NASA Contractor Report 3796

Final Report Phase IV: Research Opportunities in Muscle Atrophy

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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.
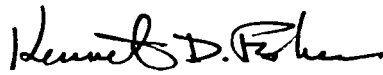
This technical report was developed for the National Aeronautics and Space Administration (NASA) in accordance with the provisions of Contract NASW 3728. It was prepared and edited by Gerald J. Herbison, M.D., Department of Rehabilitative Medicine, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, who served as Key Biomedical Scientist for this effort and John M. Talbot, M.D., Senior Medical Consultant, LSRO.

The LSRO acknowledges the contributions of the investigators and consultants who assisted with this study. The report reflects the opinions expressed by an ad hoc study group that met at the Federation on July 18-19, 1983. The study participants reviewed a draft of the report and their various viewpoints were incorporated into the final report. The study participants and LSRO accept responsibility for the accuracy of the report; however, the listing of these individuals in Section VIII does not imply that they specifically endorse each study conclusion.

The report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to NASA by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent Societies.

January 25, 1984
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      (date)

Kenneth D. Fisher
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Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office

SUMMARY

Atrophy of skeletal muscles, especially of those used for locomotion, maintaining posture, and counteracting gravity on Earth, occurs during space flight. When the gravitational loading of the musculoskeletal system is removed, as in weightlessness, one of the body's responses is muscle atrophy, particularly in the legs and thighs. This is reflected by a reduction of muscle volume, mass, strength, exercise capacity, and neuromuscular coordination. Metabolic manifestations of disturbed protein turnover in the muscles of space travelers include marginal or negative balances of nitrogen and potassium, as well as a persistent rise in urinary excretion of nitrogen, amino acids, and 3-methylhistidine.

Although there are no reports that muscle atrophy associated with space flight has compromised any manned mission to date, decrements in strength, exercise capacity, and locomotor coordination have been observed after most manned space missions. Moreover, muscular deconditioning may have contributed to the tachycardia noted during extravehicular activity in the Gemini, Apollo, and Skylab programs and to the cardiac arrhythmias and marked fatigue experienced during lunar surface activities and return to Earth in the Apollo 15 mission. Full recovery of muscular strength following space flights of medium (weeks) to long (months) duration requires from several days to several weeks. Data are not available to show conclusively whether full recovery of muscle bulk takes place.

In the weightlessness of orbital flight, the functional load on the musculoskeletal system is insufficient to maintain normal physiologic status of the musculature. There is no need for muscular opposition to gravity or for maintaining terrestrial posture, and the effort needed to move about is greatly reduced. The types of physical performance required of astronauts (except for voluntary physical exercises) and the confined volume of their spacecraft contribute to a marked reduction of physical activity. Whether the muscle atrophy is caused by zero-G or a combination of factors in the spacecraft environment has not been fully established, but weightlessness seems to be the dominant etiologic factor. Lack of production of customary muscular force in zero-G is probably an important contributory factor, and deviations from normal hormonal balances may influence muscle protein turnover.

Daily regimens of vigorous physical exercises during space missions are used by both U.S. and U.S.S.R. spacecrews as a means of counteracting muscle atrophy. Inflight diets are formulated to provide all required nutrients to maintain positive nitrogen and energy balance. In addition, Soviet inflight preventive

measures include electrostimulation of muscles and wearing a motion-resisting garment. However, despite these measures, skeletal muscle atrophy continues to progress during space flight, resulting in progressive loss of muscle and negative nitrogen balance.

Although scientific knowledge about the physiologic and pathologic effects of use and "disuse" of skeletal muscle is abundant, there is still much to be learned. Lack of data on the basic biologic mechanisms of muscle atrophy and hypertrophy hampers the quest for a solution to the problem of muscle atrophy in space. Consequently, the National Aeronautics and Space Administration (NASA) supports research on the basic mechanisms of muscle atrophy and efficient methods of prevention or control. The present report is part of an effort by NASA to identify promising lines of research for future program planning. It is based upon a review of available knowledge and the opinions and suggestions of a group of expert investigators (the LSRO ad hoc Working Group on Muscle Atrophy) whose names are listed on page 81.

The report includes background information on muscle biology and atrophy, a review of muscle atrophy associated with actual and simulated space flight, and the findings of the ad hoc Group with respect to important gaps in knowledge, desirable research approaches, and the present NASA research program on muscle atrophy. A majority of the participants concluded that acquisition of essential data from inflight measurements of spacecrew personnel is important for designing more meaningful ground-based and inflight experiments. Such measurements should be representative of a typical day's activities. They would be practical, designed not to interfere with crew duties, and would assess muscle strength, velocity of contraction, levels of electrical activity, and fatigability. The data would be compared with results of measurements of the same parameters in the same individuals in a typical day of ground activity.

Suggested approaches to determining basic mechanisms of disuse atrophy involve studies of: (1) the effects on muscle protein turnover of altered tissue concentrations of and sensitivities to anabolic hormones such as growth hormone and the somatomedins; (2) promoters of muscle protein synthesis such as leucine, other branched chain amino acids, and their metabolites; (3) identification and characterization of the enzymes responsible for changes in rates of muscle protein synthesis and degradation in response to unloading and relative inactivity; and (4) identification and test of inhibitors of muscle proteases. A major breakthrough would be discovery of the molecular stimuli that lead to changes in rates of muscle protein synthesis and degradation in response to increased or decreased use of skeletal muscle.

Use of the rat head-down suspension model for inducing
hypokinesia and hypodynamia of the hind limbs has yielded experi-
mental results on muscle atrophy similar to those derived from
studies inflight. While this is a good model for ground-based
studies, efforts should continue to develop and improve models for
simulating zero-G, including comparative studies of such methods
as joint pinning, casting, paraplegia, denervation, and pharmaco-
logic nerve block. Human patients with spinal cord injury might
be tested ethically to determine the minimum amount of electri-
cally-induced exercise that would prevent muscle atrophy; data
from such tests could be used in designing inflight exercises.

To acquire other data for improving inflight exercises,
pre- and postflight measurements of maximal voluntary contractions
of selected muscle groups such as the flexors and extensors of the
arms and legs should be done on all personnel who participate in
space flights. Complementary ground-based studies in a model of
hypokinesia/hypodynamia such as bed rest should be done with human
subjects to determine minimum amounts of strength or endurance
exercises, or combinations of these, needed to prevent muscle atro-
phy. The role of eccentric contractions for maintaining muscle
strength and bulk in models of hypokinesia/hypodynamia should be
explored. Finally, more data are needed to settle questions
related to optimal preflight physical fitness of space flyers.

Examination of NASA's research on muscle atrophy indi-
cates that it is a young, evolving program based on expert guid-
ance received from multiple sources including formal scientific
advisory groups. Most studies in the Biomedical Research Program
on Muscle Atrophy are consistent with the governing program docu-
ments. However, future program planning should include refine-
ment, if possible, of the research objectives and approaches and
closer matching of these with ongoing and planned research. The
Biomedical Research Program on Muscle Atrophy is complemented by
other valuable ground-based studies in the Space Biology Program
and by muscle studies scheduled for Spacelab 4. Finally, the
ad hoc Working Group on Muscle Atrophy concluded that the research
suggestions in this report offer opportunities for future planning
that would enhance the likelihood of achieving NASA's objectives
in muscle atrophy research.

TABLE OF CONTENTS

I. INTRODUCTION

One of the problems addressed by the Biomedical Research Program of the National Aeronautics and Space Administration (NASA) is the atrophy of skeletal muscles that occurs during space flight. Numerous observations of American and Soviet space travelers, animals flown in space, and subjects exposed to simulated weightlessness have generally demonstrated skeletal muscle atrophy. Associated effects include decreased muscle strength and reduced work capacity (Pestov and Geratewohl, 1975). The biomedical results of the Gemini, Apollo, and Skylab programs included several features in common that were referable directly or indirectly to skeletal muscle effects: minimal to moderate loss of muscle nitrogen, weight loss, and postflight decrease in exercise tolerance (Dietlein, 1977). Similar effects have been reported by Soviet space medical scientists (Gazenko et al., 1981).

The muscle atrophy experienced to date, in missions from a few weeks to six months, has apparently not compromised crew effectiveness inflight and seems to be reversible following mission completion. Daily, vigorous exercises of the major muscle groups appear to retard the muscle deconditioning; however, the reliability and effectiveness of exercises have not been adequately demonstrated from a scientific standpoint. In fact, some evidence suggests that, despite all measures at intervention that have been attempted, muscle atrophy continues throughout orbital flight, featuring progressive loss of muscle mass and negative nitrogen balance (Whedon, 1982; Whedon et al., 1977).

Although the muscle atrophy experienced to date by U.S. astronauts appears to have been innocuous inflight, it may have interfered to an unknown degree with the physiologic efficiency of astronauts engaged in extravehicular activity including exploration of the lunar surface. Postflight, it contributes to a temporarily reduced state of physical fitness and orthostatic intolerance. In addition, leg volumes of astronauts are diminished upon return to Earth. Thus, space-related muscle atrophy represents a significant biomedical problem.

NASA's quest for a solution to this problem is hampered by a lack of knowledge of the biologic mechanisms of muscle atrophy; hence, in a continuing effort to resolve the problem, NASA supports intra- and extramural research ranging from basic studies to applied technology. Part of NASA's responsibility in management of research is to review and revise the research program periodically in order to take advantage of new knowledge and expert opinion. In connection with this process, NASA requested that the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) review and

evaluate available knowledge and ongoing research and provide
additional scientific input for future research programming in
muscle atrophy. This has been done with the assistance of an
ad hoc Working Group of outstanding scientists, supplemented by
other prominent investigators, who are identified in Section VIII.

II. OBJECTIVES AND SCOPE OF THE STUDY

The objectives of the LSRO study of the problem of muscle atrophy associated with space flight are:

(1) to review extant knowledge of the subject;

(2) to examine NASA's current and projected research program;

(3) to identify all significant gaps in essential knowledge;

(4) to formulate additional suggestions for future research consideration by NASA; and,

(5) to produce a documented report of the foregoing items that can be used for NASA research program planning.

With respect to NASA's research and development in muscle atrophy and methods of coping with the problem, the primary emphasis in this report is on the ground-based Biomedical Research Program on Muscle Atrophy. However, the review includes pertinent information from NASA's Space Biology Program and the muscle experiments planned for Spacelab 4. In addition, the report emphasizes the essential importance of acquiring as soon as possible, human data on muscle physiology during all inflight opportunities, and suggests experiments that could be done with minimal encroachment upon the schedules of the spacecrews.

The scope of topics that were reviewed, as is indicated in the Table of Contents, covers the basic biologic disciplines, certain clinical aspects, possible means of intervention, and the areas of models, methods, and equipment. The major portion of the report (Section V) is devoted to the observations of the ad hoc Working Group during their meeting at FASEB and their follow-up contributions including critiques of the draft report.

III. ATROPHY OF SKELETAL MUSCLE

A.   NORMAL MUSCLE

Only a small part of the literature in the broad field of skeletal muscle biology is cited in the following paragraphs. Some additional sources that are not cited in the report are appended to the list of references (see p.79). Table 1 is an outline of certain anatomic features of skeletal muscle. The muscles which are of primary concern in this study include most of the muscles of the lower extremities, the gluteal muscles, the trunk muscles, extensors of back and neck, and their antagonists.

1.   Muscle function

The sliding filament model is generally accepted as the basic contractile system of striated muscle, and the sarcoplasmic reticulum and transverse tubular system, in concert with Ca^{2+}, link neuromuscular excitation and muscle contraction (Fuchs, 1974). The complex process of muscle contraction was outlined by Fuchs (1974):

> Briefly, force generation is believed to result from the cyclic attachment and detachment of cross-bridges projecting from the thick (myosin) filaments and interacting with the thin (actin) filaments in such a way as to draw them toward the center of the sarcomere. Cross-bridge activity is energetically coupled to the splitting of adenosine triphosphate (ATP), catalyzed by the cross-bridges themselves, and is regulated by the (free) Ca^{2+} concentration in the sarcoplasm. The sarcoplasmic reticulum (SR) membranes contain an ATP-dependent Ca^{2+} pump which maintains the sarcoplasmic Ca^{2+} concentration in resting muscle at a level ($<10^{-7}M$) below that needed for activation of cross-bridge interaction. Upon stimulation, an electrical signal is transmitted along the transverse tubules (T-tubule) to the terminal cisternae of the SR, thereby causing a rapid release of Ca^{2+} and an elevation of sarcoplasmic Ca^{2+} concentration to $10^{-5}M$. Cross-bridge attachment is promoted by the binding of Ca^{2+} to the thin filaments. The activating effect of Ca^{2+} is mediated by two proteins, tropomyosin and troponin, bound to the thin filaments. In the resting state, cross-bridge attachment is inhibited by these two proteins, and this inhibition is overcome only when Ca^{2+} binds to the troponin. During the relaxation phase, Ca^{2+} is reaccumulated within the SR, and the cross-bridges detach from the thin filaments.

Table 1. Outline of the Anatomy of Human Skeletal Muscle*

Anatomic Unit	Description	Dimension/Size
individual muscle	collection of muscle fasciculi enclosed in the muscle sheath (epimysium), with integral blood supply and neural network and attachments to tendons, aponeuroses, or faciae	length: 2 mm->60 cm (sartorius)
muscle fasciculus	longitudinal bundles of 12 or more muscle fibers enclosed by a collagenous, elastic membrane, the perimysium	
muscle fiber	a muscle includes thousands of generally cylindrical fibers: large, elongated, multi-nucleated cells enveloped by endo-mesial connective tissue and consisting of hundreds or thousands of myofibrils, sarcoplasm, sarcoplasmic reticulum, mito-chondria, and other common cellular elements	length: same as above diameter: 10-100 μm
myofibril	each myofibril contains approximately 1500 myosin filaments and 3000 actin filaments which interdigitate and are the contractile elements of muscle	diameter: ≪20 μm
myofilaments	large, polymerized protein molecules; the major contractile proteins are myosin (thick filaments) and actin (thin fila-ments); tropomyosin and troponin, bound to thin filaments, participate in regu-lation of muscle contraction. Cross-bridges project from the myosin filaments to interact with the actin filaments	myosin filament has ~200 myosin molecules length of myosin filaments: ~1.6μ diameter: ~15-20 nm myosin m.w. 490,000 G-actin m.w. 4700
neuromuscular junction	motor nerve ending supplying each muscle fiber; its branches form a complex of termi-nals called the end-plate; mitochondria to make acetylcholine abound in the end-plate nerve terminals	

* Sources: Ganong, 1973; Gray, 1973; Guyton, 1981; Young et al., 1983. Excludes blood supply and neural network.

2. Energy metabolism in muscle

The energy required for muscular activity is ultimately derived from carbohydrates, whose breakdown is oxidative for highest muscular efficiency and endurance (Brobeck, 1979), and from free fatty acids (Ganong, 1973). For brief, intensive activity, muscle can use energy supplied anaerobically via ATP and creatine phosphate (CP), and by anaerobic glycolysis, during which the muscle incurs an "oxygen debt".

