

Chapter 10

Muscle Structure and Metabolism

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Research on the structural and functional responses of skeletal muscles to microgravity conditions began in the 1960s with the Kosmos biosatellite program and continues into the 1990s. Experiments conducted in the Kosmos, Space Shuttle, and space station programs have generated the primary body of data regarding the direction and severity of adaptive changes in skeletal muscles in microgravity.

Unfortunately, complete examinations of muscle structure, metabolism, and function are rarely possible in flight experiments, particularly histophysiological analyses, partly because of the invasiveness of the procedures and partly because the complexity of the analyses precludes their being done during flight. Flight data thus have been supplemented with ground-based experimental techniques that simulate the effects of some spaceflight factors on skeletal muscles in humans or animals. The spaceflight factors of interest include: 1) the reduced mechanical load on muscles; 2) the elimination of the need to counteract gravity; and 3) the redistribution of body fluids.

Small laboratory animals (e.g., rodents) can be suspended, either horizontally or in a head-down position, to mimic these effects. Animals can be suspended by their tails^{1,2} or by the skin above the sacrum to which a bearing cable or ring is affixed^{3,4} such that their hind limbs are unloaded. Alternatively, the animal's entire body can be suspended in a hammock device.⁵ Suspension and spaceflight induce many similar effects,⁶⁻⁸ but caution has been expressed that suspension produces some features unique to that model.⁹

For humans¹⁰⁻¹⁷ and primates,¹⁸ mechanical load is reduced, the lower limbs are unweighted, and body fluids are redistributed either through *immobilization* (limiting the amount of movement) or by horizontal or head-down *bed rest* (hypokinesia). The effects of bed rest on the structure of human muscles have been thoroughly studied. However, the elimination of gravitational loading—a key element in microgravity—cannot be reproduced fully with bed rest, since gravitational force still acts on the subject, albeit in the horizontal rather than the vertical plane. Another means of eliminating gravitational loading used in Russian investigations is immersion,^{19,20} in which the support function is distributed homogeneously and the loading differential is eliminated. Swedish and U.S. researchers have used a technique in which limbs on one side of the body are suspended or immobilized^{21,22}; however, this technique does not allow the potential involve-

ment of the central nervous system (CNS) in muscle adaptation to be assessed.

This chapter provides a review of how muscles are thought to adapt to spaceflight and simulations thereof, both in terms of structure and function. Brief descriptions of muscle structure and the differences between muscle fiber types are followed by a review of changes that have been noted after spaceflight or microgravity simulations in muscle composition and contractile properties. Potential changes in the system by which energy is supplied to the muscle are discussed as well. The chapter concludes by reviewing some explanations that have been advanced to explain the observed results, such as changes in contractile activity, innervation, afferentation, muscle length, hormonal factors, and blood supply.

I. Skeletal-Muscle Composition

Skeletal-muscle function depends on both contractile and metabolic properties of the muscle. Muscle is quite “plastic,” adapting quickly to changes in activity, innervation, or hormonal milieu. Skeletal muscles are composed of fasciculi (bundles) of fibers, which themselves constitute bundles of successively smaller subunits. Each muscle fiber is a single, multinucleated cell, and can be classified as type I (slow-twitch) or type II (fast-twitch) according to its metabolic properties, as explained in further detail below. These myofibers consist of myofibrils, which are enveloped in units by the sarcolemma (the sarcotubular system). The myofibrils are divisible into individual filaments. Finally, the filaments are made up of the contractile proteins actin, myosin, and others.

Type I and type II fibers differ from each other in terms of contraction speed and metabolism, which in turn depend on the relative proportions of myosin ATPase isoforms.²³ The light chain constituent of myosin has five isoforms, and the heavy chain has three isoforms (one slow and two fast). The isoforms are encoded by a family of genes that are probably clustered on the same chromosome; the predominant isoform thus is referred to as a “myosin phenotype.”

