space suit pressure provides resistance to movement of the shoulders, elbows and fingers. Overexertion of the arms can easily become a limitation in work performance in EVA. Even well before the onset of neuromuscular exhaustion, a reduction in the quality of performance is almost certain to occur. Perhaps, the greatest fear in EVA should be the loss of concentration and attention associated with the greater susceptibility to discomfort and pain which accompanies localized muscle fatigue. A single critically inaccurate movement resulting from these types of distractions could cause an accident. Human factors such as these will impact safety as well as productivity if accommodations in the design of space crafts and related facilities such as a space station are not made. At one stage in the planning of this station, it was being assumed by the architects that there would be as many as 6-8 hours of work per day during EVA and that this would be repeated several days per week while constructing the space station "Freedom". Fortunately, this is no longer the case. The critical question remains, however, "What is an acceptable work schedule given the EVA apparatus to be used?".

The glove of the pressurized space suit presents one of the greatest limitations to work productivity in space . The fine control of the fingers is reduced markedly. There is the obvious loss of the usual touch sensations. In addition, the fingers must grasp objects by overcoming the restrictions in the basic design of the glove and the elevated atmospheric pressure within the glove which creates considerable resistance to grasping movements. The tips of the fingers have become chaffed from the continuous abrasion between the skin and the internal surface of the glove during prolonged EVA tasks . One way to minimize some of these limitations in hand control and other associated limitations in the absence of gravity, has been to devise special tools for EVA activities. During the development of specialized tools for EVA, their use often requires extensive practice in underwater simulations. An additional challenge in the design and use of tools specialized for EVA tasks is the limitation in visibility inherent in the helmet of the spacesuit. The curvature or wrap-around visor of the helmet causes some visual distortion. This distortion actually may be more of a problem in the practice sessions underwater than in space because of the greater refraction due to water. On the other hand, the diffraction caused by the water results in an enlarged image, an advantage that is not available during repair tasks in space.

In planning the construction of structures in space, considerations of human factors must be at a level of sophistication which transcends the point of view that an astronaut or cosmonaut can perform some physical task and survive. Safety and the optimization of productivity in human performance need more emphasis in efforts to expand human presence in space .

When humans enter a microgravity environment, there is an immediate and dramatic reduction in the activation of the extensor musculature required to maintain an upright posture at 1G. The electrical activity (electromyography, EMG) of flexor and extensor muscles in the resting position of the neck, trunk, hip, knee and ankle reflect a generalized flexor bias in flight compared to 1G . This bias has been observed during spaceflight in astronauts when asked to stand upright and this effect is independent of whether or not their feet are anchored to a surface. Further, when they are asked to stand erect with a few degrees of forward tilt, the magnitude of the forward tilt may be as much as four times greater (~12 vs 3°) at 0G than 1G, indicating a relative decrease in extensor activity and/or increase in relative flexor activity. The sites and kinds of sensory information that trigger this exaggerated forward tilt are not understood. This residual flexor bias even after returning to 1G provides a clear indicator of a general adaptation strategy for organizing movements in a 0G environment.

Although a flexor bias persists during flights even after adaptation to 0G, the activity levels of some of the extensor muscles progressively increase within a few days of continued exposure to the 0G environment. This recovery of extensor activity and continued elevation of flexor activity has been clearly documented in ground-based models of weightlessness. For example, extensor EMG activity essentially disappears immediately upon unloading of the hindlimbs in rats. Within hours, however, some EMG activity reappears during continued hindlimb suspension and by 7 days the total daily amount of activation is near normal levels. This pattern has been observed in both predominantly slow (e.g., the soleus) and fast (e.g., the medial gastrocnemus) ankle extensors. In contrast, the EMG activity of the tibialis anterior, an ankle flexor is significantly elevated throughout the suspension period. The "recovery" to normal or near normal levels of extensor EMG activity while remaining "unloaded" suggests that the CNS is "programmed" so that general extensor bias continues as it does at 1G under normal gravitational loads. This apparent residual bias may have been permanently acquired during development as a result of the daily sensory cues of a 1G environment. Alternatively this extensor bias could be inherent in the design of the CNS, i.e., independent of any activity-dependent events associated with movement control in a 1G environment.

The ability to perform movements, including posture and locomotion at 1G, is adversely affected by exposure to as little as one week of spaceflight. All crew members tested to date have experienced some postural instability for 1-2 weeks, or even longer in some instances, following spaceflight. This instability, which varies markedly from crew member to crew member, reflects alterations in perception, sensitivity, and responsiveness. In many cases the altered motor functions may not be readily apparent due to use of compensatory mechanisms such as maintaining a wider stance, taking shorter steps, greater dependence on visual cues and generally being more cautious.

There are a number of physiological measures which reflect altered movement control following spaceflight, particularly altered postural responses to horizontal perturbations e.g. unusual magnitudes and durations of activation of extensor and flexor motor pools. Based on studies of the visiting crews in the Salyut-6 missions ranging in duration from 4-14 days (most for 7 days), the EMG response of the soleus and tibialis anterior to perturbations of the standing position was almost doubled and the response time to the perturbation was 3 times longer after than before flight. Severe postural disruptions following 4-10 days of spaceflight on the shuttle also have been reported. A rapid recovery rate was evident immediately after flight with most of the recovery occurring within the first 10-12 hours post-flight followed by a slower recovery over the next 2-4 days. Further, it was estimated that 50% of the recovery occurred within 3 hours postflight. Adverse postural effects, however, persisted for as long as 42 days after a 175-day flight.

As was true for performance in a maximum torque-velocity test of the plantarflexors, the duration of the spaceflight has proven to not be an important determinant in the severity of postural stability. For example, cosmonauts that had been on the Mir station for 326 days had a similar EMG amplitude response to postural perturbations immediately after flight as before flight. In contrast, the EMG response was doubled in cosmonauts from either a 160-day or a 175-day spaceflight.

Another clear example of the modification in the input-output ratio of the motor system was demonstrated after 7 days of dry immersion. Before immersion the subjects were able to increase the force in relatively constant increments up to about 50% of maximal voluntary contraction in a succession of about 10 trials. After flight, the subjects overestimated the target force considerably even at the lower force levels and the force differential became even more distorted at the higher torques.

Although many adaptations are clearly manifested during the performance of motor tasks at 1G, after having adapted to spaceflight conditions for a specific duration, many details regarding the specific adaptations to spaceflight are not available because of the absence of well-controlled experiments . All studies of humans reflect some unknown combination of the effects of the spaceflight conditions, the measures used to counter spaceflight effects, and the individual differences in responsiveness to both spaceflight and the countermeasures used.