Excitation-contraction coupling, the process by which the muscle action potential starts the contraction, derives its energy from the interaction of ATP with muscle proteins (Young et al., 1983). The anaerobic breakdown of ATP and CP yields energy for muscle contraction, but the stores of ATP and CP in muscle are sufficient for only a few seconds of sustained maximal muscle contraction (Guyton, 1981). However, the aerobic reactions that follow decarboxylation of pyruvic acid to acetate and its conversion to acetyl coenzyme A yield the greatest amount of energy. Although the lactate that is formed during anaerobic muscle contraction may be used in exercise, its fate is difficult to ascertain, and data on adaptations in the glycolytic enzyme system consequent to changes in muscle activity are less certain than for the enzymes involved in end-terminal oxidation (Saltin and Gollnick, 1983). Small amounts of energy are needed to restore the regulatory calcium ions from the sarcoplasm to the SR and to pump sodium and potassium ions through the membranes of the muscle fibers (Guyton, 1981).

B. ATROPHIC MUSCLE

1. Definition

According to Stewart (1968) atrophy may be considered as a decrease in size or wasting away of a body tissue or, in growing organisms, as arrested development. In this report, skeletal muscle atrophy associated with space flight is classed as a type of "disuse" atrophy, with acknowledgement of the lack of a completely satisfactory definition of the term. Disuse atrophy is widely used in the scientific and clinical literature; however, its appropriateness with regard to muscle changes associated with space flight is questionable.

Abramson (1948) noted difficulties in defining the atrophy of disuse; he suggested that decrease in size of tissues resulting from their inability to develop full function might be a general definition. Robbins and Cotran (1979) list decreased workload as one of the apparent causes of muscle atrophy, and Saltin and Gollnick (1983) note that, with disuse or inadequate nutrition,

there is a loss of muscle mass associated with a decrease in cross-sectional area. The LSRO ad hoc Working Group on Muscle Atrophy suggested that an acceptable, basic definition might be a reduction in muscle size or mass in contrast to hypertrophy, with implications for associated physiologic and functional effects.

Pathophysiologic features of disuse muscle atrophy include a shrinkage in the size of muscle cells by partial losses of structural components and organelles such as mitochondria, myofilaments, and endoplasmic reticulum (Robbins and Cotran, 1979). Atrophic cells are not dead; eventually, however, with marked degrees of disuse, muscle cell death may occur, giving way to replacement by fibrous tissue (Crowley, 1976; Robbins, 1967).

As noted in Section IV, underuse of the skeletal musculature by space travelers affects mainly the anti-gravity muscles, is only a partial or relative type of disuse, and has not resulted in marked degrees of atrophy during space missions lasting up to 6 mo.

2.   Causes of muscle atrophy

As mentioned, a decrease or lack of function of living tissues results in their shrinkage or wasting away (Abramson, 1948; Robbins and Cotran, 1979; Stewart, 1968). Atrophy of muscles of the legs and thighs was reported in human volunteers kept at strict bed rest while wearing removable lower body plaster casts for 6-7 wk (Deitrick et al., 1948) and in fracture patients (Sargeant et al., 1977). Similar effects were reported from other medium- to long-term bed-rest studies (Buznick and Kamforina, 1973; Kakurin et al., 1966; Krupina et al., 1982; Panov et al., 1969; Parin et al., 1971; Petukhov and Purakhin, 1971; Rodahl, 1969; Triebwasser, 1968).

Mechanical immobilization of joints leads to weakening and atrophy of the associated musculature in human subjects (Danckwardt-Lillieström and Sjögren, 1976; MacDougall et al., 1980; Sargeant et al., 1977; Stillwell et al., 1967; Young et al., 1980, 1982) and in animals (Booth, 1982; Cooper, 1972; Fournier et al., 1983; Goldspink, 1977; Herbison et al., 1978; Tabary et al., 1972; Thomas and Luco, 1944). According to Saltin and Gollnick (1983), loss of muscle mass associated with joint immobilization results from a decrease in the cross-sectional area of the muscle.

Muscles of immobilized limbs may decrease in size by 25-50% in 30 d (Åström and Adams, 1981; Guyton, 1981). Denervated muscles undergo rapid atrophy, with a loss in bulk of 70-80% in a period of 120 d (Åström and Adams, 1981). Clinical causes of atrophy include: (1) denervation of the musculature as a result of trauma

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or disease of the spinal cord or motor roots; (2) the spinal muscular atrophies; (3) the peripheral neuropathies; (4) certain stages of the progressive muscular dystrophies; (5) the inflammatory myopathies; and, (6) certain myopathies that are associated with metabolic or endocrine disorders (Walton, 1981). Investigative models for study of disuse atrophy in laboratory animals are, for example, surgical denervation or pharmacologic block of nerve conduction; chronic tenotomy, spinal cord transection or isolation, joint immobilization, and suspension of rats to produce a head-down body tilt with unloading of the hind legs (Fournier et al., 1983; Morey-Holton and Wronsky, 1981; Musacchia et al., 1980, 1983; Steffen et al., 1981) . Table 2 lists examples of conditions that result in muscle atrophy.

Interpretation of data on muscle atrophy derived from observation of patients with fractured, immobilized limbs should take into account the evolving knowledge of proteolytic factors that appear to lead to rapid muscle wasting during trauma or sepsis (Baracos et al., 1983a; Beisel, 1983; Clowes et al., 1983a).

In this report, primary interest is in the atrophy of the anti-gravity muscles, whose customary roles in maintaining body posture on Earth are drastically modified in weightless flight. This unloading of the musculoskeletal system in zero-G results in a unique form of disuse. Available data on muscle atrophy associated with space flight are presented in Sections IV and V.

3.   Prevention of muscle atrophy

Except for countermeasures against muscle atrophy in simulated or actual space flight , studies of prevention of disuse atrophy have concerned clinical problems that are complicated by atrophy, such as those mentioned above.

Reinnervation. Reinnervation of denervated muscle following trauma reverses atrophy and restores physiologic function. Nerve impairment from trauma varies from transient blockage without disruption of the axon to complete division of the nerve. When axons are damaged, but supporting connective tissue and the Schwann cell basement membrane remain intact, regeneration occurs at 1-2 mm/d. When damage is more severe, but the perineurium and fascicular structures are preserved, regeneration also takes place, but less efficiently than in the preceding example (Bradley, 1981). Surgical correction is required when the damage precludes unassisted nerve regeneration. Thus, if it occurs before atrophy becomes irreversible, nerve regeneration is an optimum type of prevention of irreversible muscle atrophy following nerve damage. Nerve regeneration within 3-4 mo of injury may restore muscle function fully, whereas reinnervation after two years rarely restores any muscle function (Guyton, 1981).

Table 2. Examples of Conditions That Result in Atrophy

	Activation			Responses to Activation		
	Supra-spinal	Spinal	NMJ*	Muscle Force	Muscle Velocity	Metabolic
Loss of motoneurons (poliomyelitis)	+	0	0	0	0	0
Absence of supraspinal control (spinalization)	+	0	0	0	0	0
Muscular dystrophy (?)	+	+	+	†	0	0
Loss of testosterone, growth hormone or somatomedin	+	+	+	+	+	+
Reduced forces (immobilization) (?)	†	+	+	†	0	+?
Reduced forces (tail suspension§) (?)	+	+	+	†	++?	+
Weightlessness (?)	+	+	+	†	+?	+?

* neuromuscular junction
† decreased
§ rat head-down body tilt model

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Electrical stimulation. Prevention or retardation of atrophy of denervated muscle by electrical stimulation has been demonstrated in the rat (Fischer, 1939; Grodins et al., 1944a,b; Herbison et al., 1971; Kosman, et al., 1947a,b; Shaffer et al., 1954; Stillwell and Wakim 1962; Wehrmacher et al., 1945), the rabbit (Gutmann and Guttmann, 1944), and the dog (Kosman et al., 1948). Grodins et al. (1944b) also reported preservation of maximum tetanic contraction potential by use of a 25 hertz, 6-7 ma current in denervated gastrocnemius-soleus muscles of dogs. It is well established that current intensities must be high enough to produce vigorous muscle contractions to prevent or retard atrophy in denervated muscles (Fischer, 1939; Herbison et al., 1971; Wehrmacher et al., 1945).

Opinions vary about the utility of electrostimulation in treating neuromuscular disorders (Herbison et al., 1971, 1983; Laughman et al., 1983). In disorders involving motor denervation, electrostimulation is the only practical means of inducing muscle contraction (Karpovich, 1968); however, vigorous contraction of the afflicted musculature in such cases requires current intensities that exceed the comfort tolerance of the patient. Basic data appear to be too limited to permit rational scientific understanding of the effects of electrostimulation on human muscle (Eriksson et al., 1981; Moreno-Aranda and Seireg, 1981). However, there is some evidence to support the use of electrostimulation in clinical situations with muscle atrophy when the motor innervation is intact (Eriksson and Haggmark, 1979; Gould et al., 1982, 1983; Romero et al., 1982). Moreover, data from animal studies (Herbison et al., 1971) suggest that electrostimulation may prevent or retard atrophy of denervated muscle. With regard to muscle atrophy resulting from weightless flight, the opinion of the ad hoc Group as to the use of electrostimulation is presented in Section V (see p.38).

Exercise. Physical exercise by voluntary contraction of muscle groups has long been used to restore atrophied muscle following injury and disease (DeLorme, 1945). To determine the effectiveness of quadriceps-setting exercises in retarding loss of strength in fracture patients with immobilized lower extremities, Stillwell et al. (1967) studied 22 normal subjects and 21 patients with leg fractures. All 43 persons tested had one lower extremity in a long leg cast. The exercises consisted of static contraction of the quadriceps in the casted limbs, held for a count of 10 and repeated 10 times per hour (exercised patient group) and a single, 6-sec maximal isometric contraction of the quadriceps and hamstrings four times per day (normal, casted-exercised group). Another control group consisted of 10 normal subjects who were not in casts but who exercised isometrically at a knee angle of 120° or 165°. The normal, exercised subjects in casts maintained pre-casting isometric tension at a knee angle of 120°, maintained 10 repetition maximum, and increased isometric tension at a knee angle of 165°.

In the patients, isometric tension and 10 repetition maximum decreased in both exercised and nonexercised groups; however, the decline in 10 repetition maximum was smaller in the exercised patients, suggesting some preventive value in terms of endurance strength.

Other approaches. Alternative approaches to preventing or retarding disuse atrophy have been suggested by certain lines of investigation; for instance, the use of aids to muscle protein synthesis such as supplemental leucine (Buse and Reid, 1975; Fulks et al., 1975; Goldberg and Tischler, 1981), substances that reduce muscle protein degradation in vitro such as leucine and α-ketoiso-caproate (Goldberg and Tischler, 1981), and substances that reduce muscle protein degradation in vivo such as mixtures of the branched-chain amino acids (BCAA) (Stewart et al., 1982). The influence of anabolic hormones on muscle is also of interest. Goldberg and Goodman (1969), for example, reported that growth hormone reduced weight loss and induced growth in denervated muscles in hypophysec-tomized rats. In another study, restoration of muscle weight, electrical activity, contractile capacity, and work performance of the gastrocnemii of immobilized hind limbs of rats treated with human growth hormone were reported by Apostolakis et al. (1980).

Another possible means for preventing or controlling mus-cle atrophy involves methods of inhibiting the factors that mediate muscle proteolysis. For example, cyclooxygenase inhibitors such as aspirin and indomethacin block muscle proteolysis associated with the release of interleukin-1 in patients with sepsis or trauma (Baracos et al., 1983a,b). However, from a clinical point of view, this appears somewhat controversial (Clowes et al., 1983a,b; Moldawer et al., 1983); nevertheless, if similar proteo-lytic factors should be discovered in the search for mechanisms of disuse atrophy, the concept may have merit. Further elaboration of the roles of the proteases and their inhibitors found in skele-tal muscle (Bird et al., 1980) might lead to practical means of pharmacologic or biochemical intervention. Beneficial effects of the protease inhibitor, pepstatin, in a mouse model of muscular dystrophy were reported by Schorr et al. (1978); however, Enomoto and Bradley (1977) observed no benefit of treatment with pepstatin, antipain, or leupeptin in mice with heredity muscular dystrophy.

4.   Rehabilitation

Experience in rehabilitating atrophic muscles has been largely in the clinical setting following immobilization of limbs as a result of injury or disease. The basis of muscular rehabilitation is voluntary exercise with regimens chosen to suit individual needs (DeLateur et al., 1968; DeLorme, 1945; Karpovich, 1968; Liberman and Asa, 1959; Müller, 1970). Restoration of the musculature to its pre-atrophic bulk and power appears to be

difficult in many cases and perhaps impossible in some. Stillwell and colleagues (1967) noted that, with the best available techniques, 3-8 wk were required to restore the quadriceps muscle to its normal strength, and Karpovich (1968) observed that, often, definitive treatment ends and rehabilitation starts only after a long period of time. Discussion by the LSRO ad hoc Group suggested that, in patients recovering from disuse atrophy, young persons including teenagers, are more likely to recover muscle bulk than adults, including young adults (see Section V, p.37).

IV. MUSCLE ATROPHY ASSOCIATED WITH MANNED SPACE FLIGHT

A.   NATURE AND OCCURRENCE

In the weightlessness of space flight, the functional load on the musculoskeletal system is insufficient to maintain normal physiologic status of the musculature. There is no need for active opposition to gravity or to maintain customary terrestrial posture, and the effort required to move the body and its appendages is remarkably reduced (Pestov and Geratewohl, 1975; Smith, 1978).

Numerous observations of the astronauts and cosmonauts, of human and animal subjects of ground-based hypokinetic and limb immobilization studies, and of animals flown in space have demonstrated skeletal muscle atrophy (Berry, 1973; Cherepakhin and Pervushin, 1971; Deitrick et al., 1948; Dietlein, 1975, 1977; Gazenko et al., 1980a; Nicogossian and Parker, 1982; Oganov, 1981; Pestov and Geratewohl, 1975; Sargeant et al., 1977; Thornton and Rummel, 1977; Whedon, 1982; Whedon et al., 1977; Whittle, 1979). Several authors reported postflight decreases in human muscle volume and mass, particularly in the lower extremities (Pestov and Geratewohl, 1975), and data from the Skylab series of space flights showed reduction in muscle strength of the limbs (Thornton and Rummel, 1977) and confirmed losses of mass of the leg muscles (Whittle, 1979). Associated effects include decreased muscle strength and "tone" and reduced work capacity (Pestov and Geratewohl, 1975). The biomedical results of the Gemini, Apollo, and Skylab programs included several features in common that were referable directly or indirectly to skeletal muscle effects: minimal to moderate loss of muscle nitrogen, postflight weight loss, and postflight decrease in exercise tolerance (Dietlein, 1977).

Oganov et al. (1980) defined the changes in skeletal muscle associated with long-term space flights as "functional atrophy" and noted that they included loss of muscle mass, decline of muscle "tone", strength, and endurance, primarily of the muscles of the legs and torso. Increased protein catabolism including breakdown of skeletal muscle has been a consistent finding in space flight. A reduction of the volume of the lower extremities and a persistent rise in urinary nitrogen, phosphorus, amino acids, and 3-methylhistidine are some of the typical associated findings (Nicogossian and Parker, 1982; Whedon et al., 1977). Whether these changes are caused by zero-G or other factors in the space flight environment has not been fully established, but weightlessness is generally thought to be the main etiologic factor (Bricker, 1979; Gazenko et al., 1980b).