Type I (slow-twitch) fibers are served by large numbers of capillaries, have many mitochondria and aerobic respiratory enzymes, and have high concentrations of myoglobin.^{24,25} Type II fibers, by comparison, have a lesser capillary supply, fewer mitochondria, and less myoglobin. They are adapted to respire

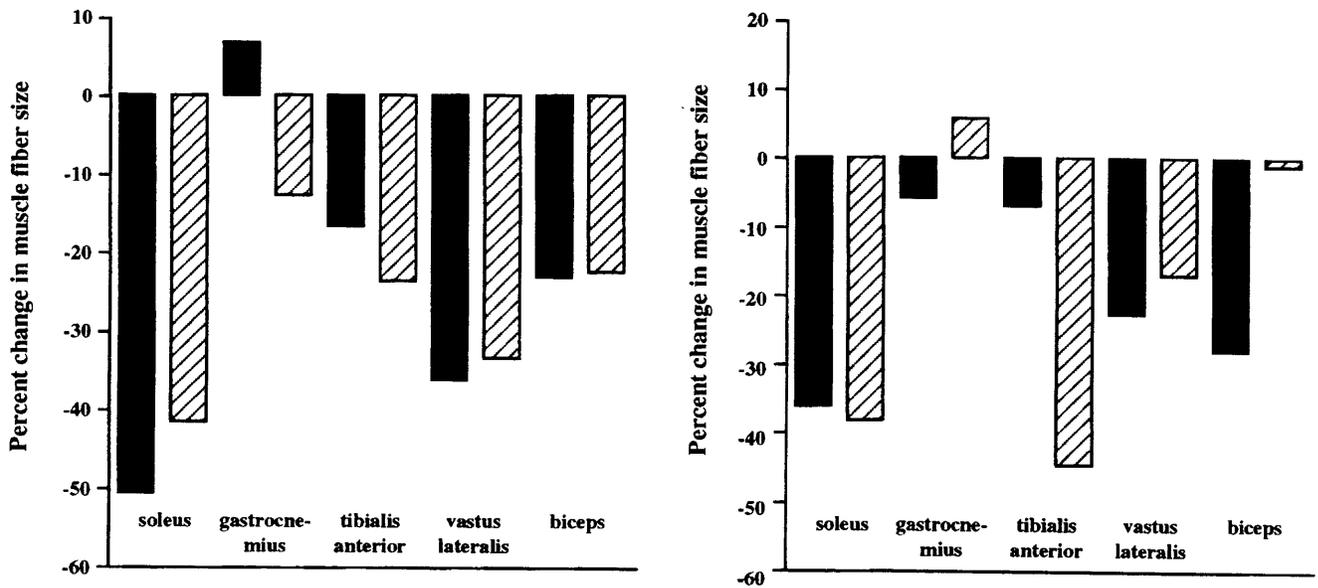


Fig. 1. Relative changes in muscle fiber size in two monkeys after biosatellite flights. Black bars, slow-twitch (type I) fibers; hatched bars, fast-twitch (type II) fibers.

anaerobically by having large stores of glycogen and high concentrations of glycolytic enzymes. The relative volume of the sarcoplasmic reticulum (a membranous labyrinth that surrounds each myofibril) tends to be greater in type II fibers than in type I fibers.^{24,25} Muscles containing many type I fibers (e.g., the soleus) respond slowly, have a long latency, and are adapted for long, slow contractions, such as those needed to maintain posture. Muscles containing mostly type II fibers (e.g., the extraocular muscles and some hand muscles) contract much more quickly than type I fibers, have a greater threshold of excitation, and also fatigue more quickly.²⁶ The specific set of myosin isoforms in a fiber seems to be determined by the innervation of that fiber; the impulse frequency for "slow" motoneurons is 10–15 Hz, and that for "fast" motoneurons is 40–50 Hz.²⁶

The relative proportions of the two main types of muscle fibers in a given human muscle determine the composition of that muscle. As would be expected, the relative concentration of type I fibers in a muscle is closely correlated with aerobic productivity, anaerobic threshold, local endurance of the muscle, and period of semirelaxation.^{27,28} The proportion of fast-twitch fibers is correlated with the velocity and strength with which the muscle contracts, i.e., the speed of a single contraction, the gradient of voluntary contraction, the nature of the velocity-strength curve, and the maximum strength at high angular velocity of movement in the joint.²⁹