Body movement perception is affected when the magnitude of the gravitational vector is altered. There are immediate and longer-term effects of these altered forces on perception. It is clear, for example, that there are disturbances in oculomotor control, vestibular function, pain sensitivity, muscle stretch sensitivity, joint position sense, and cutaneous sensitivity to vibration, all of which may play some role in modification of motion-position perception in response to spaceflight. Altered perceptions of speed of movement, the effort it takes to perform a movement, and movement of the body relative to its surroundings have been reported when alternating periods of 0G and 2G are imposed during parabolic flights. When subjects raised or lowered their body from a squat position during the 2G phase of the parabolic flight, perceptual distortions of movement were evident. These findings were interpreted as indicating that the motor control of skeletal muscles had been calibrated to a 1G reference level, and that these illusions resulted from mismatches between the efferent control signals and the expected patterns of associated spindle activity.

These studies were continued using perception of upper limb position during parabolic flights, with and without vibration of the biceps or triceps brachii tendons. Because tendon vibration is thought to activate sensory Ia and to some extent IIa afferent fibers from the muscle spindles, and because these receptors are thought to be sensors of angular displacement, these studies provided some insight into the potential role of spindles in the diminished accuracy of position sense observed after spaceflight . The perceived magnitude of displacement from the apparent limb position upon tendon vibration was 1.8G>1G>0G. The subject's perceptions of displacement were consistent with the actual displacements. The results of these experiments suggest that higher G forces on the body required greater postural tonus and an altered gain for the muscle spindles.

Many astronauts have reported that they are not aware of the position of their limbs when they shut their eyes to sleep or relax while weightless; one crew member stated, "It is almost as if the limbs are gone". When they tense their muscles, the position sense returns. One explanation for this phenomenon is not that sensitivity of the receptors is blunted, but that the stimulus is reduced. Interestingly, this sensation is the antithesis of the phantom-limb phenomenon described by amputees, i.e., sensing the presence and even the movement of a limb even though the limb has been amputated. . A consistent observation by those who have experienced 0G for prolonged periods has been upon return to 1G a sensation of heaviness of the body, particularly of the head. Although the selective atrophy of the extensor musculature associated with weightlessness could contribute to this sensation of heaviness. This is not the only factor given that this sensation of heaviness disappears rapidly within a few hours in some crew members. Performing a task with atrophied muscles will require a sense of greater effort than normal since more motor units must be recruited at a higher frequency of activation. In turn, this elevated recruitment is likely to increase the activation of muscle proprioceptors.

The ability to produce maximum plantarflexor torque at velocities ranging from 0 to 180 ^{o}/sec is reduced in short-term (7-14 days) and long-term (75-237 days) spaceflight. After short-term spaceflight maximum isometric torque decreased by 18% and at 60 ^{o}/sec by 38%. After long-term spaceflight maximal torques were 25, 12, 10 and 18% lower than preflight values at 0, 60, 120 and 180 ^{o}/sec, respectively. The changes in torque among the cosmonauts varied considerably ranging from -60 to +15% of preflight values. Although muscle atrophy almost certainly contributes to the reduced torques commonly observed after short- and long-term spaceflights, the characteristics of neural activation of the motor pools also are affected. The highly variable losses in torque at high speeds in some cases and at low speeds at others cannot be easily explained by changes in the muscle properties alone.

Some of the adaptations in the motor responses noted above may reflect, at least in part, the effects of muscle atrophy. The reduced force potential could exacerbate the postural instability of the astronauts and cosmonauts usually attributed to the neural control system upon return to 1G. This possibility seems particularly feasible since the fibers innervated by the motoneurons that have the larger role in maintaining routine posture (i.e., the slow motor units) are the ones that seem to atrophy the most. Further, if the nervous system is not aware of the reduced muscle force potential and does not adjust the output signal accordingly, then the motor output will be reduced. This inappropriate neural input to output relationship will result in an exaggerated movement or sway during standing and may even result in the loss of balance.

In summary, during and after spaceflight the effectiveness of the neuromotor system clearly is compromised. There could be a degradation in functioning of the muscles, synapses within the spinal cord, reception of sensory information by the brain and, in some cases, interpretation and perception of the environment. Dysfunction at any one of these levels at some critical time during a flight could have a major impact on the success of a mission and the safety of the crew members.

B. Implications of Neuromuscular Adaptations for Rapid Egress Capability

The possibility for the need for a rapid egress in case of an accident upon reentry has been reconsidered since the Challenger accident. While some improvements have been made in preparing for an accident upon landing of the shuttle, a clearer understanding of the performance capability of crew members in such a scenario is needed. For example, how rapidly will the crew members be able to escape from the craft in case of an emergency? Based on the experience of both the cosmonauts and the astronauts, it is apparent that the ability to egress suddenly will be limited unless effective countermeasures for the loss of neuromuscular performance are identified and adhered to rigidly during prolonged spaceflights. However, another limiting factor in the egress potential is the flight gear that are worn in reentry. This gear provides significantly elevated loads and heat challenges that could limit egress regardless of success of any countermeasure.

IV. Mechanisms of Striated Muscle Plasticity In Response To Weightlessness

This section examines the effects of unloading on the potential stimuli likely inducing the muscle adaptations to spaceflight as well as the cellular/subcellular processes involved in the adaptive response. Adaptations occurring at the cellular level that result in a change in the quantity and/or quality of protein expression in response to reduced mechanical activity can be regulated theoretically at several levels of control involving transcriptional, pretranslational, translational, and post translational processes. In considering the types of adaptations reported above in the rodent model, available evidence suggests that all of these processes are likely playing a pivotal role.

A. Neuromuscular Activity And Its Role In Plasticity

1. Hindlimb Suspension

Adaptation to chronic unloading of skeletal muscles is determined in part by the manner in which the muscles are activated. The activity patterns of the soleus, medial gastrocnemius and tibialis anterior muscles have been monitored from the same chronically implanted intramuscular electrodes before and during one-month of hindlimb suspension. Total daily EMG activity (mV.sec), measured in the soleus and medial gastrocnemius, was significantly reduced on the day of suspension, was similar to control levels by 7-10 days post-suspension and continued at near-normal levels for the remainder of the experimental period. Daily EMG levels of the tibialis anterior were above normal during all post-suspension days. In addition, the interrelationships of the EMG amplitude patterns, a reflection of the recruitment patterns, between the soleus and medial gastrocnemius were altered on the day of suspension, but recovered to a normal pattern by day 7 post-suspension. These data indicate that the neural mechanisms controlling hindlimb muscles initially change in response to the unloaded environment, but might return to normal within a short period of time after the suspension began.