In the manned Skylab missions (flight durations were 28, 59, and 84 d), nitrogen and phosphorus balances were negative during the first 2-3 wk, then negative or slightly positive for

the remainder of each mission (Rambaut et al., 1979; Whedon et al., 1977). Total caloric intakes of the nine Skylab crew members varied from 35.8-49.7 kcal/kg body wt, having been set at 10% below preflight values for the 28-d mission and 8-10% above preflight levels for the 56- and 84-d missions (Leonard et al., 1983). Compared with preflight values, five of the crew members decreased, and four increased their mean caloric intakes during flight. Of the mean inflight total body weight loss of 2.7 ± 0.3 kg (SD) in the nine astronauts, more than half was estimated to be from loss of lean body mass (Leonard et al., 1983).

U.S. astronauts and Soviet cosmonauts have typically developed negative potassium balance during flight, manifested postflight by decreased values of serum and urinary potassium, total body content of potassium-40, and exchangeable potassium (Gazenko et al., 1980a; Leach and Rambaut, 1977; Leach et al., 1975). This negative balance has been ascribed to a reduction of the intracellular potassium depot as a result of a decrease in cell mass, particularly in skeletal muscle. The negative potassium balance has persisted for as long as 6 d postflight (Gazenko et al., 1980a).

Changes in strength of the arm and leg extensors and flexors of each of the three Skylab crews were estimated by pre- and postflight dynamometry (Thorton and Rummel, 1977). Muscle strength of the crew of Skylab 2, whose sole inflight exercise device was the bicycle ergometer, was measured 5 d postflight. Leg extensor strength was about 25% below preflight levels. Decrements in arm extensor strength were considerably less than in the legs. There was no loss in arm extensor strength in the Commander, who had pedaled the bicycle by hand as well as by leg (Thornton and Rummel, 1977). In the Skylab 3 mission (59 d) average loss of strength in the leg flexors was about 18% and about 21% in the leg extensors. Again, losses of strength in the arm extensors and flexors were generally less than in the lower extremities, which probably reflect the relatively greater workload for the arms during flight. Thornton and Rummel (1977) noted that the legs receive virtually no effective loading.

Soviet scientists have stated: "The obvious consequences of the effects of weightlessness on the motor system included slight muscle mass losses, visible atrophy of leg muscles, long and wide back muscles and decrease of muscle tone" (Gazenko et al., 1981). Kozlovskaya et al. (1981) reported the following muscular effects in crew members of the 75-, 140-, 175-, and 185-d Salyut missions: (1) "atony" of the calf muscles rear group and atrophy of the long muscles of the back; (2) slight "subatrophy" of the latissimus dorsi muscles; (3) slight decrease in strength of the gastrocnemius muscles at velocities of 0 and 60°/sec; (4) a noticeable decrease in strength of the tibialis anticus muscle at all velocities tested except at 180°/sec; (5) a significant decrease in strength/velocity relationship of the neck muscles. Apparently

these decrements in muscle performance capability persisted for 6 or more wk postflight (Kozlovskaya et al., 1981). Magnitude of the muscle changes bore no clear relationship to flight duration, but appeared to be inversely proportional to the amount of whole body exercise done inflight.

Anthropometric measurements of space crews provide additional data on changes in skeletal muscles during flight. The range of reduction of leg volume during the Skylab missions averaged from about 7-11% of the preflight values. More than half the loss in leg volume probably resulted from the cephalad shift of blood and tissue fluids that accompanies exposure to zero-G; the remainder is considered a loss of muscle mass (Thornton and Rummel, 1977). Similar results have been reported by the Soviet space medical scientists (Gazenko et al., 1981). In the long-term flights, decreases in leg volume were pronounced in the first 3 wk, then fluctuated between large decreases, periods of stability, and partial recovery (Nicogossian and Parker, 1982).

Postflight stereometric analysis of the Skylab astronauts by means of a stereophotogrammetric method showed major losses in volume of the abdomen, buttocks, and calves, and less pronounced losses in the thighs (Whittle, 1978; Whittle et al., 1977). From these studies, Whittle (1979) estimated that eight of the nine Skylab astronauts probably lost muscle from the legs, the largest amount being 1.43 kg and the average amount, 0.52 kg.

Finally, integrated electromyograms (IEMG) of the gastrocnemius muscles of the crew of Skylab 3 added further evidence suggestive of muscle atrophy (LaFevers et al., 1975). On the first postflight day, the average predominant IEMG frequency was in the higher bands compared with preflight measurements. Similar shifts in the patterns of dominant EMG frequencies have been observed in patients with nonneurogenic muscular dystrophies (Lenman, 1981), suggesting that such changes in frequency may characterize muscle that is undergoing atrophy from nonneurogenic causes. Postflight IEMG analysis of crew members in long-term Soviet missions showed more than a two-fold increase in IEMG value of a standard muscular effort (Nicogossian and Parker, 1982; Yegorov, 1980).

In summary, exposure to weightlessness as well as hypokinesia/hypodynamia, leads to decreases in muscle "tone", strength, and work (exercise) capacity (Pestov and Geratewohl, 1975). Full recovery of muscular strength, especially in the legs, following space flights of medium (weeks) to long (months) duration requires from several days to several weeks, and data are not available to show conclusively whether full recovery of muscle bulk takes place. However, the average leg volumes of the Skylab 3 astronauts reached preflight values by postflight day 10 (Thornton and Rummel, 1977).

Studies in the rat. Rats exposed to zero-G in Cosmos biosatellites for approximately 20 d showed gross and microscopic and biochemical evidence of atrophy and a decline of contractile force and work capacity of such antigravity muscles as the soleus and triceps brachii (Gazenko et al., 1980b; Oganov, 1981). The data suggested that an adaptive transformation of the phenotype of the muscle fibers may occur; for instance, slow, antigravitational soleus muscle acquired features of fast muscle. Possible myopathic effects of the forces of deceleration during reentry and landing and other possible untoward environmental factors on the ground prior to recovery were not mentioned (Oganov, 1981). Myofibrillar and sarcoplasmic proteins were decreased in the soleus, but not in other muscles examined (Gayevskaya et al., 1976). Muscle glycogen content and activities of glycogen phosphorylase, adenylate cyclase, and phosphodiesterase of the space-flown rats did not differ from controls (Nesterov et al., 1979). Whole muscle demonstrated accelerated rates of contraction (soleus) and a decrease in strength, elasticity, and endurance (soleus and extensor digitorum longus). These changes in functional properties were consistent with those observed in intact space-flown rats; for example, a reduced tolerance to static loads (Gazenko et al., 1980b). All observed changes in the rats' musculature disappeared by the 25th postflight day.

B.   COUNTERMEASURES

Most evidence suggests that, despite attempts at intervention such as diet and exercise, skeletal muscle atrophy continues to some extent throughout orbital flight, manifesting progressive muscle loss and negative nitrogen balance (Leach et al., 1975; Nicogossian and Parker, 1982; Rambaut et al., 1975; Whedon, 1978; Whedon et al., 1977). However, operational experience with the astronauts and cosmonauts has strongly suggested that vigorous inflight physical exercise retards the process of physiologic deconditioning of skeletal muscle as well as the cardiovascular system (Gazenko et al., 1981; Nicogossian and Parker, 1982; Thornton, 1981). Therefore, in view of the lack of alternative preventive methods, daily regimens of physical exercises during flight represent the primary countermeasure against muscle deconditioning. Exercise devices facilitate the process; for example, NASA has developed a compact, teflon-coated panel which can be attached at an angle to the deck of the spacecraft which, when used with body tiedowns, simulates a treadmill and permits walking, running, and even limited jumping. Other exercise devices that have been developed and used in the U.S. space flights include the bicycle ergometer and the "MK-I" (modified Mini Gym™) and "MK-II" (chest expander) devices for exercising arms and trunk. NASA scientists concluded that use of the bicycle ergometer is inadequate for maintaining leg strength sufficient for normal walking at 1-G postflight (Thornton and Rummel, 1977). Comparison of the relative

degrees of muscle deconditioning of the three Skylab crews sug-
gested that the greater amounts of exercise used in missions 3 and
4 may have accounted for the superior postflight muscular condi-
tion of the Skylab 3 and, particularly, the Skylab 4 crews.

By 1975, the recommended inflight regimen for Soviet
cosmonauts prescribed three exercise periods daily for a total of
2.5 h (Dodge, 1976); more recently, Soviet practice has employed
two 40-min periods daily (Kakurin, 1981). Among the estimated
exercise requirements for inflight use, Thornton (1981) listed:
(1) for preventing or minimizing loss of strength and muscle mass
in the legs, walking and running at an equivalent load of 1-G;
(2) for endurance capacity of the legs, walking for 30 min/d at an
equivalent velocity of 6-7 mph, 5/d/wk. On the bicycle ergometer,
inflight exercises at 80 watt-min/d/kg (4.8 kJ/d/kg) lean body
mass (LBM) (thighs) to 100 watt-min/d/kg (6kJ/d/kg) LBM (calves)
were estimated as the levels of effort required to prevent atrophy
of the thigh and leg muscles (Whittle, 1979). These high levels
of exercise, equivalent to 30-60 min of hard cycling, support the
idea (Thornton and Rummel, 1977) that the bicycle ergometer is
inefficient for maintaining muscle mass and strength.

Current NASA flight schedules include 40 min daily for
exercise. On the other hand, typical Soviet practice in long-term
missions specifies between 1.3 and 2.5 h/d for exercise (Kakurin,
1981; Yegorov, 1981). In the U.S.S.R., attempts are made to
select exercises which involve every muscle group, and they include
use of devices such as a rowing machine, bungee cord exercisers,
a treadmill that permits in-place walking, running, and jumping,
and a bicycle ergometer, all of which are used in each exercise
period.

Other countermeasures. Electrical stimulation of the leg
extensors and possibly other muscle groups is a part of the Soviet
approach to inflight maintenance of muscle. In studies of 18 human
volunteers exposed to head-down bed rest of 5° for 182 d, electric
stimulation of various muscle groups for 10 min/d for 10-15 d re-
portedly was effective as part of a group of methods aimed at pre-
venting or reducing the cardiovascular deconditioning associated
with space flight (Kakurin, 1981). In addition, the cosmonauts
wear an elasticized garment, the "Penguin" suit, which opposes
body movement and, to an extent, compensates for the lack of
gravity on the antigravitational parts of the musculoskeletal
system in the trunk and lower extremities (Gurovskiy et al., 1975;
Nicogossian and Parker, 1982). Electric stimulation and load
suits have not been used operationally by the U.S. astronauts.

In summary, the primary means of intervention upon which
both the U.S. and Soviet space flyers rely for preventing or mini-
mizing muscular deconditioning of space flight is vigorous physical
exercise, mainly of the dynamic type. Operational experience with

long-term space missions suggests that carefully designed exercise regimens scrupulously carried out by spacecrews are effective. However, studies of nitrogen and mineral balances suggest that muscle atrophy continues to progress during exposure to weightlessness regardless of the use of available countermeasures.

V. OBSERVATIONS OF THE LSRO AD HOC WORKING GROUP
ON MUSCLE ATROPHY

The meeting of the LSRO ad hoc Working Group on Muscle Atrophy took place at FASEB Headquarters on July 18 and 19, 1983 (see p.81 for list of participants). The agenda included presentations on NASA's program of research on muscle atrophy by scientists from NASA Headquarters, the Ames Research Center, and the Johnson Space Center. A wide scope of topics was discussed, with considerable emphasis on identifying important gaps in knowledge, research that should be done, the most suitable models for ground-based and inflight research, and a pressing need for certain flight-derived data that would be used for validation of ground-based models and design of meaningful experiments.

A.   NATURE, CAUSES, AND MECHANISMS OF MUSCLE ATROPHY
      ASSOCIATED WITH SPACE FLIGHT

As noted in Section IV, the skeletal muscle atrophy that has occurred inflight has apparently not compromised crew function during missions [except, possibly, during extravehicular activity (EVA) and lunar surface EVA in Apollo 15 (see below)], nor has it proved markedly disabling postflight. Nevertheless, recovery of normal muscular strength, bulk, and exercise tolerance has, in some cases, required from several days to several weeks. In missions lasting from about 3 wk to 6 mo, crew members who engaged in vigorous leg exercises have demonstrated an ability to maintain inflight aerobic exercise capacity as measured by bicycle ergometry. However, a postflight decrement in muscle strength and endurance has been universally observed, albeit to varying degrees.

Few instances have been reported of spacecrew exposure to extraordinary muscular demands during long-term missions, such as strenuous EVA, in which high muscular efficiency may be at a premium. However, high heart rates accompanied EVA during the Gemini, Apollo, and Skylab missions. For example, peak rates exceeded 160 beats/min in four of the Gemini EVA experiences (Nicogossian and Parker, 1982). During the lunar surface activities, two of the Apollo 15 crew developed cardiac arrhythmias and extreme fatigue; the arrhythmias recurred during the return flight to Earth (Berry, 1974; Pestov and Geratewohl, 1975). Postflight, the Apollo 15 crew demonstrated potassium deficiency and had marked difficulty in readjusting 1-G (Berry, 1974). Two years after the mission one of the crew who had cardiac arrhythmias during the mission suffered a myocardial infarction (Nicogossian and Parker, 1982). Berry (1974) noted that, compared with the other Apollo missions, the foregoing untoward responses appeared to be an anomaly.

Skeletal muscle atrophy was one of several adaptive responses, such as cardiovascular deconditioning, that probably contributed to the tachycardia, arrhythmia, and fatigue mentioned

above. It is noteworthy that EVA is scheduled in several of the Space Shuttle missions. In view of the fact that crew effectiveness has apparently not been compromised significantly by the muscle atrophy, one might conclude that it is of no practical consequence. However, this position would be fundamentally inconsistent with good preventive medical care of space flyers, the goal of which is to take all necessary precautions against any adaptive responses to space flight unless they are shown to be beneficial; that is, to stop the changes before they occur so that weightlessness can be written off as a harmful influence. Thus, muscle atrophy is a significant biomedical problem of space flight. It justifies sufficient investigative effort to determine the exact causes and mechanisms involved, and, ultimately, some practical, efficient means of prevention or control that will cause minimum interference with the astronauts' demanding schedules before, during, and after space missions.

Opinions of the ad hoc Group varied on the question of full recovery of atrophic muscle following space flight. Some participants were convinced the atrophy is fully reversible; others, based on clinical experience with patients following limb immobilization and other data (Danckwardt-Lillieström and Sjögren, 1976; Salter, 1957), believed that full recovery of preflight muscle bulk may not occur; however, full recovery of muscle strength and endurance is likely. There have been reports of persistent decrements in strength and coordination in such activities as tennis in cosmonauts following long-term missions, but no quantitative data are available.

1. Causes of muscle atrophy in space flight

Opinions of the ad hoc Group varied as to the probable cause(s) of muscle atrophy in space flight. Of the several prevalent environmental influences such as weightlessness and the relative hypodynamia and hypokinesia imposed by the spacecraft dimensions and types of crew activities, all agreed that the unloading of the antigravity parts of the musculoskeletal system is the primary cause. Again, at the level of the whole organism, a majority believed the lack of production of customary muscular force is a key causal factor. Probably related to this are clinical observations that a stimulus for muscle growth is pull across the corresponding joints. Production of muscle force-velocity in space probably requires activation of fewer motor units than are needed for the same level of contraction on Earth. In ground-based studies, care should be taken to simulate the force-velocity parameters that prevail in space flight, a factor that emphasizes the need to acquire more data of this sort from astronauts inflight.