II. Skeletal-Muscle Adaptations during Spaceflight and Its Simulations

A. Changes in the Contractile Apparatus

One of the best known consequences of exposure to microgravity³⁰ or bed rest^{12,13} is muscle atrophy or loss of muscle

mass, which is thought to reflect a loss in myofibril volume. Muscle mass is lost to varying extents in different limbs, and in different portions of the limbs as well. For example, lean muscle mass in human subjects during a 17-week bed-rest study was unchanged in the arms, but was reduced by 12.2% in the thighs and by 11.2% in the calves.¹² Cross-sectional area of the thigh muscles in another bed-rest study shrank by 8%, and that of the calf by 5%, after 30 days of bed rest.¹³ Individual muscles (even synergists) also atrophy to different degrees. In another 30-day bed-rest study, magnetic-resonance imaging revealed that the cross-sectional dimensions of the soleus decreased by 12.8%, but those of the heads of the triceps surae and the anterior calf muscles decreased by only 8.1–8.7%.¹¹ The greatest change in muscle mass after suspension or spaceflight for rats and primates has been noted in the soleus, although the mass of other muscles has been diminished as well.^{31–33}

Type I (slow-twitch) muscles tend to atrophy more in response to gravitational unloading than do type II muscles. This is particularly true for muscles that maintain posture on Earth. Atrophy in the soleus in response to hind-limb suspension in rats typically is attributed to shrinkage of the myofibers rather than reductions in the number of fibers.³¹ Type I and type II fibers atrophied to roughly the same extent after seven days of suspension, both by about 35–45%. However, longer suspensions produced more profound atrophy in type I fibers, which reached 60–70% by day 30–35, but atrophy of type II fibers remained at about 35–45%.^{31,34–36}

Spaceflights as brief as five to seven days have led to atrophy of both type I and II fibers in the soleus of rats.^{6,37} Longer flights (12.5 to 14 days) or ground-based experiments of the same duration tended to produce more severe atrophy in type I fibers of postural-tonic^{8, 38–41} and other muscles.⁴² Atrophy of type II (fast-twitch) fibers, on the other hand, tended to be

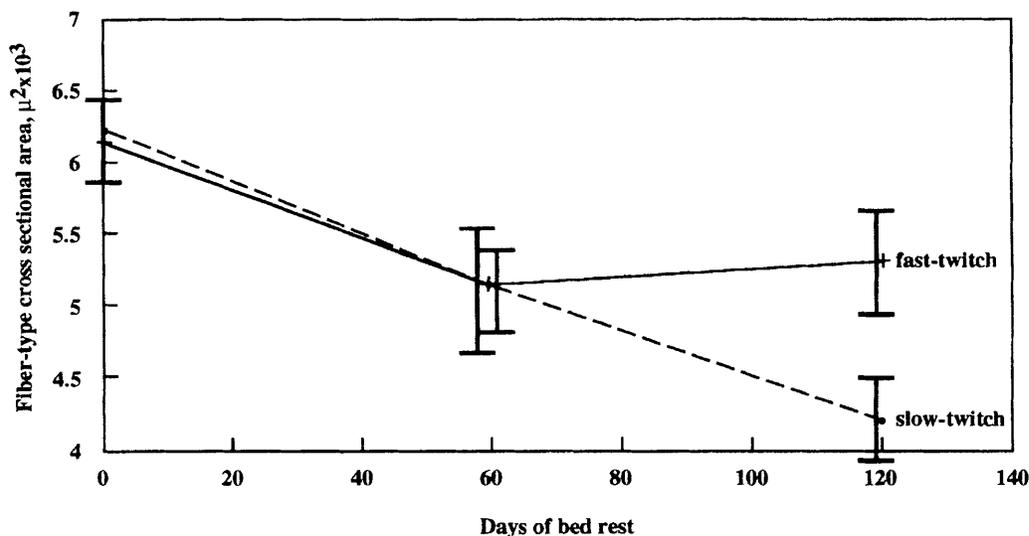


Fig. 2. Changes in muscle-fiber size in women during a 120-day bed-rest period.

less severe. Both fiber types atrophied to roughly the same extent in the soleus, vastus lateralis, and biceps brachii of two monkeys flown on the 13-day Kosmos-2229 mission³³ (Fig. 1). Fiber atrophy was greatest in the soleus, although some reduction in the fiber dimensions in other muscles also was present. Unexpectedly, postflight atrophy in the tibialis anterior was greater in the type II (fast-twitch) fibers than in the type I fibers. In contrast, Bodine-Fowler and others⁴³ did not detect signs of atrophy in the primate soleus after the 13.5-day Kosmos-2044 mission. This discrepancy in results could be related to differences in sample-processing methods.