Riley et al. digitized 16 min of continuous EMG activity per day from the soleus on presuspension days 7 and 4, as well as after 4 and 7 days of suspension. Average total time of soleus activity (normalized per hour) in suspended rats was about 12% when compared to presuspension values and the activity was reported to have a "phasic" compared to a "tonic" pattern. The amplitude (root mean square) of the signals was smaller (25-50%) during compared to before suspension. Bonen et al. recorded 90 minutes of activity from the soleus and plantaris muscles (both primary ankle extensors) over several days before and after suspension; both overall mean amplitude and frequency of motor unit action potentials (based on a "turns analysis") were significantly decreased during suspension compared to normal cage activity.

These data indicate a general decrease in activation duration and amplitude of extensor muscles during the first week of suspension. On the other hand, after longer periods of unloading extensor EMG activity may return to normal. Although chronic tension levels in muscles of suspended rats have not been recorded, it is reasonable to assume that forces in the plantarflexors were small. In addition, it is likely that the plantarflexors were further unloaded when in the plantarflexed position, the usual position during suspension. In contrast, loads on the tibialis anterior were most likely slightly elevated with the muscle maintained in a "stretched" position. It seems unlikely, however, that the greater activity (3-4 times) of the tibialis anterior was due to increased stretching of the muscle during suspension compared to that during routine cage activity since most muscle stretch receptors accommodate rapidly to sustained stretch. In any case the effects of suspension on the actual loading properties of muscle need to be substantiated by recording muscle forces pre-, during, and post-suspension.

2. Spaceflight

The effects of spaceflight on the chronic neuromuscular activity in rats are less substantiated than for hindlimb suspension. Presumably muscle forces during spaceflight would be minimal, although no force data are available. In humans during spaceflight the tonic activity (EMG) of the soleus (a plantarflexor) is reduced, whereas the tonic activity of the tibialis anterior (a dorsiflexor) is enhanced during postural adjustments. This activity reversal of extensors and flexors normally observed at 1G has also been reported during parabolic flights in humans and in monkeys after short-term flights. No chronic EMG or muscular force data from either humans or animals during spaceflight have been published.

B. Reductions in Muscle Strength and Power

Studies on both humans and animals clearly show that the force generating capacity of extensor muscles of the hindlimb are reduced to varying degree following either spaceflight or hindlimb unloading. This reduction has been attributed to a) a decrease in muscle mass reflecting a reduction in the cross sectional area of the muscle fibers; b) a reduction in the capacity to activate the muscle via supraspinal pathways; and c) a reduction in the specific force of the muscle (reduced force corrected for fiber cross sectional area). While it is reasonable to conclude that the reduced force due to atrophy is due to a loss in contractile protein contributing to the contraction process, the underlying mechanisms responsible for the inability to activate the motor unit pool is poorly understood. The same holds true for the factors involved in the reduction in specific tension. Clearly more extensive research is needed on this important problem.

C. Mechanisms of Muscle Atrophy

During states of hindlimb unloading the rate of total protein synthesis (a translational process) is significantly reduced within the first few hours of creating the unloaded state. This is coupled to a subsequent transient increase (over the next several days) in the net rate of protein degradation thereby resulting in a ~ 50% smaller protein pool comprising the muscle, i.e., the muscle becomes significantly atrophied. While both the initiating events and the signal transducing process(es) associated with the atrophy response remains largely unknown (see above), the involvement of either growth factor(s) down regulation or the catabolic actions of other hormones appear to be involved. For example, mRNA signals for insulin like growth factor-1 (IGF-1) expression in skeletal muscle is reduced in hindlimb muscle when the weight bearing activity of the animal is reduced. In contrast, recent findings suggest an opposite response when a skeletal muscle is functionally overloaded, i.e., IGF-1 expression is enhanced. Recent studies on cardiac muscle further suggest that IGF-1 expression is linked to the loading state imposed on the system. Whether there are additional hormonal factors involved in the atrophy response is uncertain.

In this context, there appears to be a critical interplay between mechanical factors and growth-stimulation factors such as growth hormone in the maintenance of muscle mass when challenged by a state of unloading. Furthermore, it has been shown that the time course of the muscle atrophy response to unweighting is altered when cellular glucocorticoid receptors are pharmacologically blocked. Also, under conditions involving muscle wasting in response to exogenous glucocorticoid treatment, a key enzyme, glutamine synthase, is upregulated by elevations in the circulating level of this hormone. This enzyme is thought to regulate both the formation and release of the amino acid, glutamine (i.e., the primary amino acid to which most amino acids are converted during the protein degradation process) from the muscle during the wasting process. Experiments in which the level of glutamine is artificially elevated in both the plasma and muscle during glucocorticoid treatment, markedly reduces both the atrophy process and the decrease in total protein and myosin protein synthesis rates that occur under these conditions. On the other hand, agents that are thought to inhibit the proteosome axis component in the cascade of protein degradation processes appear to be partially effective in ameliorating the atrophy response to weightlessness. The above information clearly illustrates that more basic research is needed to examine the interaction of hormonal and activity factors in the regulation of protein synthetic and degradation processes, especially in the context of the atrophy response associated with muscle unloading.

D. Alterations In Myosin Phenotype

Recent findings involving both cardiac and skeletal muscle suggest that transcriptional and pretranslational control of the slow MHC gene is highly regulated by thyroid hormone (T3). For example, T3, in conjunction with its nuclear receptor and other nuclear regulatory proteins, acts as a negative modulator of transcription of the beta (slow or type I) MHC gene while concomitantly exerting positive transcriptional control of the cardiac fast, alpha MHC gene. Thus, it is interesting that the down regulation of the slow myosin gene typically seen during states of unloading can be inhibited by making the animals hypothyroid. Collectively, these findings suggest that changes in loading state may alter the muscle's responsiveness or sensitivity to thyroid hormone. Furthermore, recent findings on cardiac muscle also suggest that transcription of the beta (slow, type I)MHC gene can be positively regulated by expression of a nuclear factor(s) that binds to a specific DNA sequence (designated as beta e2) upstream of the gene's transciptional initiation site. This factor can be upregulated in the rodent heart in response to pressure overload. Thus, there appears to be a complex interaction of mechanical (loading state)- and hormonal-induced transcriptional factors that are involved in regulating MHC plasticity in response to altered states of muscle loading. Understanding the regulatory factors associated with slow-myosin gene expression is important, because it is predominantly the slow-myosin isoform that is sensitive to gravity state. Further, motor units expressing slow-myosin are the one's predominantly recruited for posture control and low intensity movements.