However, there was some reluctance to accept lack of production of muscle force as an etiologic factor in the absence of data on mechanisms of "nonexercise" atrophy and of exercise hypertrophy. Additional factors such as hormonal imbalance may be

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involved although it is known that muscle growth occurs both in the skeletal muscle in response to extirpation of a synergist (Goldberg, 1967) and cardiac muscle in response to a pressure overload (Tipton and Tcheng, 1971) in hypophysectomized rats.

An important question related to muscle atrophy that NASA should answer is: What events occur or do not occur in a space environment that do or do not occur at 1-G that could cause muscle atrophy? (Table 3).

Table 3. Comparison of Some Macro-Level Events in Space and on Earth That May Be Important Factors in Inducing Muscle Atrophy

Response*	Earth	Space
EMG	++++	+++
Force	++++	+
Velocity	+++	++++[†]
Metabolic	++++	+++[§]
Neurohormonal	+++	++++

* normal or optimum = ++++; minimal = +
[†] assumed to increase until subject adapts to zero-G
[§] hypothetically, fewer muscle fibers are activated for limb and body movements in zero-G

Practical approaches are available for defining the problem of muscle atrophy in astronauts. For example, when muscles are activated, varying force and velocity combinations are produced by each muscle and muscle group. With very minor adaptations of existing technology, muscle activation (electromyography), forces (strain gauges) and velocities (video or potentiometers) can be monitored in astronauts on Earth and during space flight. For example, electrogoniometers and software are commercially available which record in three planes and are lightweight and easily adaptable for use in spacecraft. The foregoing measurements should, and can, be done at least intermittently over a 24-h period. This information probably will provide the answer to the critical question posed above. Such a direct approach, with both human and animal subjects, probably offers the best likelihood of yielding practical data leading to: (1) an understanding of the cause(s) of space-related muscle atrophy; (2) identifying the best ground-based models for study; and, (3) designing more meaningful experiments and countermeasures (see also, Research suggestions, p.30-31).

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2. Mechanisms

It is generally acknowledged that the exact biologic mechanisms that induce muscle atrophy are unknown and that this is true of muscle hypertrophy also. Approaches to investigation are suggested by certain established principles of muscle biology and some of the known biologic responses in models of disuse atrophy, examples of which include the following:

o Decreased rates of muscle protein synthesis, appearing within 6 h in immobilized rat limbs (Booth, 1982) return to normal rates within 6 h after remobilization (Booth et al., 1982).

o Insulin responsiveness for 2-deoxyglucose uptake at the 24th hour decreases in the same model (Booth, 1982; Seider et al., 1982).

o Insulin appears to be an important hormonal factor for short-term regulation and maintenance of positive protein balance in skeletal muscle (Goldberg et al., 1980a).

o Possible retrograde influences of muscle may affect motor nerves (Booth, 1982).

o Marked differences occur in rates of atrophy of stretched immobilized muscle versus muscle immobilized in the resting or shortened positions (Booth, 1977, 1982; Simard et al., 1982; Spector et al., 1982; Thomas and Luco, 1944).

o An intact, functioning nerve supply is necessary to maintain skeletal muscle in a normal physiologic state (Guyton, 1981). When muscle is denervated, strong electrical stimulation may retard atrophy (Karpovich, 1968).

o In vivo, sarcolemmal resting membrane potentials have been shown to decrease in denervated muscles (Stanley and Drachman, 1980) and, in muscles of immobilized limbs, to decrease (Mills et al., 1978) or to remain unchanged (Fischbach and Robbins, 1971; Goldberg et al., 1980b).

o Elevated blood cortisone levels have been reported during limb immobilization (Ganong et al., 1955) and space flight (Leach and Rambaut, 1977).

o   Alkaline serine proteinases such as those present in mast
    cells have not been found in muscle cells; however, their
    tissue concentrations increase dramatically in the muscu-
    lar dystrophies, starvation, and endocrine imbalances
    (Bird et al., 1980). Their possible role in conditions
    that feature accelerated degradation of myofibrillar pro-
    teins may deserve further study.

o   Intracellular Ca^{2+}-activated proteinases may offer ap-
    proaches to investigating the regulation of muscle pro-
    tein turnover (Dayton et al., 1976; Reddy et al., 1975).

o   Cathepsins B, D, H, and L and associated inhibitors such
    as pepstatin and leupeptin may be involved in myofibrillar
    protein degradation of disuse atrophy (Bird et al.,
    1980).

o   An apparent increase has been reported in glucocorticoid
    receptors in the cytosol of immobilized gastrocnemius
    muscle cells (DuBois and Almon, 1980).

o   The somatomedins stimulate both proliferation and dif-
    ferentiation of muscle cells in vitro. Insulin is active
    only at grossly supraphysiological concentrations, and
    probably cross-reacts with the somatomedin receptors
    (Ewton and Florini, 1981).

o   Passive tension or repetitive stimulation retards protein
    degradation in isolated muscle preparations (Goldberg,
    1979; Goldberg et al., 1975).

o   Muscle protein degradation may be induced by thyroid hor-
    mones (Goldberg et al., 1980a). Increased postflight
    levels of thyroxine in the Apollo (Sheinfeld et al., 1975)
    and Skylab (Leach and Rambaut, 1977) astronauts, suggest
    heightened thyroid gland activity during missions.

o   Intracellular leucine concentrations may influence the
    rate of protein synthesis in disused muscle (Morgan
    et al., 1981).

o   Inactivity of skeletal muscle induced by joint immobili-
    zation or by pharmacologic or surgical denervation is
    associated with an increase in extrajunctional acetyl-
    choline receptors (Fischbach and Robbins, 1971; Lavoie
    et al., 1976; Pestronk et al., 1976a).

B.   SELECTED PHYSIOLOGIC FACTORS

1.   Nutrition

          The essential importance of adequate nutrition for
the maintenance of positive nitrogen balance is well recognized.
Consequently, a great deal of care goes into the provision of well-
designed meals that offer ample amounts of calories and all the
macro- and micronutrients in accordance with modern nutritional
practice.   Data from the U.S. and Soviet manned space program were
discussed by the ad hoc Group.   Reports of Soviet missions lasting
up to 6 mo (Gazenko et al., 1981; Yegorov, 1981) suggest that the
cosmonauts were able to maintain their body weight with the diets
provided and the daily schedule of activities including physical
exercise.   Metabolic studies carried out in the Skylab program led
to a conclusion that, despite the provision of well balanced, care-
fully formulated diets, the astronauts experienced a net negative
nitrogen balance, part of which has been ascribed to loss of mus-
cle mass.   Although adequate nutrition is provided for spacecrews,
the meals are not always taken systematically or consumed com-
pletely, especially during the first few days of a space mission.
However, in the opinion of the ad hoc Group, and with the assump-
tion that the astronauts consumed adequate food during past space
flights, nutrition was not considered to have been a significant
factor in the etiology of muscle atrophy.   Consequently, additional
nutritional intervention, with the possible exception of the BCAA,
was not considered a promising investigative approach to the prob-
lem of muscle atrophy.   However, the possibility that supplemental
BCAA or their alpha keto analogues might benefit synthesis of mus-
cle protein deserves consideration (Goldberg and Chang, 1978;
Goldberg and Tischler, 1981; Morgan et al., 1981; Stewart et al.,
1982).   In addition, for maintenance of optimal muscular strength
and endurance, a well-balanced diet is essential.

2.   Metabolic changes

          The mineral and nitrogen metabolic study of the
Skylab astronauts, known as Experiment M 071 (Rambaut et al.,
1977, 1979; Whedon et al., 1977), was carefully planned and car-
ried out.   It involved critical efforts of the investigators and
extraordinary cooperation of the astronauts to maintain constant
dietary intake and continuous daily urine and feces collection for
periods spanning 3-4 wk preflight, continuously inflight, and
finally, about 2.5 wk postflight.

          Discussion of the results of Experiment M 071 suggested
that, despite its excellence, certain shortcomings in specimen
collection and analysis may have led to overestimation of the
reported, inflight, negative nitrogen balance.   The nitrogen excre-
tion rates reported were high, much higher than those reported from

human bed-rest studies. Nevertheless, the available data seem to indicate that the nitrogen balance of the Skylab astronauts during the space flights varied from negative to only slightly positive. In addition, other evidence from the Skylab biomedical studies, such as a negative shift in potassium and phosphorus balances, points toward degradation of skeletal muscle as the main source of the negative or marginal nitrogen balances (Leach and Rambaut, 1977; Thornton and Rummel, 1977; Whedon et al., 1977; Whittle et al., 1977). Total hydroxylysine excretion also increased, suggesting breakdown of collagen (Leach and Rambaut, 1977).

Soviet scientists have reported that the inflight physical fitness and nutritional measures used in their long-term missions have succeeded in preventing undue muscle atrophy and have preserved body weight (Gazenko et al., 1981; Yegorov, 1981). However, maintenance of the cosmonauts' body weight may have been, in part, at the expense of muscle mass. Soviet investigators have reported decreases in blood levels of free amino acids postflight in the crews of Salyut missions lasting 21-, 140-, and 185-d (Popov and Latskevich, 1983a,b,c). As a result, cosmonauts' diets have been supplemented with amino acids.

In light of the available information, the ad hoc Group considered that a negative nitrogen balance and some degree of muscle atrophy occur in weightless flight, but that it is possible to retard the muscle deconditioning by exercise regimens that have already been demonstrated inflight. In contemplating the gross dimensions of muscle atrophy, it is useful to recall that muscle is 20% protein; thus, for example, loss of 300 g muscle protein would represent a loss of 1.5 kg of muscle tissue.

3.   Neurophysiologic and kinesiologic aspects

Considerable discussion was devoted to neurologic and neuromuscular aspects of disuse muscle atrophy such as myoneural junction physiology, neurotrophic factors, motor unit recruitment, and various means of manipulating the motor innervation of muscle to produce study models including models of disuse atrophy. The latter are treated in Section V-E (p.41).

Some of the key questions pertaining to neuromuscular function in relation to space flight include: (1) What level of activation of muscles and what forces, and perhaps velocities of movement occur in a normal day's activities of an astronaut on Earth and in space? (2) What is the level of neuromuscular potential output prior to, during, and after space flight? (3) Is the neuromuscular fatigability of astronauts affected during space flight? The atrophy that occurs during space travel is almost certainly muscle mass lost in cross-sectional area and not in the length of fibers as can occur in some immobilization studies. So,

changes in muscle force may reflect changes in the degree of atrophy. Another possibility, however, is that during prolonged flight there will also be a change in the maximum level of neuro-muscular excitation that an astronaut can produce. The strength test is the best test for this in that it is functional, simple, and can be performed easily. If atrophy occurs without a loss in strength, then this too would be useful information. The EMG signal will provide information relative to the level of excitation of the muscle group being tested.

A good deal of experimental evidence supports the view that one of the key neurotrophic factors influencing muscle function and integrity is the neuromuscular transmitter, acetylcholine (Ach), and its associated regulatory processes at the myoneural junction (Drachman, 1974; Drachman et al., 1982a,b). Pharmacologic blockade of Ach transmission changes the resting membrane potential (RMP) and the number of extrajunctional Ach receptors in skeletal muscle in a manner quantitatively equal to that of surgical denervation (Drachman et al., 1982a,b), suggesting to the investigators that Ach transmission is the neurotrophic factor that regulates the two properties studied. In addition, the data suggest that spontaneous, nonquantal Ach release may regulate other properties of skeletal muscle that have been ascribed to non-impulse-mediated, "forward" neurotrophic factors such as substances delivered to muscle via axonal transport in motor neurons (Guth and Albuquerque, 1977; Guth et al., 1981; Gutmann, 1975, 1976).

Members of the ad hoc Group noted that, while the term "trophic" has acquired different meanings in various branches of biologic science, fundamentally it means nutritional, and the etymology of neurotrophic should indicate whatever the motor nerve does to maintain the integrity of the muscle. According to Gutmann (1976) the term "neurotrophic relations and functions" should be restricted to long-term regulation not mediated by nerve impulses. The question whether such nonimpulse, forward neurotrophic factors are involved in skeletal muscle maintenance has been debated for decades and remains unresolved. The ad hoc Group's opinion on this was divided; however, the question appears to have little relevance to the etiology of space-related muscle atrophy where the nerve supply remains intact. Nevertheless, it is important in terms of the types of animal models that should be used in the study of disuse atrophy.

Another question concerns the effect of hypokinesia, hypodynamia, and limb immobilization on neural activation of muscle. There are only a few published reports in which the quantity of neuromuscular electrical activity has been measured in muscles of immobilized limbs over, for instance, a 24-h period (Fischbach and Robbins, 1971; Fournier et al., 1983). Integrated EMG values were remarkably decreased in some experiments, but not abolished, and

inter-study variation in values was substantial. Fischbach and Robbins (1971) reported no changes in junctional sensitivity to Ach and muscle membrane sensitivity in their immobilized rat model, and they considered it unlikely that any form of immobilization in which the innervation remains intact would result in complete synaptic silence. However, the significance of sustained neuromuscular electrical activity in immobilized limbs in terms of muscle atrophy is not clear.

Finally, it was noted that motor nerve denervation does not always result in muscle atrophy. Examples are hypertrophy of denervated diaphragm and anterior latissimus dorsi muscles of chickens (Feng et al., 1962, 1963; Sola and Martin, 1953; Sola et al., 1973). Reasons for the apparent paradox are not known, but muscle stretch was suggested as a possible mechanism.

4. Endocrine changes

With respect to the significance of the hormonal changes that have been reported from manned space flight, the degree of change, as reflected by plasma and urine levels, was probably insufficient to influence muscle integrity and function. This opinion was based on evidence from both animal experiments and clinical experience with endocrinological disorders suggesting that substantial deviations from normal levels of circulating hormones are needed to cause muscle wasting. On the other hand, some participants believed that further investigation of hormonal interactions with skeletal muscle is justified in attempting to advance the quest for mechanisms of muscle growth, hypertrophy, and atrophy as well as metabolic regulation. Although it seems unlikely that alterations in growth hormone and/or somatomedin levels during space flight would cause disuse atrophy, it is possible that these hormones (or agents that cause their secretion) could be very useful in the treatment of the condition.

In addition, data from experiments with a rat model of hypokinesia (head-down suspension) showed significant changes in glucocorticoid levels and density of glucocorticoid receptors in hindlimb muscles, which were consistent with increased muscle protein degradation (DuBois and Almon, 1980, 1981; Steffan and Musacchia, 1982). However, one member of the ad hoc Group emphasized that circulating hormone levels, not tissue receptor levels, usually determine the level of a tissue response.

The animal castration model (Hanzlikova and Gutmann, 1978) was not considered appropriate for studies of space-related muscle atrophy. Finally, the question whether there is a significant central hormonal effect on muscle atrophy associated with disuse or weightlessness appears unresolved.

5.   Research suggestions

Experiments should be planned to test the effects of
dietary supplements of the BCAA, particularly leucine, and the
keto-analogues of the BCAA in both ground-based and space-flown
animal models of disuse atrophy.