For humans, suspending one leg for six weeks or remaining in head-down-tilt bed rest for 30 days led to reductions in the cross-sectional area of both type I and II fibers in the vastus lateralis.^{17,22} The lower-limb suspension resulted in 11–12% reduction in type I fiber area, and 12–18% in type II fiber area.²² Bed rest, in contrast, produced 11% reductions in type II fiber cross-sectional area, but no reductions in type I fibers.¹⁷ Subjects who had large fibers before the bed-rest period began underwent more intense atrophy. Type I and II fibers atrophied by 10–45% in three subjects who underwent 49 days of bed rest.¹⁴

Although “before-and-after” comparison studies are fairly numerous, few reports are available concerning the *dynamics* of human muscle-fiber atrophy during gravitational unloading. In one such study conducted in our laboratory,^{15,16} type I fibers in the lateral gastrocnemius had decreased to 74% of their baseline size by day 60 of head-down bed rest, and type II fibers to 88% of baseline. By day 120, the size of type I fibers had increased slightly, reaching 80% of baseline, and the type II fiber size had returned to baseline values. By day 180, 40–50% reductions were present in both type I and II fibers, despite the fact that subjects were exercising in bed. By day 240, fiber size had recovered to baseline values, but the type I fiber size tended to decrease somewhat thereafter. Similar dynamics were evident in another study in which

women were confined to bed for 120 days (cf. Fig. 2). In this latter study, both fiber types showed atrophy after 60 days (23% for one and 15% for the other). However, type II (fast-twitch) fiber size had reached a plateau by day 120, at 16% less than baseline; atrophy of type I (slow-twitch) fibers continued, reaching an eventual nadir of 33% below baseline.

Needle-biopsy samples taken from the vastus lateralis of astronauts before and after 5- to 11-day Space Shuttle flights revealed significant muscle-fiber atrophy.⁴⁴ The cross-sectional area of type I fibers diminished by a mean of 15%, and that of type II fibers decreased by 22%. No correlations were found with flight duration or physical exercise during flight.

1. Atrophy at the Cellular Level

Studies with rats have revealed that muscle-fiber atrophy usually results from loss of myofibril volume⁴⁵ and is accompanied by selective lysis of myofibril proteins.⁴⁶ Myofibrillar destruction has been noted after hind-limb suspension in rabbits,⁴⁷ after brief spaceflights in rats and primates,^{48–51} after a three-day immersion in humans,^{19,20} and after head-down bed rest in humans^{15,16} (Fig. 3–6). Some investigators have maintained that these changes, which resemble the myofibril damage induced by eccentric loading, reflect readaptation to normal gravitational conditions—a transition that is equivalent mechanically to eccentric loading. For example, Krippendorf and Riley^{52,53} reported that the myofibrillar ultrastructure was disrupted in animals that had been allowed to readapt for 2–6 hours after having been suspended; however, the myofibrillar ultrastructure of animals killed immediately after the suspension period remained within normal limits. Nevertheless, we contend that the myofibrillar damage noted during bed rest^{15,16} could not be a result of readaptive processes, because the biopsies were performed while the subjects maintained their head-down position.

In hind-limb-suspended rats, the earliest effect of gravitational unloading is a decrease in the rate of protein synthesis in muscles,