V. Fundamental Concepts Impacting the Effect Of Countermeasures

A. Basic Physiological Principles For Developing Exercise Countermeasures

Any exercise-related countermeasure for the preservation of skeletal muscle function will be manifested via the spinal mechanisms which regulate the order and number of motor units recruited. In essence, all movements represent the net effect of the number of motor units recruited and which combination of motor units for each muscle that will be recruited, combined with the mechanical restraints placed on the muscles. The selection of which and how many motor units will be recruited is defined in some manner when kinematic features of the motor task is selected. Muscle activity also can be imposed by electrical stimulation of its nerve where it is generally assumed that the most readily stimulated muscle fibers will be those innervated by the largest axons (and thus probably belonging to the largest motor units). Such a recruitment order determined largely by axon diameter, is opposite to that normally used by the central nervous system.

Otherwise, the same general principles as addressed below apply to electrical stimulation of muscle as a potential countermeasure.

In designing an exercise countermeasure, the major variables to modulate are the "level of effort", i.e., the number (and frequency to some degree) of motor units recruited, and the speed at which the muscle will shorten or lengthen. For any given level of recruitment, the changes of muscle length will be defined by the mechanical conditions under which the motor units are activated. The force produced will be a function primarily of the number of motor units (and thus muscle fibers) recruited, and the mechanics which define the velocity and direction of movement. Because the force-velocity relationships are somewhat predictable, the "types" of exercise (high resistance, high power, low resistance, etc.) largely reflect of the number of motor units recruited and the temporal pattern for their recruitment. Whether that force is sufficient to shorten or lengthen the muscle and at what speed the displacement will occur depend on the loading conditions. A high resistance exercise is one in which a high proportion of the units within the appropriate motor pools are recruited and a high load is imposed, resulting in a relatively slow velocity of shortening. If the same recruitment pattern occurs and the load is reduced, then the velocity of movement will increase hyperbolically.

Although these basic physiological concepts derived from isolated (e.g., in situ) experiments are well recognized and generally accepted, they have not been translated into a rational and systematic approach for developing more effective countermeasures for the neuromotor deficits that develop during prolonged spaceflight. Further, a more integrative rather than reductive approach to motor performance is needed. A more integrative physiological perspective also must be maintained in assessing exercise countermeasures with respect to the metabolic consequences and the corresponding adaptations to spaceflight and exercise. Given the interdependence of the motoneuronal and muscle metabolic properties, however, recruitment and metabolic responses of recruitment are essentially inseparable.

Relevant questions for maintaining normal muscle tissue properties appear to be the following: 1) What combinations of forces and velocities will most efficaciously maintain the normal physiological status for each type of motor unit and muscle fiber type? 2) What are the differences in the responsiveness of fiber types and muscle types to specific muscle force-velocity events? For example, does this responsiveness differ in arm versus leg, flexor versus extensor, etc. musculature? and 3) What durations and intermittencies, i.e., work-rest ratios of the mechanical stimuli are necessary to maintain a muscle fiber?

An implied assumption in the above questions is that there are some mechanical event(s) associated with exercise that produce the necessary stimuli for cell maintenance. However, these stimuli could be metabolic or some other event related to excitation-contraction coupling. In any case, the same considerations of the variables noted above would be appropriate for each potential physiological modulator.

B. The Quantity of Activity Needed for Muscle Homeostasis

To counter the atrophic effects of spaceflight one needs to know the means by which the space environment induces the flight effects. Two of the prevalent hypotheses are that muscles atrophy during flight because of a reduction in 1) the activation of the muscles; or 2) the muscle forces associated with the reduction in activation. For example, a common concept which has prevailed for many years is that muscles enlarge when they are active and atrophy when they are inactive. Further, a linear and direct relationship between muscle fiber size and neuromuscular activity or exercise level is often assumed. It is clear, however, that this assumption is incorrect or at least misleading. For example, within a given muscle those muscle fibers which are used (i.e., recruited) the least often are usually the largest fibers. Analyses of biopsies from endurance-trained swimmers and weight-lifters also illustrate that the amount of activity is poorly correlated with fiber size. Thus, it is apparent that the effectiveness of an exercise as a countermeasure for muscle atrophy cannot be based solely on the quantity (total time, number of repetitions, etc.) of exercise. To maintain muscle mass, it appears that a relatively small amount or duration of activity per day is needed and that the amount needed varies widely among fiber types and specific muscles. The more important factor appears to be the mechanical load on the muscle during activation. This view certainly appears to be true in hindlimb suspended rats when the animals are exercised intermittently. These studies suggest that 6 minutes per day of climbing a grid with attached weights (i.e., a relatively high load exercise) had a similar effect of ameliorating muscle atrophy as 90 minutes of daily treadmill exercise (i.e., a relatively low load exercise). Whether a rat exercises for a few minutes or up to 2 hours per day, similar effects are observed on the muscle mass in hindlimb suspended rats. Thus, some minimum amount of muscle activation and force may be required to maintain muscle mass.

In defining exercise protocols and devices to counter the effects of spaceflight on skeletal muscle, the most efficacious exercise may be unique for each muscle group, e.g., extensors vs flexors and muscle type (i.e., muscles that are comprised predominantly of slow vs fast fibers). Further, an exercise regimen that may prevent muscle atrophy may not be the most efficacious in preventing demineralization of bone. It seems likely that reasonable compromises in exercise prescriptions during spaceflight can and must be defined so that a crew member will not need to exercise several hours each day in order to maintain an acceptable functional state while spending prolonged periods in space and during periods of reduced gravitational forces while on the moon or Mars.

C. The Impact of Activity-Hormonal Interactions

Neuromuscular activity may play a facilatory rather than a direct role in maintaining muscle mass. For example, it is becoming increasingly obvious that there can be important interactive effects between exercise and hormones. Glucocorticoids can induce marked and selective atrophy of fast muscles, and weight-lifting or treadmill exercise during glucocorticoid administration can greatly reduce the severity the atrophic response. Similarly, growth hormone alone can significantly decrease the severity of atrophy induced by hindlimb suspension of rats. Interestingly, this effect is greatly amplified when the growth hormone treated suspended rats are exercised (climbing a 1 meter grid inclined at 85^o with weights attached as little as 15 times/day). Further important examples of activity and growth factors are discussed above in, "Mechanisms of Muscle Atrophy".

D. Defining the Acceptable Limits of Muscle Dysfunction in Microgravity

From an operational point of view, some consensus needs to be formulated regarding how much loss of function can be tolerated without a significant compromise in safety and possible long term consequences. For example, one 10-min exercise period per day may be sufficient to maintain 90% of normal function of the extensors of the ankle, knee, hip, trunk and neck, while it may require 90 min/day to maintain 95% normal function. Does 90% of normal function provide an acceptable margin of safety? Similar operational issues are relevant for each physiological system. Also individual differences among the flight candidates should be taken into account, in particular since the results from virtually every study of spaceflight and ground-based models of spaceflight have demonstrated marked individual differences in the response of the neuromuscular system. These unique individual responses may hold the key to a better understanding of the etiology and magnitude of these specific effects. An integrative physiological perspective and experimental approach in determining the adaptability of humans to spaceflight is essential.