In view of the limited knowledge about the rates of loss
of nitrogen during space flight, consideration should be given to
undertaking additional human metabolic studies in suitable future
space missions. Useful data could be derived from such an experi-
ment in the Shuttle program; however, more meaningful data would
require longer-term missions such as those contemplated for the
space station.

To obtain data on the neuromuscular activity during an
astronaut's typical day, terrestrial as well as inflight measure-
ments are needed. These should include: (1) electromyography,
with surface electrodes, of the quadriceps and hamstrings as well
as the dorsi- and plantarflexors of the feet; (2) forces produced
on the heel and bases of the metatarsals via transducers built
into the footwear; and, (3) joint movements by means of sensors on
the knee and ankle. Each parameter can be recorded directly on
small units similar to those used for ambulatory electrocardi-
ography. Techniques are available for all the suggested measure-
ments; however, some equipment development may be necessary for
item (2).

It would appear that these devices can be integrated
without any infringement on the existing planned programs. There
should be no significant effects on the astronauts. They should
not have to modify their planned programs and there should be
little or no discomfort to them. The experiment is simply to
determine what they do with respect to movement during their nor-
mal activities. It will require no additional time inflight or
preflight once the appropriate sensors are instrumented.

For acquiring human data on the level of neuromuscular
potential output prior to, during, and after space flight, the
following is suggested: measure the maximum force that can be
produced at zero velocity for the knee extensors, knee flexors,
and the dorsiflexors and plantarflexors of the feet. The neces-
sary tension-recording device can be installed into the existing
hardware of the spacecraft. The strain gauge could weigh only a
few milligrams. The same device used for recording EMGs could be
used for these maximum force data.

A more nearly functional assessment of neuromuscular
activity would be to test the ability to exert a maximum force at
some selected velocity, or better, to produce some target force at
some target velocity. This is technically within the state-of-the-
art, but would require more development for inflight use than the

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previously mentioned test. It would also require some time commitment from the astronauts. These tests would not be useful in detecting muscle atrophy, but they would determine whether there is a functional change in movement control that might occur as a result of muscle atrophy. This information would be very important because of the fine movement control that is presumably needed in routine operations during flight.

To investigate the question of neuromuscular fatigability during space flight, measure the maximum force that can be produced over a period of 2 min while exerting a maximal effort once every second, with simultaneous recording of the EMG. This test should be done several times preflight, within a week of launch, and as soon after return as possible (within 1 d). The muscle group to be tested initially should be perhaps the plantarflexors of the foot. The recording devices could be the same as in the previously described experiment. Other muscle groups should be tested eventually, e.g., dorsiflexors of the foot and elbow flexors and extensors. Also, if an arm exercise is being performed, some venous blood samples could provide an indication of significant changes in the metabolic potential of the muscle group. This experiment is important because there is the general idea that disuse results in a rapid, significant loss of a muscle's metabolic potential.

Three properties of skeletal muscle that should be considered for study in the rat model of hypokinesia (e.g., the tail-suspension model) are RMP, extrajunctional Ach receptors, and isometric muscle strength. Additional studies are needed to determine whether the decrease in IEMG activity reported from experiments on immobilized limbs (Fischbach and Robbins, 1969; Fournier et al., 1983) influences the degree of associated muscle atrophy.

Consideration should be given to the extension of studies such as those of Florini and associates (e.g., Ewton and Florini, 1981) and Almon et al. (e.g., DuBois and Almon, 1980; 1981) to include the effects on mature muscle cells, isolated muscle preparations, and intact muscles in vivo, of altered levels of hormones and possible changes in their receptors that are known to result from various models of hypokinesia and hypodynamia including actual weightlessness (e.g., Tigranyan et al., 1982). Studies are needed, as well, on the influence of growth hormone and the somatomedins (e.g. Florini et al., 1977; Goldberg and Goodman, 1969) and anabolic steroids (Powers and Florini, 1975) on muscle protein synthesis and muscle atrophy in animal models of hypokinesia/hypodynamia. However, these studies should be designed with full awareness of the whole animal studies done by Florini's group in the 1960s.

C.   BIOCHEMICAL ASPECTS

        Discussion involved mainly the loss of myofibrillar pro-
tein, regulation of protein synthesis and degradation, alterations
in metabolic potential, and associated enzymatic changes in muscle
atrophy induced by hypokinesia/hypodynamia.

        The main problem in understanding muscle atrophy is that
some basic questions concerning muscle biology still remain unan-
swered. For instance, although a wealth of information exists
about the biochemistry of protein synthesis, the basic mechanisms
of muscle protein synthesis and degradation in biologic responses
such as muscle atrophy and hypertrophy are not well understood
(Millward et al., 1980a,b). Conceivably, decreased rates of pro-
tein synthesis might reflect specific adaptations to altered
energy demands rather than to disuse, per se; however, the availa-
bility of energy does not appear to be rate-limiting in protein
synthesis (see p.33). Muscle protein degradation was reviewed
recently by Millward et al. (1980a). It has been demonstrated
that a portion of the cellular protein is degraded within lyso-
somes (Goldberg and Chang, 1978), and to some extent this portion
of protein degradation is sensitive to growth factors such as
insulin. However, this association is not sufficient to implicate
the lysosome in the degradation of normal actin and myosin or in
the accelerated degradation seen in disuse atrophy. Little is
known about the mechanism of disassembly and degradation of the
contractile apparatus. It is equally possible that the lysosome
is involved in the degradation of membrane receptors and certain
macromolecules which require hydrolytic action to release specific
precursors or cofactors and not contractile proteins (Stauber
et al., 1981).

        Two examples illustrate such an alternative role for the
lysosome in muscle metabolism. The first and best known is the
uptake and degradation of low density lipoproteins (LDL) by receptor-
mediated endocytosis. Here LDL are delivered to lysosomes where
the protein is degraded to amino acids and the cholesteryl esters
to free cholesterol to be used by the cell for synthesis. The
second is the transport of cobalamin (vitamin B_{12}) via a protein
carrier, transcobalamin II. Again the lysosome is utilized to
digest the carrier to release the active cofactor. Thus, it is
desirable to investigate the role of lysosomes in muscle metabolism,
but from a broad point of view. Considerable cytochemical informa-
tion on lysosomes in muscle is available that is pertinent to pro-
teolytic enzymes, pathways, and regulatory mechanisms of protein
degradation during disuse atrophy (Trout et al., 1979a,b; 1981),
but it has not helped to explain a possible role of lysosomes in
muscle atrophy. Two alkaline proteases have recently been identi-
fied in muscle, and their possible role in activation of lysosomal
proteases has been demonstrated (Stauber et al., 1983). It is
likely that the list of proteases in or associated with muscle
will continue to expand.

Technical problems in the measurement of rates of protein degradation in skeletal muscle have impeded progress in this area (Goldberg and Dice, 1974; Goldberg et al., 1980a). Consequently, data on muscle protein turnover should be interpreted with caution, particularly in terms of quantitative changes. For instance, it may be premature to reach firm conclusions on muscle protein synthesis and degradation from experiments involving prelabeling of muscle and measuring release of phenylalanine in a model of hypokinesia. Nevertheless, it is generally accepted that there is a loss of myofibrillar protein in muscle atrophy, with a reduction in cross-sectional area of the muscle fibers and a change in metabolic potential. A fundamental problem is the lack of an identified mechanism for explaining exercise hypertrophy in muscle, that is, to bridge the gap between increased turnover of ATP to increased muscle protein synthesis. An important research goal is to isolate the substance in exercising muscle which stimulates synthesis of the myofibrillar proteins (Saltin and Gollnick, 1983). Such a discovery could lead to more precise experiments on the mechanisms of muscle atrophy induced by inactivity.

1. Metabolic capacity

Much information has been generated in recent years about the adaptability of skeletal muscle to various modes of use and under-use (Saltin and Gollnick, 1983). Numerous studies in rats and other species have shown that endurance training increases the capacity of the citric acid cycle, fat oxidation, and the electron-transport system. However, data on the effect of inactivity on the metabolic capacity of muscle are relatively limited. Joint immobilization in experimental animals has been shown to reduce the oxidative capacity of muscle, but to a lesser degree than inactivity produced by denervation (Saltin and Gollnick, 1983). For example, changes in muscle cell mitochondria reflected by reduced capacities to oxidize glucose, pyruvate, palmitate, and β-hydroxybutyrate have been reported in a rat model of disuse (Rifenberick and Max, 1974; Rifenberick et al., 1973). On the other hand, relatively small changes in metabolic capacity have been reported after prolonged immobilization of primate hindlimbs (Edgerton et al., 1975). From their recent literature review, Saltin and Gollnick (1983) noted a general concensus that there are no major changes in the contractile characteristics of skeletal muscle as a result of various types of physical training or inactivity.

It is known that in normal skeletal muscle, about 99% of the ATP that is hydrolyzed is used for contraction; large changes in the amount of available energy in the cell occur without affecting nucleic acid synthesis. Moreover, there is no evidence that the availability of energy is rate-limiting in protein synthesis. However, the effects of genetic regulation are relatively well established, and are rate-limiting in situations in which plenty of energy is supplied. This appears to be a promising area of investigation.

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The lowering effect of inactivity on mitochondrial size and numbers and on the aerobic capacity of muscle has been shown in studies that demonstrated a close correlation among these properties and levels of muscle activity. For example, Saltin and Gollnick (1983) cite 32 reports from studies in the 1960s and early 1970s of adaptations of mitochondrial enzymes of human skeletal muscle in response to endurance training. The largest increases in muscle mitochondria occur in response to submaximal, prolonged exercise where lactate levels rarely rise very high. However, with heavy resistance exercise, high lactate levels are produced and muscles increase in mass, but not in numbers of mitochondria. In immobilized limbs of rats, loss of respiratory control and malate dehydrogenase activity in the gastrocnemius and plantaris muscles promptly followed skeletal fixation and there was a reduction in the yield of mitochondrial protein throughout the course of atrophy (Rifenberick et al., 1973). Energy metabolism in the same model decreased in the atrophying muscles (Rifenberick and Max, 1974), suggesting to the investigators that deficiencies in energy metabolism may be significant in the progression of muscle atrophy.

It is known that, following limb injuries, athletes can restore muscle strength in the affected limb within about 30 d; however, return of muscle endurance may require 6 mo or longer (Sherman et al., 1981). Measurement of mitochondrial enzyme markers was suggested as an approach to following the responses of muscle to reduced activity such as in space flight. However, some participants considered that the mitochondrial response to inactivity may be either unrelated to or too variable to provide a firm basis for estimating muscle atrophy. For instance, in cross-reinnervation/innervation experiments in cats, there was no muscle atrophy and the mean tension of motor units in the cross-reinnervated and reinnervated muscles was normal (Chen et al., 1982). In addition, the slow-oxidative, fatigue-resistant muscle maintained a high oxidative capacity as was shown histochemically, and a resistance to fatigue even though the muscle was reinnervated by fast, low-oxidative, and fatigable motoneurons (Edgerton et al., 1980). Thus, some members of the ad hoc Group believed the significance of mitochondrial change in relation to the atrophic process has not been firmly established.

2. Research suggestions

In the search for mechanisms of muscle atrophy resulting from inactivity or under-use, studies of mechanisms of exercise-induced hypertrophy should be considered. Key targets in such investigations include identification of the specific stimuli generated by exercise and determination of how such stimuli are communicated as specific chemical signals to the genes to induce the synthesis of proteins involved in muscle hypertrophy. For

example, a major breakthrough would be to isolate a protein or other agent which is secreted by, or found in, exercising muscle, which stimulates the reading of the DNA of actin and myosin.

Investigations of the effects of inactivity or under-use of skeletal muscle on the synthesis and degradation of muscle proteins need to be rigorously controlled in order to yield useful quantitative data. Results of some experiments appear questionable because of uncontrolled variables such as reutilization of amino acids of degraded muscle proteins and lack of data on rates of synthesis and degradation in the models used.

D.   COUNTERMEASURES

Discussion of methods of intervention to prevent or control muscle atrophy associated with space flight focused on physical exercise, nutrition, pharmacologic or biochemical approaches, and electrostimulation. Rehabilitation of atrophic muscles was discussed also, although it was recognized that NASA's objective is to obviate the need for rehabilitation by prevention or control of muscle atrophy.

1.   Exercise

Available data seem to indicate that daily, vigorous physical exercise inflight such as can be done with the aid of various devices (see p.18) retards the rate and degree of muscle atrophy during long-term missions (Gazenko et al., 1981; Nicogossian and Parker, 1982; Thornton and Rummel, 1977). However, the available evidence of a continuing negative or marginal nitrogen balance (Leach and Rambaut, 1977; Whedon et al., 1977) as well as the disproportionate amount of time devoted to exercise, such as the 1.3-2.5 h/d prescribed for Soviet missions, emphasizes the need for improvement in methods of intervention. Thus, further investigations are indicated to determine types and amounts of physical exercise that would help to preserve muscle strength, endurance, and mass with the least daily expenditure of time and energy. The literature is enormous on exercise and work physiology, physical fitness training, strength and endurance training, and muscle rehabilitation following injury or disease. However, the limited data on the effects of space flight on muscle strength and endurance suggest a need for additional information that can be obtained from inflight experiments (see p.30, 31), and ground-based simulation studies. Even without additional data, expert analysis of available knowledge should permit some improvement in recommended types and amounts of exercise by judicious selection of methods between the known extremes of one daily isometric contraction of one second's duration at two-thirds of maximum strength to maintain strength (Hettinger and Müller, 1953) and the 1.3-2.5 h/d combination of exercises used by the cosmonauts.

One possible reason suggested for the apparent utility of the treadmill-type device as an aid to inflight exercise is that it includes eccentric contractions, that is, the lengthening of muscle while it is developing tension (Seliger et al., 1980). According to unpublished information presented during the ad hoc meeting, recent clinical experience has shown that pure eccentric exercises used following hand surgery resulted in dramatic rehabilitation. It has also been shown that creatine kinase (CPK) is released to a far greater degree during eccentric than concentric contractions (Newham et al., 1983a). However, it appears that muscle damage and muscle soreness are more likely with eccentric than with other forms of exercise (Hikida et al., 1983; Newham et al., 1983b). Since the question whether eccentric contraction is superior to concentric modes for rehabilitation and strength training and for retarding muscle atrophy in models of inactivity has not been settled, it deserves additional study.

The matter of preflight, optimal physical fitness for withstanding the adverse effects of weightless flight appears to be unresolved. In terms of resistance to certain effects of muscle atrophy, some evidence suggests that physical training before experimental immobilization provides a "reserve" of neuromuscular function that retards loss of voluntary strength and reflex potentiation, compared with untrained control subjects (Sale et al., 1982). It has been customary, incidentally, for space flyers to keep themselves in a high state of preflight physical fitness. However, some investigators believe that a high level of preflight fitness based, for example, on endurance training, tends to increase susceptibility to orthostatic intolerance postflight (Klein et al., 1977). These investigators suggested postflight orthostatic tolerance depends, in part, on the size of the vascular bed in the leg muscles, which is known to decrease in atrophic muscle. Thus, the hypertrophy of muscle which results from some types of physical training would appear to be a disadvantage during the immediate postflight period (Whittle, 1978).