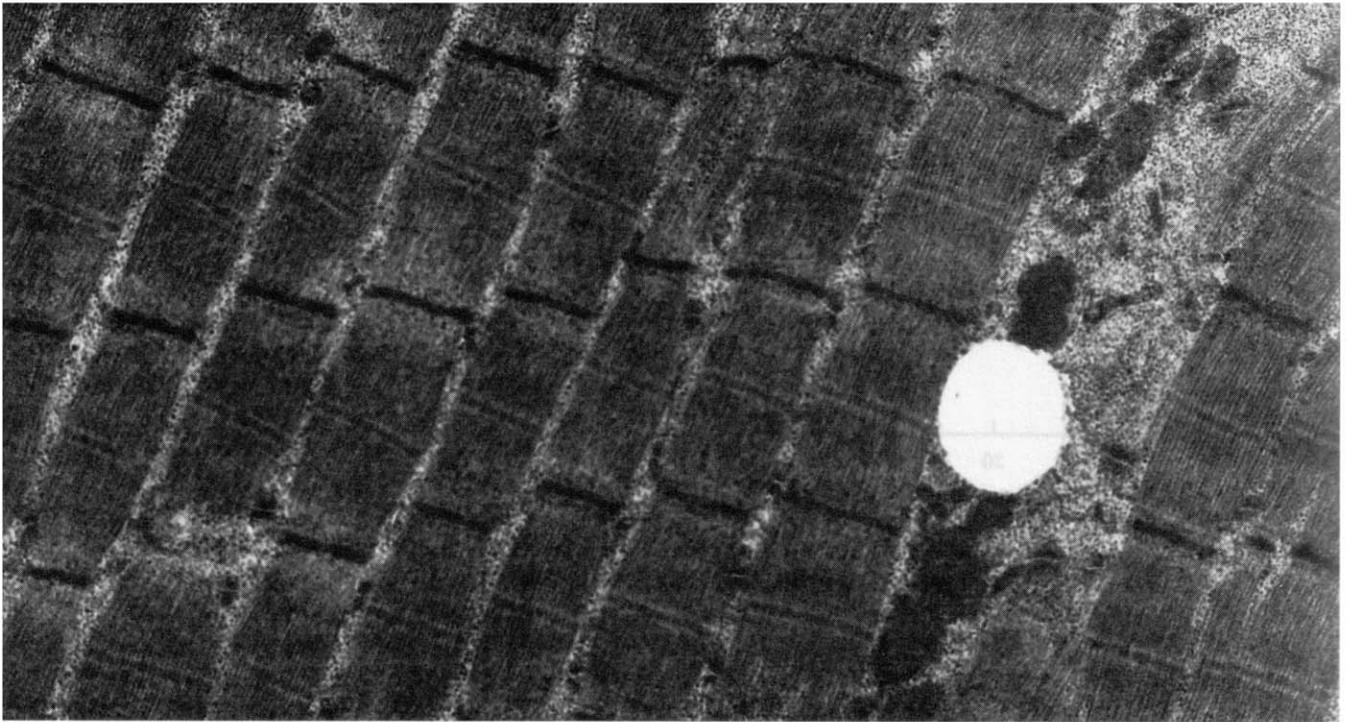


Fig. 3. Human lateral gastrocnemius, control. Ultrastructure is virtually intact; isolated lipid droplets are visible. Magnification $\times 13,500$.