E. Lessons Learned From Ground Based Models on Humans

In humans, one model which has been used to study the effects of changing gravitational loads on the neuromuscular system involves wearing a weighted (~13% of body weight) body vest throughout the waking hours. Bosco and coworkers have shown that wearing this weighted vest for 3 weeks resulted in a shift to the right in the force-velocity curve and an increase in the power generated during squat jumping in highly trained athletes. The authors suggested that the subjects had acclimated to a 1.1G environment and when the load was removed for the final testing, the subjects were experiencing the relative sensation of a 0.9G environment. Because of the relatively short experimental period (i.e., 3 weeks), the adaptive responses were thought to be more related to neurogenic (e.g., greater effective activation of motor units) than myogenic (e.g., fiber type adaptations or hypertrophy) factors. It is clear, however, that muscle atrophy occurs very rapidly in response to flight. For example, the rat soleus can atrophy by 25% within 4 days of the initiation of flight. Furthermore, it appears that significant atrophy can occur in humans after 5-11 days of flight.

Kuznetsov and co-workers studied the effects of bedrest with head-down tilt for 30, 120 and 360 days on the size of gastrocnemius fibers. Thirty days of bedrest resulted in ~15% atrophy in both slow and fast fibers. Treadmill exercise of a moderate intensity for 60 min/day for the first 24 days and 120 min/day for the last 6 days did not ameliorate the atrophy. In fact, the fast fibers in the exercised group were 27% smaller than control compared to the non-exercised group. The longer duration study involved two exercised groups. One group started exercising early in the experiment (at 21 days) and included relatively strenuous passive, strength building and locomotor exercise. The second group started a relatively milder exercise program on day 121. The duration of the exercise was either 60 or 120 minutes. Early onset of exercise resulted in the maintenance of fiber size nearer to control values at both 120 and 360 days. The overall mean fiber size was decreased by ~40% in the second group and only by ~15% in the first group. These data suggest that acclimatization to any exercise routine during the early phase of long-term flight, when the rate of atrophy is the highest, may have a significant residual effect by maintaining a critical level of responsiveness to exercise training during the latter phases of a mission.

Greenleaf et al. studied the effects of 30 days of bedrest at a -6^{o} tilt in healthy men. Two groups of subjects exercised in the supine position for two 30-min periods/day 5 times per week. One group performed short-term variable intensity isotonic exercise while the other group followed an intermittent high-intensity isokinetic program. All subjects were tested weekly for muscle performance and peak oxygen uptake. Compared to control, peak torque for the knee extensors progressively decreased showing an ~12% decline after 4 weeks. The peak knee extensor torques were not significantly different among the two exercise trained and the control groups. No consistent effect of bedrest or exercise was observed for the knee flexors.

Cherephakin and co-workers studied healthy males after 7 weeks of bedrest (-4 to 6^{o} tilt). In 3 subjects, the cross-sectional area of the "red" and "white" fibers of the soleus decreased by an average of 28 and 35%, respectively. Some lysis (separation of myofibrils) was evident in the fibers. Leg circumference was decreased by 13% and endurance time for a bicycle test was decreased by 10% following bedrest. The strength of the postural muscles was significantly decreased as well. When a combination of exercise (intermittent bouts of bicycling at a relatively high heart rate in the antiorthostatic position) and electrostimulation was used (25-30 min/day, once or twice/day), the magnitude of all of these adaptations was reduced. In a static endurance test, exercise before electrostimulation had a more positive effect (52% increase) than exercise after electrostimulation (36% increase). During a 30 day bedrest study, 3 subjects had their knee and ankle extensors and flexors in the dominant leg stimulated twice daily for a total of 40 minutes per day on a 3-day on and 1-day off schedule. The electrical stimulation program appeared to have a slight beneficial effect on maintaining the torque-velocity properties of the knee extensors, but not the knee flexors, during the bedrest period. As stated by the authors, however, these data were preliminary and quite variable.

The effectiveness of specific exercise protocols to counter the effects of long-term bed rest on neuromuscular performance has been studied. In a 182-day 4o headdown tilt bed rest study, 18 normal subjects were assigned to three groups: 1) those who exercised with protocols similar to those generally used by cosmonauts on the Mir station; 2) those who exercised about half that intensity; and 3) those who did not exercise. Two measures of neuromotor performance made before and during bed rest were the maximal plantarflexor torque (60 ^{o}/sec) and the EMG amplitude associated with a fixed plantarflexor effort requiring about 10% of the maximum torque. Subjects who exercised at the highest level showed no change in either parameter throughout the study. Subjects who exercised at half that level (i.e., similar to MIR station protocols) showed no loss of maximal torque, but the torque: EMG amplitude ratio was only one third of pre-bed rest levels. For the no exercise group, maximal torque declined by about 40%, while the torque: EMG amplitude ratio declined by 59% at 182 days. These data suggest that exercise protocols similar to those used in spaceflight are sufficient to maintain neuromuscular torques for prolonged periods without weight-bearing. It also appears that reducing the exercise volume by half results in some loss of function, but the loss may be principally in the neural system.

Based on the evidence available to date from laboratory animals and humans, the mass of the extensor muscles of the legs, hip, trunk and neck are likely to be the more difficult ones to maintain. It also appears that these muscles will be affected the most by spaceflight. This might be expected because the difference in the functional demands of these muscle groups at 1G compared to 0G will be greater than for those muscle groups which have less of an antigravity function.

A key question is: "How much and what pattern of activation and resulting force is essential per day to maintain muscle mass?" For each physiological property of the muscle or each muscle protein, the same question must be asked. Further, it remains to be determined whether the altered activity and force patterns in spaceflight are the primary stimuli that account for the changes that occur in the muscles. For example, modulation of hormonal and/or other tissue growth factors during spaceflight also may contribute to the etiology of spaceflight-induced muscle atrophy.

F. Confounding Problems In Assessing the Effectiveness of Countermeasures

The effectiveness of existing exercise protocols and descriptions and recommendations of new exercise protocols based on the requirements of astronauts to perform intravehicular and extravehicular activities in microgravity is an evolving process. From the start of the human space program significant attention has been given to the question of how to counter the potential (expected) detrimental effects of spaceflight on the neuromotor system. This issue has not been resolved largely because the "pure" effects of microgravity have not been elucidated and thus it is not clear what effects must be countered. Also contributing to the delayed resolution of this issue has been the occasional absence of full and accurate disclosures of the actual physiological impact of spaceflight on some crew members. It is evident that the postflight physiological status of crew members reflects the net effect of the individualized countermeasures (exercise and others) and the adaptive effects of spaceflight itself. Despite these limitations considerable insight has been gained by carefully observing a wide range of responses to many flights of varying in duration. In one 5-year period (1982-1986), during the Salyut-7 flights and the first year of the Mir space station, 21 crew members accumulated 2,208 person days in space (7 crew members with more than 130 days and 2 with 366 days). These cosmonauts performed 97 person hours in extravehicular activity with 2 crew members accumulating almost 32 of those hours.