It has long been known that immobilizing a muscle in a stretched mode will markedly retard the rate of disuse atrophy for a limited number of days or weeks (Booth, 1977, 1982; Summers and Hines, 1951; Thomas and Luco, 1944; Thompson, 1934). Moreover, stretch-induced hypertrophy of skeletal muscle has been reported in animal models such as the chicken (Holly et al., 1980; Sola et al., 1973). Discussion of the possible practical utility of this property of muscle suggested that stretch results in a longer, not a stronger muscle fiber; that is, stretch does not result in an increase in cross-sectional area of muscle, which is a key parameter in muscle strength. While muscle atrophy may be retarded in the stretched muscles, atrophy of their antagonists, placed in the shortened mode, may be accelerated (Fournier et al., 1983; Simard et al., 1982; Spector et al., 1982). Stretching of muscles was not considered a practical approach to intervention of muscle atrophy associated with space flight.

The time course of recovery of muscle strength following injuries or neurologic disorders appears to differ from that of muscle bulk. Strength frequently returns in a matter of weeks, provided suitable exercise is used. However, when a limb has been immobilized for a short period for orthopedic reasons, it is very difficult to rehabilitate the atrophic muscles to normal bulk (Danckwardt-Lilliestrŏm and Sjŏgren, 1976; Salter, 1957).

Documentation of the degree of decrement in endurance of the leg muscles of astronauts appears to be limited, suggesting that additional pre- and postflight measurements should be made. Opinion varied as to whether significant changes in muscle strength and endurance would occur during 7-10-d space flights. For example, the estimated rate of muscle protein synthesis in the hind limbs of rats declined 37% after 6 h of limb immobilization, suggesting to the authors that very early changes occur in molecular events that regulate protein synthesis in disused or immobilized muscle (Booth and Seider, 1979). Krieger et al. (1980) reported that immobilization of rat hind limbs for 2 d resulted in a decrease in state III respiration and the respiratory control index of the sarcolemmal, but not the intermyofibrillar, mitochondria of gastrocnemius muscles. However, there are no reports of such short-term changes in strength and endurance performance of immobilized muscles in the rat. Moreover, it appears that endurance properties of muscles change little after prolonged limb immobilization in such species as the guinea pig (Maier et al., 1976), rat (Witzmann et al., 1983), and subhuman primate (Edgerton et al., 1975). Human subjects exposed to simulated weightlessness for 7 d by means of immersion in water demonstrated a 30-40% decrease in maximum dynamic and isokinetic strength of the leg extensors and in the isokinetic strength of the tibial muscles (Grigor'yeva and Kozlovskaya, 1983). The authors regarded these rapidly developing changes as reflexive responses to the removal of load bearing. Since little is known about the time of onset and rate of progression of muscle atrophy in space flight, a majority of the participants favored taking advantage of opportunities for such studies in the Space Shuttle Program (see also p.30, 31).

Review of the Skylab data indicated that exercise with the bicycle ergometer apparently reduced the amount of leg atrophy to be expected, but it was considered an inefficient method compared with other types of exercise made possible by devices such as the "treadmill" equipped with elastic tiedowns for the user (see p.18). There was general agreement that inflight exercises for astronauts should include types for maintaining both strength and endurance. Two-to-three d/wk would probably suffice for strength-building exercises, and another 2-3 d/wk for endurance training.

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2. Electrical stimulation

Animal and human studies have demonstrated that electrical stimulation of inactive muscle, such as exists in denervation or immobilization, can retard and perhaps prevent muscle atrophy (Fischer, 1939; Grodins et al., 1944a,b; Herbison et al., 1971; Kosman et al., 1947a,b, 1948; Laughman et al., 1983; Shaffer et al., 1954; Stillwell and Wakim, 1962; Wehrmacher et al., 1945). With regard to space application, Soviet investigators reported beneficial effects of electrostimulation of muscles in human subjects exposed to prolonged simulated weightlessness (Kakurin et al., 1973; Georgiyevskiy et al., 1979). Daily electrostimulation of the muscles of the abdomen, back, thighs and legs during a 45-d bed-rest experiment was credited with favorable effects on muscle "tone", strength, and static and dynamic endurance. Soleus muscle biopsies showed a "positive effect of electrostimulation ... preventing development of the atrophic process" (Kakurin et al., 1973). In a similar study, 8 of 12 healthy volunteers received electrical stimulation of the anterior and posterior muscles of the legs and thighs as well as back and abdomen for 2 daily 30-min periods, six times/wk while remaining at bed rest for 45 d in a 6.5° head-down tilt position (Georgiyevskiy et al., 1979). Although all subjects showed decreases in circumferences of legs and thighs as measured on day 40 of the experiment, the mean change in the stimulated group was significantly less than in the controls. The authors noted that the "general condition and endurance ... were better among individuals whose muscles were submitted to stimulation." It is understood that electrostimulation is used operationally in the Soviet space program as a part of their system of countermeasures against the adverse effects of space flight.

After discussion, the ad hoc Group considered that electrostimulation is not a useful technique for prevention of muscle degradation during space flight, for several reasons: (1) voluntary contraction of muscle is the most efficient and physiologic means; (2) the intensity of electric current required to produce a maximum contraction is intolerable in most subjects; and (3) the fact that the effectiveness of electrostimulation is dependent upon the electric impulse density, which, in muscle, diminishes markedly only 10 mm from the point of stimulation. The use of pad electrodes applied to the skin would probably result in stimulation of only the superficial fibers in a muscle.

However, it is possible that electrically-induced muscle contractions employing easily tolerated amounts of current may offer some advantage in terms of sensory perception of the associated limb movement, a sort of biofeedback to train individuals to contract their muscles maximally.

3. Other approaches

Other ideas that were mentioned include the possible utility of a motion-resistive carapace or exoskeleton for wear by space flyers, and pharmacologic or biochemical means of intervention. Soviet authorities advocate use of a load suit except during hours of relaxation and sleep (Gurovskiy et al., 1975). This garment, which is known as the "Penguin" suit, is said to provide partial compensation for zero-G by opposing body movements and simulating a constant gravitational load on the muscles of the trunk and legs (Nicogossian and Parker, 1982).

Leucine possesses some apparently unique regulatory and metabolic properties in muscle, including the promotion of protein synthesis and inhibition of protein degradation (Goldberg and Chang, 1978). These properties of leucine and possibly of combinations of other BCAA may offer an experimental approach to a dietary or biochemical method of intervention (Goldberg and Chang, 1978; Goldberg and Tischler, 1981; Morgan et al., 1981; Stewart et al., 1982). Stewart et al. (1982) administered a mixture of branched-chain ketoacids to patients with Duchenne muscular dystrophy and observed a reduction in the rate of excretion of 3-methylhistidine (3-MeH) in the urine. The authors concluded that the mixed keto-acids reduced muscle protein degradation acutely in their patients.

Finally, pharmacologic intervention by use of inhibitors of proteolysis has stimulated interest in laboratory experimentation in disorders such as muscular dystrophy. It has been reported that microbial anti-proteinases such as antipain, leupeptin, and pepstatin inhibit degradation of denervated pectoralis muscle in chickens (Stracher et al., 1979) and chicken dystrophic muscle in tissue culture (McGowan et al., 1976). Schorr et al. (1978) reported beneficial effects of treatment of dystrophic mice with pepstatin, starting at 3 wk of age and continuing for 5 wk. However, Enomoto and Bradley (1977) found no evidence of suppression of muscle degeneration in dystrophic mice given subcutaneous injections of leupeptin and pepstatin during their remaining life spans starting at age 35 d. On the contrary, there is some suggestive evidence that, for example, elevations in lysosomal proteases (for which a few inhibitors are available) result from muscle regeneration, not muscle degradation (Griggs and Rennie, 1983; Stauber, 1980). On this basis, administration of an inhibitor could conceivably interfere with the process of muscle protein synthesis, an event presumed to be beneficial in recovery from muscle atrophy. Thus, there is currently little scientific basis for the use of protease inhibitors to prevent disuse atrophy in man; however, the subject deserves further investigation.

4. Research suggestions

A careful analysis of available data on the effectiveness of eccentric muscular contractions in terms of physical fitness training and rehabilitation of atrophic muscle should be done. If eccentric exercise has some advantages over other modes for maintenance of strength and endurance, its use as an inflight mode should be investigated, including studies with human subjects exposed to simulated space flight. Prospective investigators should be aware of the availability of versatile exercise devices whose operating modes include eccentric exercises. For example, see Knuttgen et al. (1982).

Biochemical, neurophysiologic, and other properties of muscle during adaptation to eccentric loading should be determined in an animal model to complement the human studies suggested above.

To acquire data for use in improving inflight exercise regimens, pre- and postflight measurements of maximal voluntary contraction of the flexors and extensors of the arms and legs should be done on all personnel who participate in space flights. Such measurements should be made despite the idea that missions lasting only 7-10 d probably induce little muscular deconditioning. The importance of matching the test methods to the types of exercises used should be kept in mind.

Skylab data suggest that exercise with the bicycle ergometer at a level of 80 watt-min/d/kg LBM (4.8 kJ/d/kg LBM) maintained thigh muscle mass, but 100 watt-min (6kJ) was required to prevent atrophy of the calf muscles (Whittle, 1979). If possible, ground-based studies should be devised to determine the reasons for this difference. Hopefully, the derived information could be applied to improving inflight exercise devices and regimens.

A human, ground-based study should be considered for determining the minimum amounts of strength or endurance exercises, or combinations of these, needed to prevent muscle atrophy in a model of hypokinesia.

Possible modifications of available inflight exercise regimens and devices should take into account the need to control or prevent all responses to zero-G that might benefit from various types and amounts of exercise including cardiovascular deconditioning, muscle atrophy, fluid shifts, and, possibly, the space sickness syndrome and bone demineralization. With regard to the latter, the pronounced negative calcium balance of space flight is the subject of a parallel study by LSRO, to be published under the title, "Research Opportunities in Bone Demineralization", edited by S.A. Anderson and S.H. Cohn.

Human as well as animal studies of the possible prevent-
ive benefit of supplements of leucine and/or combinations of iso-
leucine and valine should be done in models of disuse atrophy. A
complementary effort should be considered to determine whether the
effect of leucine on protein synthesis is sustainable for a pro-
longed period or is limited to an acute response. Similar data
should be sought regarding the effect of metabolites of leucine on
proteolysis.

Animal studies should be expanded to assess the possible
preventive value against disuse atrophy of administering inhibitors
of myofibrillar proteases and other proteases involved in muscle
protein turnover. Part of such investigations should be identifi-
cation of untoward side effects, which could be more onerous than
the disuse atrophy itself.

Speculation about possible reduction of sensory perception
of muscle contraction during space flight suggested a need for an
expert analysis of available data on this subject (see p.38). If
this were identified as a significant problem in achieving optimum
muscular contraction during inflight exercises, electrical stimula-
tion of muscles could be considered as a method for increasing sen-
sory perception.

Finally, the report of Sale et al. (1982) that muscle "...
training prior to immobilization provided a reserve of neuromuscu-
lar function (reflex potentiation) which attenuated the effect of
immobilization in relation to the control conditions" suggests a
need for more data on this type of approach. In addition, NASA
scientists should consider reexamining available data from ground-
based and space flight studies to explore relationships among:
(1) physical fitness training before and during real and simulated
weightlessness; (2) postexposure exercise capacity, orthostatic
tolerance, and $+G_z$ acceleration tolerance; (3) the muscle decondi-
tioning response; and, (4) the cardiovascular deconditioning
response. This should include consideration of the data reviewed
by Klein et al. (1977) and data presented by Goldwater and Sandler
(1982) suggesting an inverse relationship between aerobic fitness
and tolerance for gravitational loads. Such an analysis may aid
in resolving questions about optimal physical fitness and exercise
regimens for space flyers.

E.   MODELS, METHODOLOGY, AND EQUIPMENT

    1. Models

        The question of the most suitable models for investi-
gating muscle atrophy related to space flight received considerable
emphasis during the ad hoc meeting. This involved techniques of
simulating hypokinesia and weightlessness in human and animal
experiments, the best animal models, and the lack of acceptability
of the much-used term "disuse" atrophy.

True disuse of motor units typically results from inter-ruption of motor nerve input to the muscle and features electrically silent myoneural junctions. Thus, models of "disuse" based on such techniques as denervation do not realistically simulate the situation in space flight where the innervation remains intact. Again, with the intact neuromuscular system as one criterion, mechanical immobilization cannot truly be a model of disuse in that voluntary contractions of the involved muscles occur (Fournier et al., 1983). It is apparent, therefore, that space flyers experience a reduction in the amount and force of activity of the musculature that probably should be thought of as a type of "under-use". For studies with human subjects, the best, currently available, ground-based model appears to be bed rest with physical activity ranging from minimal to specific schedules of exercise or postural changes, depending on the experimental objectives.

To date, the best animal model for simulating the hypo-kinesia and hypodynamia of weightlessness appears to be the rat model in head-down tilt that unloads the hind legs (Feller et al., 1981; Morey-Holton and Wronski, 1981; Musacchia et al., 1983). The head-down tilt is achieved by tail suspension or a body harness. According to unpublished information presented during the meeting, comparisons of atrophic effects from experiments with the head-down tilt model, other models of "disuse", and from space-flown experiments suggest the head-down tilt model produces reasonably good simulation of weightlessness in the rat's hind legs. The usefulness of this model for studying changes in body composition has not been validated.

Although mechanical immobilization of joints is widely used as a means of producing "disuse" atrophy, it was not considered a good model for simulating the physical conditions of space flight. Nevertheless, its utility was acknowledged as a means of inducing muscle atrophy for various sorts of investigation in muscle biology including, for example, testing of techniques of intervention. Moreover, when muscle atrophy resulting from space flight becomes better characterized at both the macro- and micro-levels, mechanical immobilization may prove to be a valid research model for studies of space-related muscle atrophy.

Two other models were suggested as advantageous for certain types of studies. Human patients or animal models with spinal cord damage could provide, during certain intervals after injury, an excellent model of true disuse atrophy which could be used for special studies such as determining the minimum amount of electrically-induced exercise needed to prevent atrophy. Data of this sort could then be used in formulating optimum voluntary exercises for use in weightless flight.

The other model of a pure disuse atrophy involves pharmacologic blockade of motor nerves with tetrodotoxin, which blocks nerve impulses but not fast axonal transport (Drachman et al., 1982a,b). Otherwise, the neuromuscular anatomy and physiology apparently remain unchanged, but the resulting muscle atrophy matches that of denervation. Again, this may prove to be a useful animal model for space-related studies if it can be validated by data from studies with other models including space-flown rats and the rat head-down tilt model.

Training muscle groups to a level of hypertrophy, then stopping training and measuring various parameters such as rate of reversion to pre-training status may roughly simulate the effects of under-use of muscles during weightlessness and is applicable for human and animal experiments (Houston et al., 1979). A similar model could be used to measure changes in muscle groups trained for endurance (Faulkner et al., 1972); however, evidence is limited that fatigability of muscle increases during space flight or after immobilization.