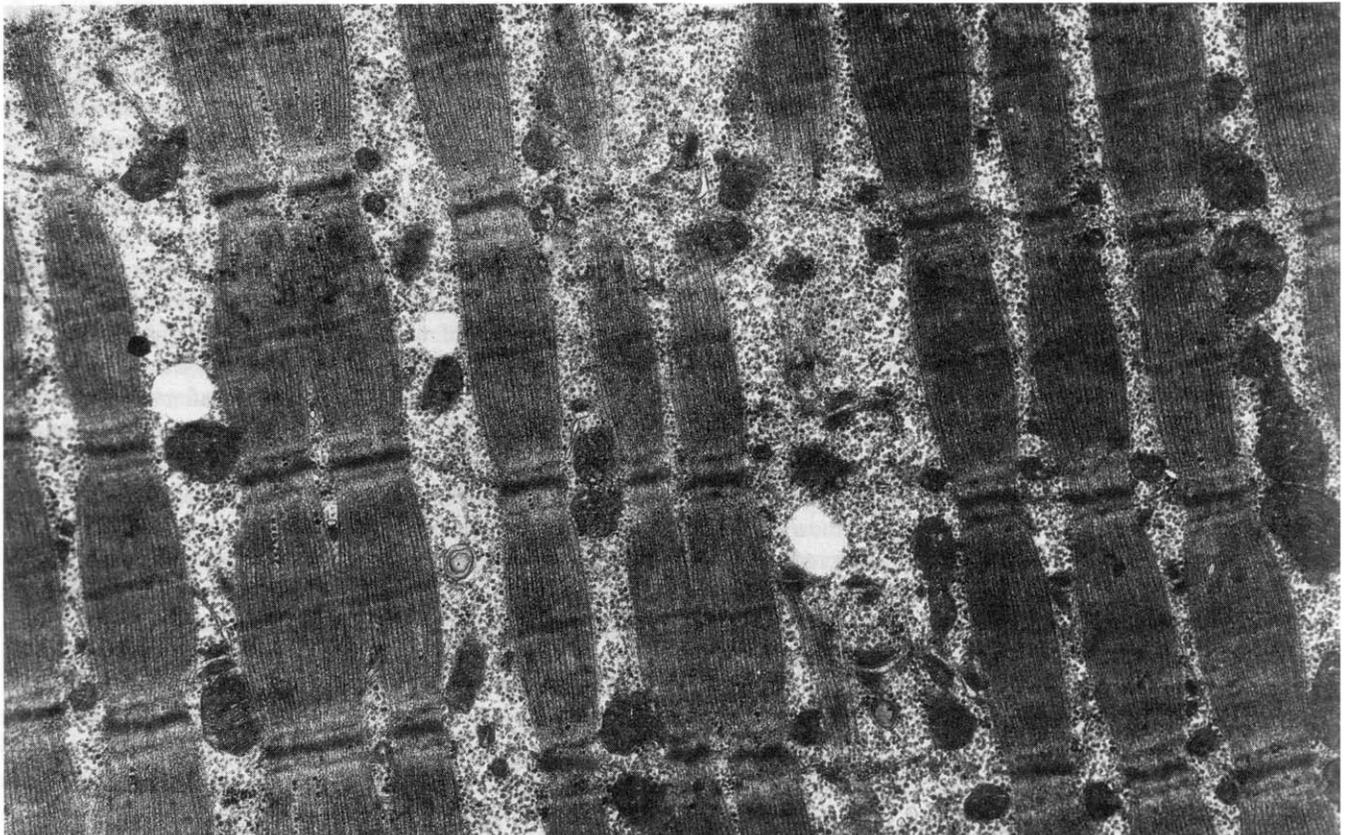


Fig. 4. Human lateral gastrocnemius after 120 days of head-down bed rest. Destruction and thinning of myofibrils are visible, as are fine lipid droplets and vacuoles with lamellar inclusions. Magnification $\times 19,400$.