Based largely on observations of 24 crew members from Salyut-6 and Salyut-7 missions and on the Mir station, Kozlovskaya and co-workers suggested that the effects of microgravity on the motor system are defined by at least 3 factors: 1) duration of exposure; 2) individual differences in sensitivity and responsiveness to flight, and 3) characteristics of the exercise regimens. The duration of the flights ranged from 60-366 days. Fourteen of the 24 cosmonauts visited the space station for the first time. For four of the crew members, the long-duration flights had been preceded by a flight of about 7 days, while 7 others had already experienced long-term spaceflights. Data were collected before flight and 2, 4, 6, 11, and 45 to 72 days after flight. Analysis of the motor responses of these 24 crew members led to reasonably clear conclusions regarding the effectiveness of exercise as a countermeasure for spaceflight-induced motor deficits. When the subjects were ranked according to their motor capacity upon return to 1G, the intensity and volume of exercise training during the spaceflight were very highly correlated with this ranking. In contrast, there was a negative correlation between the flight duration and the ranking of the motor capacity at recovery; the motor capacity was generally better in those cosmonauts who had flown for the longer periods of time. Individual differences in "space tolerance" among cosmonauts may reflect the differences in the utilization of the prescribed countermeasures because participation and the details of the countermeasures employed pre- and during flight are determined largely by individual preferences as well as the individual differences to susceptibility to spaceflight conditions.

It seems that the duration of flight need not be a critical factor for maximal torque-velocity performance, i.e., the maximum torque produced at 0, 60, 120, and 180 °/sec. For example, performance of one cosmonaut on a 330-day flight and two others tested after a 175-day flight were affected similarly. The performance of cosmonauts exposed to these longer flights was affected much less than that of two cosmonauts after a 160-day flight. It is interesting to note that the maximum plantarflexor torque of cosmonauts on the 160-day flight were reduced more at the higher velocities, whereas the opposite trend occurred for cosmonauts on the longer-term flights. Maximum torque-velocity test results for cosmonauts that flew for 366 days and for 175 days were similar. Some cosmonauts had higher torques after than before flight at the higher velocities, but this never occurred at 0 °/sec.

It is not clear whether previous flight experience enabled the cosmonauts to become more effective in preventing degradation of motor performance in subsequent flights. There was a marked similarity between performance capability and volume of exercise of crew members within the same flight. Generally, all crew members on a given flight followed similar exercise protocols, and were almost always ranked consecutively within or among the ranking of all the crew members tested. One interpretation for the apparent paradox of the longer the flight the better the motor performance postflight, is that the Soviets gradually gained considerable insight into the most effective countermeasures as they gained more experience and as the spaceflights became longer. It is clear, however, that one critical factor for successfully adapting to 1G following spaceflight is the nature of the exercise countermeasures used more than the duration of spaceflight.

VI. Status of Countermeasures Using Animal Models

Recent findings on rodent models of unloading-induced muscle atrophy suggest that bouts of resistance exercise involving high force output of either the concentric or isometric mode of contraction can be effective in partially blunting the atrophy process . These types of activity appear to affect pretranslational, translational, and post translational processes . In rodents, as little as 40-50 four-second high resistance contractions per training session, every other day, were effective in partially blunting approximately 50% of the atrophy response seen during hindlimb suspension . The potential impact of resistance training as a countermeasure to unloading-induced atrophy can be put into greater perspective by the fact that it takes only 8 minutes per week of resistance exercise compared to either 640 minutes per week of endurance running or 840 minutes per week of stationary standing to achieve about a 40-50% reduction in the degree of atrophy that occurs in rodent antigravity skeletal muscle in response to hindlimb suspension .

The period between bouts of exercise also seems to affect the ability of the muscle to maintain its mass. For example, 10-min bouts of standing, very slow walking (5 m/min) or moderate running (20 m/min) on a treadmill repeated 4 times daily (a total of 40 min exercise per day) maintained a near-normal soleus mass during 7 days of suspension. In contrast, these remedial protocols had a minimal effect on the medial gastrocnemius. Climbing a one-meter grid at an 85% incline with a load equal to 50-75% of body weight attached for 8-10 repetitions, 2 or 4 times per day (~6 min of exercise per day) resulted in significant retention of both soleus and medial gastrocnemius muscle masses, although the effect on the medial gastrocnemius was somewhat variable . These data indicate that daily periods of load-bearing can be an effective means of counteracting the atrophic response to hindlimb suspension; a very small amount (as little as 6 min) of high load-bearing activity per day can significantly attenuate the suspension-associated atrophy in the soleus and, to some degree in the medial gastrocnemius. In addition, it also appears that short, intermittent bouts of exercise interspersed throughout the day may be a more efficient countermeasure than a single long bout of exercise. Booth and co-workers speculate that intermittent bouts of exercise maintain protein synthesis at control levels during periods of unweighting.

Kirby et al. used electrically-induced (0.2 trains/sec; stimulation rate of 60 Hz; pulse duration of 0.5 sec with 16 V administered via intramuscular electrodes in anesthetized rats) maximal lengthening contractions [0.2 fiber lengths/sec over the full range (128º) of ankle excursion] of the rat soleus to counteract the suspension-induced atrophy. One leg in each rat performed 4 sets of 6 repetitions of eccentric contractions every other day during a 10-day suspension period. The contralateral leg served as the control. The soleus muscles subjected to lengthening contractions had significantly larger wet weights (30%) and noncollageneous protein contents (20%) than the contralateral control muscles. However, the attenuation of the decreases in muscle wet weight and noncollageneous proteins produced by the eccentric exercise regime was ~77 and 44%, respectively, when compared to control values from weight-bearing rats. These data further demonstrate that total time of muscle activation may not be the critical factor for countermeasure effectiveness since muscle activation utilized only 0.035% of the total non-weight-bearing time. However, Kirby et al. emphasized that, similar to all other exercise protocols used to date, this eccentric exercise regime was effective in attenuating, but not completely preventing the atrophic response of the soleus.