Other models that are considered useful for investigation of muscle atrophy involve tissue culture, organ culture, and partial-body perfusion techniques such as hemiperfusion and isolated, perfused muscle preparations. As is known, experiments based on tissue culture or perfusion techniques in which the tissues are homogenized and then measured for incorporation or disappearance of a marker sometimes yield data of questionable validity because of confounding problems such as the reutilization of amino acids from degradation of muscle proteins in experiments on muscle atrophy. A problem in using isolated, incubated muscle preparations is hypoxia or anoxia of the deeper portions if the muscle is too thick; insufficient tissue oxygenation for cells beyond those on the surface introduces uncontrolled variables. Nevertheless, certain types of muscle studies involving tissue culture (Ewton and Florini, 1981; Florini et al., 1977), organ culture or hemicorpus perfusion (Goldberg and Chang, 1978; Goldberg et al., 1980a; Jefferson et al., 1972; Li and Jefferson, 1978) have produced valuable data.

In summary, although all the models discussed have shortcomings in terms of simulating the environment of space flight and other technical flaws, those offering certain investigative advantages are identified in the foregoing. While no model is ideal, a better understanding of the nature, causes, and mechanisms of space-related muscle atrophy will permit refinement of experimental models for both ground-based and inflight studies.

2.   Methodology and equipment

Some methods for measuring muscle strength and endurance fail to take into account the accessory action of all muscle groups involved. For instance, the contribution of the iliopsoas

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and trunk muscles to extension and flexion of the knee is often included with strength values credited solely to the quadriceps and hamstrings. Definitions, methods, and apparatus seem to need improvement.

Muscles that are feasible to study in human subjects in terms of relatively isolatable EMG signals include the biceps brachii, triceps brachii, quadriceps, hamstrings, tibialis anticus, and gastrocnemius. In addition, muscles whose customary levels of activity would, presumably, not change significantly in zero-G offer useful models for comparison with muscles that are known to atrophy. Examples suitable for human studies include the masseters and temporalis muscles (provided that a normal amount and strength of chewing occur inflight), and, for animal studies, the diaphragm, anal and bladder sphincters.

The practicality of using 3-MeH as a method of following muscle protein degradation was discussed. 3-MeH has been called a unique marker because during the breakdown of muscle proteins it is released and excreted unchanged and quantitatively in the urine, not being reutilized for protein synthesis or oxidized for energy. Recent examples of reports on the method and its advantages and possible shortcomings include Afting et al. (1981), Anonymous (1983), Elia et al. (1981), Long et al. (1981), Millward et al. (1980a,b), Ward and Buttery (1978), Wassner and Li (1982), and Young and Munro (1978). Certain problems call for caution in interpreting 3-MeH excretion data. First, endogenous sources of 3-MeH other than muscle are becoming better recognized, such as skin and gastrointestinal tract (Long et al., 1981). As much as 40% of 3-MeH excreted in urine may be derived from sources other than skeletal muscle. Second, dietary sources such as meats perturb the normal rates of excretion; and, third, the values for normal rates of excretion may not be as well established as they should be for quantitative use (Long et al., 1981). In addition, little is known about diurnal variation in 3-MeH excretion and the influence of exercise.

The meeting participants regarded the 3-MeH method as useful in studies of muscle atrophy provided that (1) dietary intakes are either excluded or quantified; (2) an allowance is made for other known endogenous sources in the species under investigation; and (3) other measures of protein breakdown are included, such as nitrogen balance data (e.g., total nitrogen and urea excretion), measures of lean body mass, and creatinine excretion.

Members of the Group advised that in ground-based studies, care should be used to simulate the force-velocity parameters of muscle function in space flight. The fact that data on this are very limited reemphasized the prominent need for inflight measurements.

A method for human studies of interest to short-term missions and having such advantages as simplicity, relatively low expense, and "built in" controls, might involve bed rest with or without casting of one lower extremity (one-leg model) for 2 wk. During this period different types and schedules of voluntary exercise would be included for the control (nonimmobilized) leg along with comparative measurement of strength, endurance, and other parameters of both legs. For instance, such one-leg models have been useful in investigating the adaptive responses of human skeletal muscle to exercise (Saltin et al., 1976).

With respect to equipment and devices, discussion focused on: (1) the excellence of currently available miniature electrodes, sensors, and recorders for noninvasive acquisition of signals such as EMG; (2) means of gross measurement of muscle atrophy, strength, and limb motion; and, (3) the increasing numbers and variety of exercise devices that are of interest to biological scientists, clinicians, and specialists in physical training. Devices designed for research in both concentric and eccentric exercise modes have been described by Knuttgen et al. (1982) and Knutsson (1983).

The accuracy of assessing muscle atrophy by measuring changes in limb circumference and volume is somewhat limited because of masking by fat, extramuscular connective tissue, and changes in extracellular fluid volume. While such methods have their uses, they are inadequate for obtaining precise quantitative data and have been associated with underestimating amounts of muscle atrophy (Young et al., 1980; 1982).

3. Research suggestions

Methods and devices for measuring muscle strength, endurance, and velocity in different exercise and test modes should be improved for application to specific research on space-related muscle atrophy. Objectives should include simplification, ease-of-use, and miniaturization. More attention should be given to noninvasive means of improving the gross measurement of muscle atrophy. Promising methods that may aid in measuring muscle mass and dimensions include computer-assisted tomographic scanning (Ingeman-Hansen and Halkjaer-Kristensen, 1980), ultrasonography (Young et al., 1980), and nuclear magnetic resonance imaging.

To acquire necessary data to be used for identifying the most appropriate research model for investigating the effects of weightlessness on muscle, the following parameters should be measured in normal rats and in the several models of "disuse" atrophy that have been chosen by investigators: EMG, force, and velocity of movement of the dorsi- and plantarflexors of the feet over 24-h periods. The models should include immobilization by casting and by pinning (Fischbach and Robbins, 1969; Fournier et al., 1983), head-down tilt by tail suspension or body harness

(Feller et al., 1981), paraplegia, specific muscle group denervation, and specific pharmacologic nerve block by tetrodotoxin introduced subperineurally (Drachman et al., 1982a). These studies would be the ideal experiments. They would determine whether any of the above models is adequate to help understand space-induced atrophy by matching these results with those from space-flown rats. Comparisons also can be made with the experiments on astronauts. One problem is that not all of the above measures can be made effectively on rats. However, some strategic compromises can be made to make this experiment possible.

Because of the unique properties of 3-MeH as a convenient marker for muscle protein degradation, and in view of a scarcity of data on its behavior in such situations as heavy resistance exercise, endurance exercise, eccentric versus concentric contractions, and possible diurnal effects on its excretion rate, additional studies should be considered.

With respect to rehabilitation of atrophic muscles it is likely that the same types of exercise recommended for inflight use should be used for rehabilitation. With regard to choices of exercises some variables that should be taken into account are: (1) level of neuromuscular activation, (2) frequency of contractions, (3) number of contractions, and (4) the effect of lengthening versus shortening contractions. The suggestive evidence that eccentric contractions may be advantageous should be investigated (see p.59).

F.   THE NASA RESEARCH PROGRAM IN MUSCLE ATROPHY

Three documented components of NASA's programs of research and analysis in muscle atrophy and muscle biology came to the attention of the LSRO ad hoc Working Group on Muscle Atrophy: (1) the formally programmed Research and Technology Objectives and Plans (RTOP) document, No. 199-20-42, Muscle Atrophy; (2) several university-based studies in NASA's Space Biology Program; and, (3) one human and three rat experiments scheduled for Spacelab 4. Table 4 lists summary information on the Biomedical Research Program on Muscle Atrophy. In addition, as parts of other activities including the flight program of the Space Transportation System (Space Shuttle), NASA develops and tests exercise devices and regimens, personal protective/life support equipment and suits, and plans and conducts space medical tests and observations of the astronauts that yield data of interest to the biomedical problems of space flight, including muscle atrophy.

The ad hoc Group was concerned mainly with that part of NASA's Biomedical Research Program dealing with muscle atrophy. However, it recognized the potential of the parallel activities mentioned above. The overall program appears well conceived to embrace the key objectives and research approaches needed for

Table 4. The NASA Biomedical Research Program in Muscle Atrophy

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1. Proteolysis in muscle atrophy (Task -01). The objective of
    this task is to define the basic proteolytic enzymes, pathways,
    and regulatory mechanisms involved in disuse atrophy of skeletal
    muscle. Current emphasis is on the role of specific lysosomal
    and nonlysosomal muscle proteases in muscle atrophy. A future
    study will attempt to localize tripeptidyl aminopeptidase (TAP)
    in muscle, relate various prostaglandins to lysosomal behavior
    and control of TAP content, and determine the effect of disuse
    atrophy on concentrations of Ca^{2+}-activated proteases.
    Principal Investigator: S. Ellis, NASA Ames Research Center.

2. Growth factors and muscle atrophy (Task -02). The objective
    is to test the hypothesis that disuse atrophy results from a
    deficiency of specific growth factors originating in the nerves
    of muscles undergoing atrophy. Current studies examine the
    responses of cultured chick myoblasts to highly purified neuro-
    trophic factor (NTF) (Popiela and Ellis, 1981), and future
    efforts will: (a) investigate the presence of growth factors
    and inhibitors in normal, hypertrophic, and atrophic muscle;
    (b) determine the effects of rat and rabbit NTF on cultured
    chick myoblasts; and, (c) titrate the sensitivity of protein
    synthesis and degradation as influenced by insulin in muscle
    undergoing atrophy. Principal Investigator: S. Ellis, NASA
    Ames Research Center.

3. The role of bioassayable growth hormone in protein balance
    (Task -03). The objective is to clarify the role of growth
    hormone in protein balance by isolating and characterizing the
    major circulating forms and developing a radioimmunoassay (RIA).
    Future studies will employ the RIA to measure the hormone in
    rats that have been suspended, exercised, centrifuged, protein-
    depleted, or treated with growth hormone releasing factor.
    Principal Investigator: R.E. Grindeland, NASA Ames Research
    Center.

4. Gonadal steroids and muscle atrophy (Task -06). The objec-
    tive is to elaborate mechanisms that regulate muscle size by
    means of an androgen-sensitive muscle in the rat, the levator
    ani. The effects of androgenic or estrogenic hormones, or
    their depletion, on the size of the levator muscle and its
    testosterone receptor concentrations were studied. Future
    effort will be devoted to: (a) the regulation of cytosolic
    androgen receptors in muscle by sex steroids; (b) hormonal
    regulation of glucose turnover in normal and atrophic muscle;
    (c) oxidative metabolism in muscle following gonadectomy and
    after hormone replacement; and, (d) the nature of estrogen-
    androgen synergy in muscle. Principal Investigator: S. Max,
    University of Maryland.

Table 4. (cont.)

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5. Muscle fiber type distribution relative to muscle weakness: a
    new method (Task -07). The objective is to develop and vali-
    date a method for determining fiber types in muscles of subhuman
    primates. Percentages of fast and slow fibers in five skele-
    tal muscles have been determined in monkeys by the differential
    ratio of Sr^{2+}/Ca^{2+} concentration for activation of tension.
    Future effort will include analyses of muscle biopsy samples
    from chaired and free-moving monkeys for fiber type and myosin
    heavy and light chain content. Principal Investigator: W.G.
    Kerrick, University of Miami.

6. Mechanisms and control of disuse atrophy in skeletal muscle
    (Task -10). The objective is to define the role of stretch in
    the synthesis and activity of muscle contractile proteins and
    sarcoplasmic reticulum. Organ culture of rat soleus muscle
    was tested for viability and utility as a model for studying
    various factors in muscle atrophy such as the influence on pro-
    tein degradation, of aspirin or protease inhibitors, changes
    in twitch kinetics, and the effects of stretch on proteolysis.
    The studies will be continued along similar lines. Principal
    Investigator: J.D. Etlinger, S.U.N.Y. Downstate Medical
    Center, Brooklyn.

7. Biochemical adaptations of antigravity muscle fibers to disuse
    atrophy (Task -12). The objective is to investigate the
    molecular basis of disuse atrophy in the rat soleus muscle,
    with emphasis on protein and carbohydrate metabolism. Rates
    of synthesis of actin and cytochrome c were determined at the
    sixth hour of limb immobilization; no change was found in the
    level or activity of the reputed insulin mediator in the muscle
    after 24 h of immobilization. Future effort will probe the
    content of actin mRNA in the muscle during the first 6 h of
    immobilization and determine whether a translation of actin
    occurs during the same time period. Principal Investigator:
    F.W. Booth, University of Texas Health Sciences Center, Houston.

8. Alterations in skeletal muscle with disuse atrophy (Task -13).
    The objective is to characterize the adaptive responses of rat
    skeletal muscle to moderate and prolonged disuse by hindlimb
    immobilization, evaluate the role of motor activity in disuse
    atrophy, and elucidate factors that influence recovery such as
    the duration of immobilization, electrical stimulation, and
    exercise. Data have been obtained on: (a) responses of the
    soleus muscle to casting for 6 wk in the shortest possible
    position; (b) temporal changes in twitch duration time; (c)
    rates of recovery in terms of isometric twitch duration and

Table 4.   (cont.)

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half-relaxation time; (d) changes in rates of Ca^{2+} uptake of
sarcoplasmic reticulum from slow soleus and two types of fast
vastus lateralis fibers. Future efforts will emphasize in vitro
studies of the contractile properties of single-skinned fibers,
changes in the light chains and sarcoplasmic reticular proteins,
and Ca^{2+} uptake and release kinetics of sarcoplasmic reticula
of the three atrophying muscle fiber types. Principal Investi-
gator: R.E. Fitts, Marquette University.

9.   Immobilization/remobilization and the regulation of muscle mass
     (Task -14). The objective is to determine the role of gluco-
     corticoids in the responses of skeletal muscle to under-use
     and disuse. Baseline data were developed in young, growing
     rats on temporal changes in the sizes of the soleus and extensor
     digitorum longus and on the following biochemical parameters:
     (a) total protein; (b) total noncollagen protein; (d) total
     collagen; (d) soluble protein; (e) total myofibrillar protein;
     (f) myofibrillar noncollagen protein; (g) collagen in the myo-
     fibrillar fraction; and (h) DNA content. Future studies will
     determine glucocorticoid sensitivity of hindlimb muscles
     during immobilization and recovery and, by in vitro methods,
     analysis of atrophic muscle for glucose uptake, amino acid up-
     take and incorporation, ribosomal activity, protein degradation,
     glutamine and alanine production, and proteolytic activity.
     Principal Investigator: R.R. Almon, S.U.N.Y. Buffalo.

10. The combined influence of stretch and mobility on muscle atrophy
     caused by immobilization (Task -15). The objective of this
     new task is to investigate physical factors that influence the
     responses of skeletal muscle to immobilization. Factors to be
     studied include: (a) passive stretch in relation to muscle
     fiber development, physiologic performance, and protein turnover;
     (b) minimum force and number of muscle contractions needed to
     prevent atrophy; (c) effectiveness of negative, positive, and
     isometric contractions in producing hypertrophy and preventing
     atrophy of muscle fibers; and, (d) alterations in connective
     tissues of muscles and tendons induced by immobilization and
     inactivity. Principal Investigator: G. Goldspink, Tufts Uni-
     versity School of Medicine.

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ultimate solution to the operational problem of muscle atrophy. Periodic review of advancing knowledge in muscle biology and closely related fields and appropriate revision of the program will be an important, continuing activity of NASA management.

The Working Group took note of the muscle research in the NASA Space Biology Program and the experiments that have been planned for Spacelab 4, all of which appear to increase NASA's potential to elucidate the mechanisms and resolve the problem of space-related muscle atrophy. These researches are listed in Table 5. The experiments in the Space Biology Program explore the effects in rats of simulated weightlessness on: (a) the biochemical characteristics of changes in fast and slow muscle, regulation of acetylcholinesterase and other proteins involved in neuromuscular transmission and their axoplasmic transport (Dettbarn); (b) mechanisms of changes in protein/RNA relationships in hindlimb muscles of the rat head-down tilt model, and glucocorticoid receptor levels and sensitivities (Musacchia); (c) motor control including muscle, motor neuron, and sensory components (Stuart); (d) histochemical changes during atrophy and recovery, with emphasis on identifying the most sensitive physiologic, histochemical, and biochemical responses (Templeton and Sutko); and (e) the biochemical adaptations of muscle to nonweight-bearing conditions including the fate of excess amino acids liberated in muscle during atrophy and studies of methods of preventing muscle atrophy, such as passive stretch (Tischler).

In Spacelab 4, the human study (Stein) will examine the effect of zero-G on whole-body protein metabolism in an effort to establish whether the nitrogen loss is caused principally by decreased uptake and production of protein or by increased mobilization and metabolism of muscle protein. Measurements will include rates and levels of incorporation of ^{15}N-glycine into various proteins and hemoglobin and rates of urinary excretion of 3-methyl-histidine, hydroxyproline, hydroxylysine and their glycosides. Similar studies will be done in rats, but in addition, the animal experiments will include morphologic changes in muscles and nerves and biochemical analyses of muscle proteins. The effect of zero-G on the capacity of both rested and exercised skeletal muscle for oxidative metabolism will be investigated (Baldwin). Analysis of skeletal myosin isoenzymes will facilitate a determination of possible shifts from slow- to fast-twitch muscle fibers (Hoh). Dr. Ellis' experiments with rats in Spacelab 4 cover several physiologic, morphologic, biochemical, and histochemical aspects including observation of inflight activity patterns, electromyography, anatomic changes in slow- and fast-twitch muscle, assays of the proteolytic and mitochondrial enzymes in the muscles, and an attempt to differentiate the biologic effects in the anti-gravity muscles and nerves of launch stress, inflight atrophy, reentry stress, and late postflight recovery.

Table 5. Muscle Research in Other NASA Programs

Title/Task No.	Principal Investigator	Institution
A. Space Biology Program		
Weightlessness Simulation: Physiological Changes in Fast and Slow Muscle	W.D. Dettbarn	Vanderbilt University
Renal Function, Water and Electrolyte Balance, and Intestinal Transport in Hypokinetic Animals	X.J. Musacchia	University of Louisville
Effects of Muscle Atrophy on Motor Control	D.G. Stuart	University of Arizona
Influence of Suspension-Hypokinesis on Skeletal Muscle	G.H. Templeton and J.L. Sutko	University of Texas, Dallas
Skeletal Muscle Metabolism in Hypokinetic Rats	M.E. Tischler	University of Arizona
B. Spacelab 4		
Effect of Zero-Gravity on Biochemical and Metabolic Properties of Skeletal Muscle	K.M. Baldwin	University of California, Irvine
Electron Microscopy, Electromyography, and Protease Activity of Rat Hind-Limb Muscles	S. Ellis	NASA Ames Research Center
Skeletal Myosin Isoenzymes in Rats Exposed to Zero-Gravity	J.F.Y. Hoh	University of Sydney
Protein Metabolism During Spaceflight	T.P. Stein	University of Pennsylvania

As noted during the meeting of the ad hoc Group, the Biomedical Research Program on Muscle Atrophy is young, and the efforts of NASA program planners and managers to improve it within the constraints imposed by limitations of budget, manpower, and relative priority are recognized. The research tasks in this program are generally consistent with the recommendations in two of the more recent, formal advisory reports on NASA life sciences (Bricker, 1979; Whedon, 1978). Research that was considered by some members of the Working Group to be appropriate to the stated objectives of the program included tasks -01, -10, -12, and -13. Tasks containing some elements that appear to address the objectives include -03, -06, and -07, and the newly-initiated task -15 appeared pertinent as outlined. In general, the program seems to need sharper focusing on its stated objectives.

To aid in aligning the program in muscle atrophy with NASA's scientific and technical requirements, research suggestions are detailed in the preceding parts of Section V and in Section VI. The suggestions are for the consideration of NASA planners in the hope that incorporation of some of the described approaches may improve the program and ultimately assist in resolving the issues of space-related atrophy.

G.   CONCLUSIONS

Muscle atrophy associated with short-term space flights (e.g., 7-10 d), is apparently not grossly detectable by currently available methods, nor is it a functional problem. Nevertheless, in missions extending beyond approximately 3 wk, muscle atrophy typically progresses to a level that, while nonincapacitating in flight, may severely interefere with readaptation to 1-G. In addition, it would probably compromise physiologic efficiency for strenuous extravehicular activity.

Daily vigorous physical exercise inflight appears to retard the atrophic process, but, despite this and other preventive measures, nitrogen balance tends to remain negative or only slightly positive; the negative nitrogen balance appears to result from loss of lean body mass.

Unloading the musculature in weightlessness is generally accepted as the cause of the muscle atrophy. However, the exact biologic mechanisms involved in atrophy and hypertrophy of skeletal muscle are unknown even though a great deal of excellent research has been done on the biology of muscle in the appropriate disciplines. Since development of the optimum means of preventing or controlling space-related muscle atrophy will depend on knowledge of the mechanisms involved, NASA supports both intra- and extramural research in muscle biology. In the opinion of the LSRO

ad hoc Working Group on Muscle Atrophy, NASA should continue its program, but with some changes in emphasis to assure better consistency between ongoing and planned research and the carefully composed, highly appropriate Research and Technology Objectives and Plans on Muscle Atrophy (NASA RTOP 199-20-42).

As noted, particularly on pages 30, 31, the Working Group strongly recommends inflight studies of certain muscle functions of astronauts as soon as possible in the Space Shuttle Program as essential for acquiring data with which to improve the design of ground-based and inflight experiments and to determine the best human and animal models of space-related muscle atrophy.

The points of emphasis, important gaps in knowledge, and research suggestions presented in this report are submitted for the consideration of NASA scientists whose responsibilities include research program planning and management. Section VI summarizes the research in tabular form, in a suggested order of priority.

VI. SUGGESTIONS FOR FUTURE CONSIDERATION

The main objective of NASA's Research Program on Muscle Atrophy is the acquisition of sufficient knowledge of its etiology, pathogenesis, and underlying biologic mechanisms to enable the development of efficient means of prevention. Consequently, the LSRO ad hoc Working Group on Muscle Atrophy was concerned not only with questions of basic research, but also with identifying promising lines of applied research, operational flight testing, and associated methodology and equipment.

NASA's current and planned research in this field, perhaps modified and augmented by adoption of some of the suggested research approaches in this report, should provide the necessary knowledge for solution of the problem. However, shortcuts to discovery of the basic mechanisms of space-related muscle atrophy are unlikely to emerge. Therefore, muscle atrophy, which is a significant biomedical problem of space flight, justifies a sustained, vigorous program of research, including long-term studies, as a part of NASA's major enterprises in space.

The suggestions of the ad hoc Group that are presented in Section V are recapitulated in brief in Table 6. In each of the four groups of categories shown in Table 6 (which differ intentionally from the headings used in Section V), the suggested priority is in descending order from the top of each list.

Table 6. Proposed Orders* of Priority of Research Suggested by
the ad hoc Working Group on Muscle Atrophy

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A. BIOCHEMISTRY, ENDOCRINOLOGY, METABOLISM (see p.21-27; 29; 31-35)

  o   Mechanisms that induce muscle hypertrophy in exercise may
       also be involved in muscle atrophy resulting from inactiv-
       ity or under-use. Attempts should be made to identify
       specific stimuli generated by exercise and to determine
       how they signal the genes to induce protein synthesis.

  o   As one approach toward discovering basic mechanisms of
       muscle hypertrophy and atrophy, the role of lysosomes in
       muscle metabolism should be investigated from a broad
       point of view.

  o   Additional studies of the effects on muscle of altered
       levels of hormones and their receptor sensitivities
       induced by models of hypokinesia/hypodynamia should be
       encouraged. Test specimens may include incubated muscle
       cells, incubated whole muscles, muscles in perfused
       hemicorpus preparations, and intact muscles in vivo.

  o   Among substances that have regulatory roles in muscle
       physiology that should be studied are growth hormones
       and the somatomedins as well as insulin, corticosteroids,
       and anabolic steroids.

  o   Additional studies are needed on the endocrinologic effects
       of exposure to weightlessness and simulated weightless-
       ness combined with hypokinesia/hypodynamia.

  o   Uncertainties about the rate of onset, degree, and dura-
       tion of negative nitrogen balance in weightless flight
       suggest a need for additional human metabolic balance
       studies inflight.

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* Listed in order of decreasing priority in each separate category.
For convenience of presentation the categories in this table differ
from the headings used in Section V.

Table 6. (cont.)

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B. NEUROPHYSIOLOGY AND KINESIOLOGY (see p.27-31)

- Measurements of certain physical activities of astronauts during typical days preflight and inflight are needed for further definition of the nature of space-related muscle atrophy and for development of suitable models for ground-based and inflight animal studies. Electromyograms of quadriceps, hamstrings, dorsi- and plantarflexors of the feet; heel and metatarsal pressures, and movements of selected joints such as knee, ankle, and elbow should be included.

- Levels of neuromuscular output of the astronauts should be determined before, during, and after space flight by measuring maximum force at zero velocity for the knee extensors, knee flexors, and the dorsi- and plantarflexors of the foot. This and the immediately preceding experiment can be done with trivial imposition on the astronauts' time by means of fully developed techniques and equipment.

- A more nearly functional measurement than that in the immediately preceding suggestion would be to test the astronaut's ability to exert a maximum force at a selected velocity or, better, to produce a target force at a selected velocity. However, this would require more of the astronauts' time and additional development of equipment.

- Neuromuscular fatigability during space flight should be evaluated for further characterization of muscle atrophy. This can be done by measuring the maximum force that can be produced over a span of 2 min while exerting a maximal contractile effort every second. The electromyogram should be recorded simultaneously. The measures should be made preflight, inflight within a week of launch, and as soon as possible postflight.

- Three properties of skeletal muscle that should be considered for study in the rat model of hypokinesia/hypodynamia (e.g., the tail-suspension model) are: resting membrane potential, extrajunctional acetylcholine receptors, and isometric strength in anti-gravity and nonpostural muscles.

Table 6. (cont.)

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- Analysis of blood samples obtained during arm exercises aloft could provide an indication of significant changes in metabolic potential of the exercised muscle groups. Such data would help to characterize space-related muscle atrophy.

- The influence of neuronal circuits proximal to the motor unit on maintenance of muscle integrity and strength should be studied in models of hypokinesia/hypodynamia.

C. MODELS, METHODOLOGY, AND EQUIPMENT (see p.41-46)

- The electromyogram, force, and velocity of the dorsi- and plantarflexors of the feet should be evaluated over periods of 24 h in normal rats and in various rat models of "disuse" atrophy including limb casting, joint pinning, head-down suspension, paraplegia, denervation of specific muscle groups and nerve block by tetrodotoxin. Results of such studies would help to identify an adequate research model for muscle atrophy.

- Additional investigations of the utility of 3-methylhistidine as a marker of protein degradation in muscle atrophy should be done, including acquisiton of more normative data on urinary excretion rates and the effects of diurnal influences and exercise on excretion rates.

- Human patients with spinal cord damage could provide, during certain known intervals after injury, a model of disuse atrophy suitable for special studies such as determining the minimum amount of electrically-induced exercise needed to prevent muscle atrophy. Such data could be used to formulate improved inflight exercise regimens.

- An animal model of pure disuse atrophy that apparently preserves the integrity of motor innervation employs pharmacologic blockade of a motor nerve by subperineural injection of tetrodotoxin. All physiologic and morphologic properties of the nerve apparently remain normal except for nerve impulse transmission.

Table 6. (cont.)

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- Another technique that may offer some advantages in investigating muscle atrophy involves training muscle groups to a level of hypertrophy, then ceasing training and observing various parameters during the period of reversion to pre-training status.

- Methods and devices for measuring muscle strength, endurance, and velocity in different exercise and test modes should be improved for application to specific research on space-related muscle atrophy.

D. COUNTERMEASURES (see p.35-41)

- To acquire data for use in improving inflight exercise regimens, pre- and postflight measurements of maximal voluntary contraction of the flexors and extensors of the arms and legs should be done on all personnel who participate in space flights.

- A human, ground-based study should be considered for determining the minimum amounts of strength or endurance exercises, or combinations of these, needed to prevent muscle atrophy in a model of hypokinesia/hypodynamia such as bed rest.

- Human and animal experiments should be performed to determine possible preventive effects of dietary supplements of leucine, combinations of isoleucine and valine, or mixtures of the keto-analogues of leucine, valine, and isoleucine in models of muscle atrophy induced by hypokinesia/hypodynamia.

- An expert analysis of available data should be done on the effectiveness of eccentric muscular contractions in physical fitness training and in rehabilitation of atrophic muscles. If eccentric exercise appears to be superior to other modes, its possible advantages as an inflight mode should be investigated.

- Biochemical, neurophysiologic, and other properties of muscle during adaptation to eccentric loading should be determined in an animal model to complement the human studies suggested above.

Table 6. (cont.)

- Animal studies should be expanded to assess the possible preventive value against disuse atrophy of administering inhibitors of myofibrillar proteases and other proteases involved in muscle protein turnover. Such experiments should include a careful search for untoward side effects.

- Additional human studies are needed to evaluate the effects of preflight physical fitness training on preserving neuromuscular function inflight and retarding muscular deconditioning. Such data would aid in resolving the debate between those who advocate peak physical conditioning preflight and those who are convinced that inflight resistance to muscular deconditioning is inversely related to physical fitness.

- If possible, ground-based studies should be devised to determine the reason for observed differences in maintaining leg muscle strength and preventing leg muscle atrophy during Skylab missions, of bicycle ergometer exercises at a level of 80 watt-min (4.8kJ)/d/kg lean body mass versus 100 watt-min (6kJ)/d/kg lean body mass.

- Possible reduction of sensory perception of voluntary muscle contraction during space flight suggests a need for an expert analysis of available data on this topic. If this were identified as a significant problem in achieving optimum muscular contractions during inflight exercises, means of improving such perception could be evaluated, such as electrostimulation of muscles.

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16. Abstract

Unloading the musculature in weightlessness is generally accepted as the cause of the muscle atrophy. However, the exact biologic mechanisms involved in atrophy and hypertrophy of skeletal muscle are unknown even though a great deal of excellent research has been done on the biology of muscle in the appropriate disciplines. Since development of the optimum means of preventing or controlling space-related muscle atrophy will depend on knowledge of the mechanisms involved, NASA supports both intra- and extramural research in muscle biology. In the opinion of the LSRO ad hoc Working Group on Muscle Atrophy, NASA should continue its program, but with some changes in emphasis to assure better consistency between ongoing and planned research and the carefully composed, highly appropriate Research and Technology Objectives and Plans on Muscle Atrophy (NASA RTOP 199-20-42).

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