An interesting modification of the suspension model has been developed by Stump et al. in which one limb is placed on a platform with the leg in a position similar to that observed during standing posture. This platform provides a base against which the animal can contract or stretch the supported limb at any time during suspension. Although there has been no quantification of the amount and pattern of activation of the muscles in the supported limb, it seems logical (based on chronic EMG recordings from suspended rats) that these muscles will be producing combinations of isometric, concentric and even eccentric contractions when there is cocontraction of agonists and antagonists as the leg is extended and flexed against the platform. In addition, chronic vertical forces of ~10% body weight appear to be transmitted to the platform, indicating that weight bearing is occurring (Stump et al., unpublished observations). Muscle mass: body weight ratios of the soleus, plantaris, and gastrocnemius muscles in the supported leg were similar to cage controls after 10 days of suspension, whereas those of the freely hanging leg were significantly decreased. In contrast, the responses of the tibialis anterior and extensor digitorum were similar in the supported and unsupported legs. These data suggest that chronic low-intensity forces may be effective in preventing atrophy in those muscles that are recruited. Thus, some progress has been made toward specifying the appropriate types, durations, and intervals of neuromuscular activity required to maintain muscle properties in chronic, unloaded conditions.

Chronic passive stretch of unloaded muscles can be effective in ameliorating some of the atrophy associated with suspension. Jaspers et al. compared the atrophic response in several ankle extensors and flexors in rats suspended for 6 days with one leg moving freely and one leg immobilized with the ankle in a dorsiflexed position. Compared to the freely moving limb, the weights of the soleus, gastrocnemius, and plantaris were 106, 20 and 7% larger, respectively, in the immobilized leg. In this light, Goldspink et al. have demonstrated a significant decrease in the DNA content of the extensor digitorum longus in rats suspended with the ankle fixed in dorsiflexion. Interestingly, Jaspers et al.

reported no difference in the mass of the soleus from 6-day suspended rats when comparing the casted (plantarflexed) limb with the freely-moving limb. The mass in the gastrocnemius and plantaris muscles of the limb casted (plantarflexed) was less than these muscles in the freely-moving limb. These data are consistent with the view that muscles that are activated but unloaded atrophy more rapidly than inactive-loaded muscles . For example, it is clear that there is considerable activity in the muscles of suspended rats . It is important to note that studies in which the ankle joint is fixed in an extreme dorsiflexed or plantarflexed position the changes in muscle mass reflect changes in muscle fiber length and/or cross-sectional area . Thus, the physiological consequences of these effects on muscle mass are unclear. In addition, these effects may be short-lived since sarcomeres can be added or deleted within a few days.

Sancesario et al. used elastic bands to passively hold the ankles of one group of suspended rabbits in a dorsiflexed position and compared the effects with another group in which the ankle was allowed to hang free and assumed a plantarflexed position. Based on visual observations, the rabbits occasionally contracted both limbs physically. After 1 or 2 weeks the soleus was significantly smaller in the animals that did not have elastic bands but not in those having elastic bands at the ankle. Thus the chronic passive and/or occasional phasic loaded contractions ameliorated the atrophic response. The authors suggested that a similar device could be attached to the feet of astronauts and serve as very simple and effective countermeasure for spaceflight-induced atrophy. This approach in principle is similar to the "penguin suit", which provides resistance to movement of the legs, arms and trunk, worn regularly by cosmonauts on the Mir space station .

Other procedures could be as effective as exercise or chronic passive stretch (resistance) for ameliorating the atrophic response to unweighting. For example, centrifugation (acceleration) could be used to produce an artificially-induced gravity and thus theoretically result in an increased load on the muscles unless strategic behavioral adjustments are used to avoid the additional imposed force. D'Aunno et al. studied the effects of centrifugation at 1.5 and 2.6G for 1 or 2 hours per day on the soleus muscles of 7-day hindlimb suspended rats. Centrifugation resulted in some attenuation of the muscle atrophy for each combination of duration and intensity. There was no difference, however, between centrifugation at 1.5 or 2.6 G for either duration. In contrast, two hours of centrifugation at 1.5 or 2.6G was more effective than one hour at the same intensities. Thus, it appeared that the duration of centrifugation was more important than the intensity with respect to amelioration of suspension-induced atrophy. Interestingly, 2 hours of ground weight-support was as effective as centrifugation in preventing atrophy. In a subsequent study, D'Aunno et al. centrifuged one group of rats at 1.2G for four 15-min periods evenly spaced over a 12-hour interval during a 7-day suspension period. Another group of rats were made to weight support on the same schedule. Intermittent acceleration resulted in 42% less soleus atrophy than that in suspended-only rats, and had no effect on plantaris weight. Intermittent ground support, interestingly, had a greater effect and maintained soleus mass at 90% of control. None of the countermeasures returned muscle mass to 100% of pre-suspension control levels. The implication was that some undefined stress associated with acceleration may have interfered with protein metabolism in the soleus and the authors indicate that more studies are needed to determine the efficacy of this potential countermeasure. In any case, it appears that the key to using chronic centrifugation in rats as a countermeasure is to assume that the G-forces imposed on the body are being transmitted via the leg musculature in a standing or walking posture. Otherwise, the presumed increased forces will be ineffective for the leg musculature. Thus, when using animal models, close attention must be given to the behavior of the animals during the experiment. In a recent 2-week centrifugation study conducted at Ames Research Center, videotaped records indicated that the rats were quite immobile during the initial 2-3 days of centrifugation, and then began to move to get food and water (M. Vasques and R. Grindeland, personal communication).

In summary, a variety of countermeasures have been used in an attempt to prevent the skeletal muscle atrophy associated with chronic unloading. Based on these results it appears that: 1) short bouts of high-intensity exercise (e.g., climbing a ladder carrying a load for a few min/day) are as effective as long bouts of low-intensity exercise (e.g., treadmill running for up to 2 hours/day) in ameliorating the atrophy of the soleus muscle; 2) multiple bouts of exercise per day are more effective than a single bout of the same intensity and total duration; 3) high-intensity exercise is required to recruit the fast muscle motor pools and thus ameliorate the atrophy in fast extensor muscles; 4) the anabolic effects of growth hormone on unloaded limbs are potentiated by high-intensity exercise, such that the soleus mass is maintained at control levels during hindlimb suspension; 5) centrifugation (duration being more critical than intensity) has some potential in ameliorating atrophy in limb muscles if the animals support their weight (stand) during the acceleration phase; and 6) chronic passive stretch helps to maintain muscle mass during unloading, with some combination of fiber cross-sectional area and fiber length being affected. Some areas which should be pursued include the following: 1) the potential of eccentric exercise (lengthening contractions) on the maintenance of muscle mass and 2) the relationship between muscle activity (amounts and patterns of loading and activation) and hormonal status, particularly growth hormone and thyroxine. Eventually these countermeasure protocols must consider all aspects of the homeostatic balance of the individual.

VIII. Recommendations

A. Specific to the Countermeasure Strategic Plan

1) High resistant training paradigms, aimed at eliciting maximal force production of the major muscle groups supporting posture and locomotion, need to be initiated as soon as possible as an integral strategy for maintaining the skeletal muscle system. As an initial approach, strategies similar to those currently used to optimize strength and enhance muscle enlargement in an 1G environment should be used at the outset of such a program.

2) NASA Life Sciences and Operational Medical Programs should explore the utilization of currently available equipment that may be capable of meeting the needs of such an exercise program, rather than looking to build new equipment devices.

3) Exercises that are highly repetitive and require low forces, i.e., the endurance type, should be continued as part of a general conditioning regimen.

4) Further, activities which facilitate the maintenance of routine daily neuromotor skills involved in posture, balance and vestibular control also need to be incorporated as part of the training program.

5) NASA needs to assess the level of physical skills (strength, power, endurance, motor control etc.) necessary to perform emergency egress activities that are likely to be encountered by astronauts. These levels of skill and performance capacity should serve as the guideline(s) for establishing the level of fitness to be maintained by the exercise programs used in the countermeasures program. It seems reasonable to expect that all training programs will not maintain individuals at their respective pre-flight physical capacity, and thus more reasonable performance objectives need to be identified.

6) Long term goals of NASA, in conjunction with the Exercise Countermeasures Program at JSC, need to focus studies toward basic and applied research that identifies the mechanisms of muscle wasting and motor control and to seek more effective countermeasures for preserving an acceptable level of movement performance. Research in this area should focus on strategies for increasing the efficacy of physical activity .These studies should consider interactions of physical activity, pharmacological and hormonal/growth factor approaches to understanding the regulatory elements of neuromuscular plasticity.

B. Specific to Future Research Directions and Strategies

It is apparent from both human and animal experiments, i.e., studies seeking information on countermeasures to the deficits in muscle properties, that the conventional modes of physical activity routinely used in spaceflight (treadmill, cycling, rowing, and the use special suits to impose tension on muscle) are not successful in preventing the degree of atrophy and dysfunction that occurs following several weeks of exposure to weightlessness environments.

Future research needs to focus in greater depth on the mechanisms and processes whereby muscle protein turnover is regulated. This research should clearly involve studies that target both the processes of protein synthesis and protein degradation, because it is the balance of these two processes that determines the steady state level of muscle mass. Further, since changes in MHC phenotype (as well as other contractile components) also exert a profound impact on the functional properties of the muscle, future work must focus on better understanding the role of hormonal and activity-related signals, second messenger pathways, and the transcriptional factors involved in contractile protein gene regulation. Finally, exercise studies should more clearly define the type, patterns and amount of mechanical loading (in conjunction with the use of growth factors and hormones) necessary for maintaining muscle mass, contractile protein phenotype, and the sensory-motor properties of the musculoskeletal system.

Given today's understanding of some of the fundamental principles of motor unit function and adaptation, experiments can test the appropriateness of exercise apparatuses and protocols to be used during spaceflight. This choice relates to 1) which muscle groups will be exercised and 2) what load patterns will be imposed by the muscle action. Once the recruitment level and load are defined, then the velocity is determined; or once the recruitment level and velocity are defined, then the load is determined. As noted previously, the major issues are what load-velocity combinations are the most efficacious in sustaining normal muscle properties, and how often do these specific load-velocity events have to occur? Similar questions would pertain to maintenance of normal neural control of movement and to maintenance of some defined level of resistance to a decrement in neuromuscular performance, cardiovascular performance, etc. The combined effects of all countermeasures designed for each specific tissue must be considered in optimizing the performance of humans in space and upon return to 1G.
In examining the recent technological advances in creating an artificial form of gravity, there are several prototypes that have been designed and partially tested that have the potential to both vary g-forces on muscle and bone, exert an aerobic exercise stimulus on the circulatory system, as well as exert a positive impact on other systems (i.e., vestibular) as well. This area needs to be explored more fully as artificial gravity may have the greatest potential for maintaining in the most appropriate state for 1G .

Whether or not artificial gravity becomes a prioritized countermeasure strategy, it may be necessary to undertake more basic research, beginning first on animals models, in which mechanical activity, chiefly of the high resistance type, is interacted with hormonal and other pharmacological agents in efforts to optimize the homeostatic state of muscle, bone and connective tissue for 1G . Although our present understanding of the mechanisms of neuromuscular and musculoskeletal adaptations made not be sufficient to pinpoint the optimal exercise protocol for spaceflight, there are sufficient data to serve as a theoretical basis for conducting clinical trials. From these clinical trials it is highly likely that significant improvements could be realized with respect to the effectiveness and efficaciousness of the exercise protocols to be followed during spaceflight.

An important challenge for future studies will be to design flight experiments that will permit (1) dissociation of the effects of microgravity from those of the countermeasures, and (2) identification of the effects of flight on the neuromotor system distinct from the compensatory processes used to perform motor tasks upon return to 1G.

Success in developing an optimized battery of exercise-based countermeasures is an ultimate challenge for integrative physiology requiring the utilization of biological principles ranging from the molecular control of protein maintenance to the psychological factors that will determine whether or not a crew member chooses to utilize the countermeasure. Given the data from spaceflight and those from motor control studies from ground-based simulation studies, some conclusions and suggested general principles to develop and validate countermeasures for these motor deficits are as follows:

1) A combination of exercise modes is likely to be the most effective with each type of exercise inducing specific effects on specific muscle groups and even specific types of muscle fibers within a muscle or muscle group. It does not seem reasonable from a physiological viewpoint to assume that one specific exercise protocol would be sufficient to counteract all of the effects of spaceflight, not even for the neuromuscular system alone.

2) It appears that the execution of appropriate forces accurately and timely in a 1G environment immediately following prolonged spaceflight has a major impact on the success of a mission. Thus, careful analyses must define which components of the neuromotor system adapt and deadapt to microgravity, determine the temporal sequence and amplitude of those adaptations, and then define the mechanisms by which they are induced.

3) It is essential that baseline exercise levels and activity patterns at 1G and during spaceflight be defined for critical muscle groups. These data then can be used to determine the appropriate type and amount of neuromuscular activity that must be imposed on the baseline activity during spaceflight to reach levels comparable to that found at 1G. Based on limited data, the required amount and pattern of activity necessary to maintain the neuromotor system during spaceflight appear to be muscle and muscle fiber specific and to be somewhat unique for each individual. This individual uniqueness may reflect genetic factors as well as the physiological state of the neuromuscular system at the beginning of spaceflight.

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