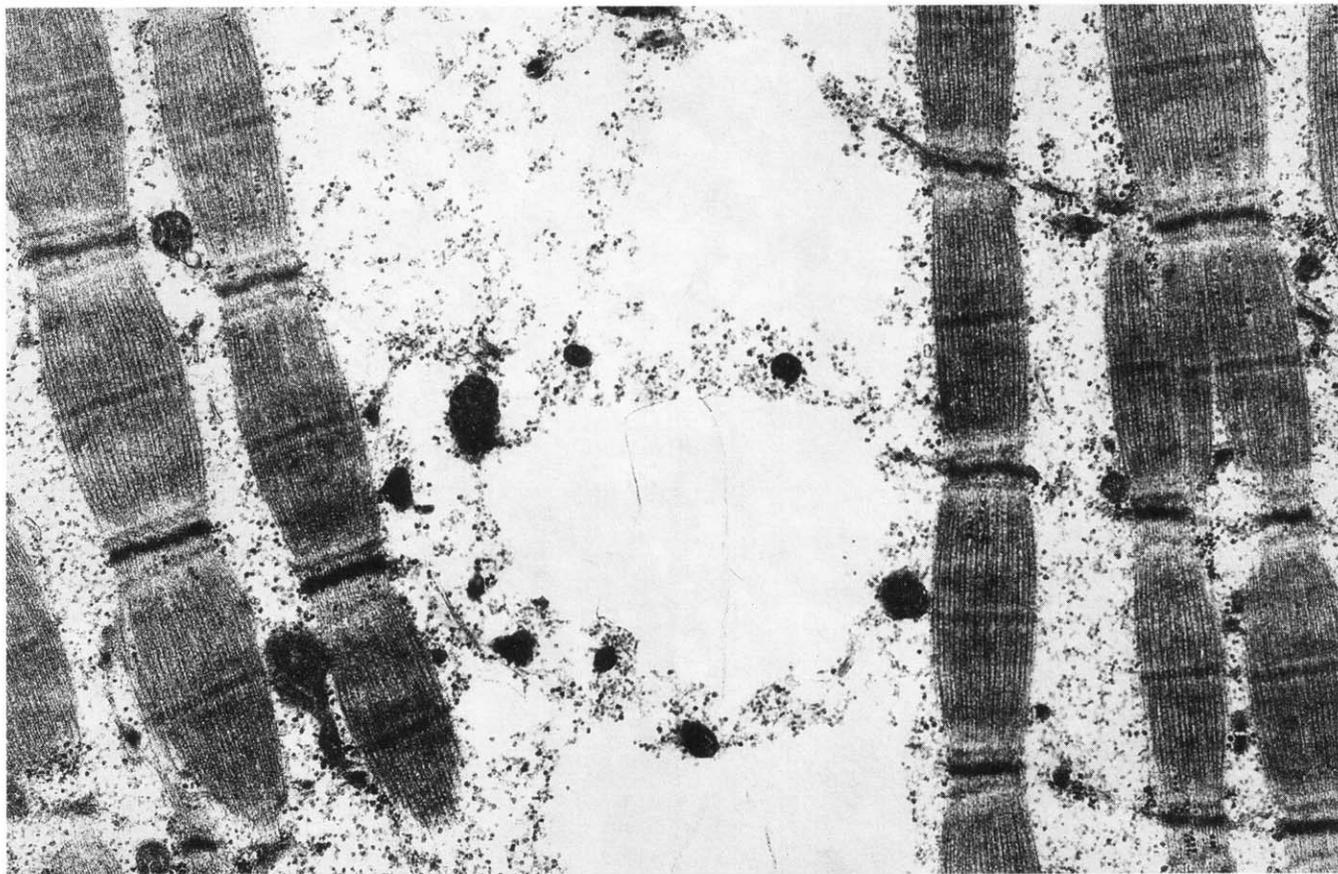


Fig. 5. Human lateral gastrocnemius after 120 days of head-down bed rest. Destruction and thinning of myofibrils are visible, as are vacuoles with laminar inclusions and diminished numbers of cytogranules. Magnification $\times 18,000$.

which becomes apparent within hours of beginning the suspension. By the fifth day of suspension, the rate of proteolysis accelerates rapidly, reaching a maximum on day 15. Thereafter, the balance between protein anabolism and catabolism stabilizes at a new level.⁵⁴ Under these circumstances, proteolysis is associated with the action of calcium-activated hydrolases in the cytoplasm; derivational atrophy, by contrast, results from proteolysis via lysosomal enzymes.⁵⁵ Thus, reduced amounts of myofibrillar proteins could reflect either increased proteolysis, decreased protein synthesis, or both.

Another potential contributor to muscle atrophy, changes in the activity of sarcoplasmic (satellite cells), has yet to be studied in depth. Results from one study⁴⁵ suggest that suspending the hind limbs of rats for five weeks led to a substantial (six-fold) increase in sarcoplasm density per unit volume of tissue; however, another group found that sarcoplasm proliferation was inhibited during the first 24 to 72 hours of suspension.⁵⁶ Inhibited proliferation of sarcoplasm may be characteristic of early adaptation to diminished functional activity; nevertheless, this issue requires considerably more study.

2. Changes in Myosin Phenotype

Gravitational unloading has been shown repeatedly to shift myosin phenotype. Hind-limb suspension in rats report-

edly increases the percentage of type II (fast) fibers and decreases the proportion of type I fibers.^{35,36,45,57} Shifts in fiber composition (toward predominance of type II fibers) were noted in the soleus and extensor digitorum longus of rats after only seven days of spaceflight^{6,37,38}; longer flights (12.5 and 14 days) have been associated with 20–25% decreases in amounts of type I fibers in the soleus and adductor longus.^{40,41,48} The proportion of type II fibers also had increased in the soleus and vastus lateralis of two monkeys flown aboard Kosmos-2229 (Fig. 7),³³ but no changes in fiber-type composition were found in these muscles after a similar experiment on Kosmos-2044.⁴³ A shift from slow to fast also was detected deep in the triceps brachii of primates after Kosmos-2229.⁵⁸

The traditional technique of staining myofibrillar ATPase to visualize myofiber proportions can be supplemented with various immunoassay techniques. In several studies, even though no shifts in the fiber ratio were found with the ATPase stains after suspension or spaceflight, the number of fibers that reacted with antibodies against “fast” myosin tended to increase, but the number of fibers reacting with antibodies against “slow” myosin generally decreased.^{8,46,59–63} In one of these suspension experiments, electrophoresis revealed the presence of a new heavy-chain myosin isoform (2d), which is characteristic of young animals.⁶¹ Increases in the numbers of fibers containing both slow and fast myosin heavy chains have

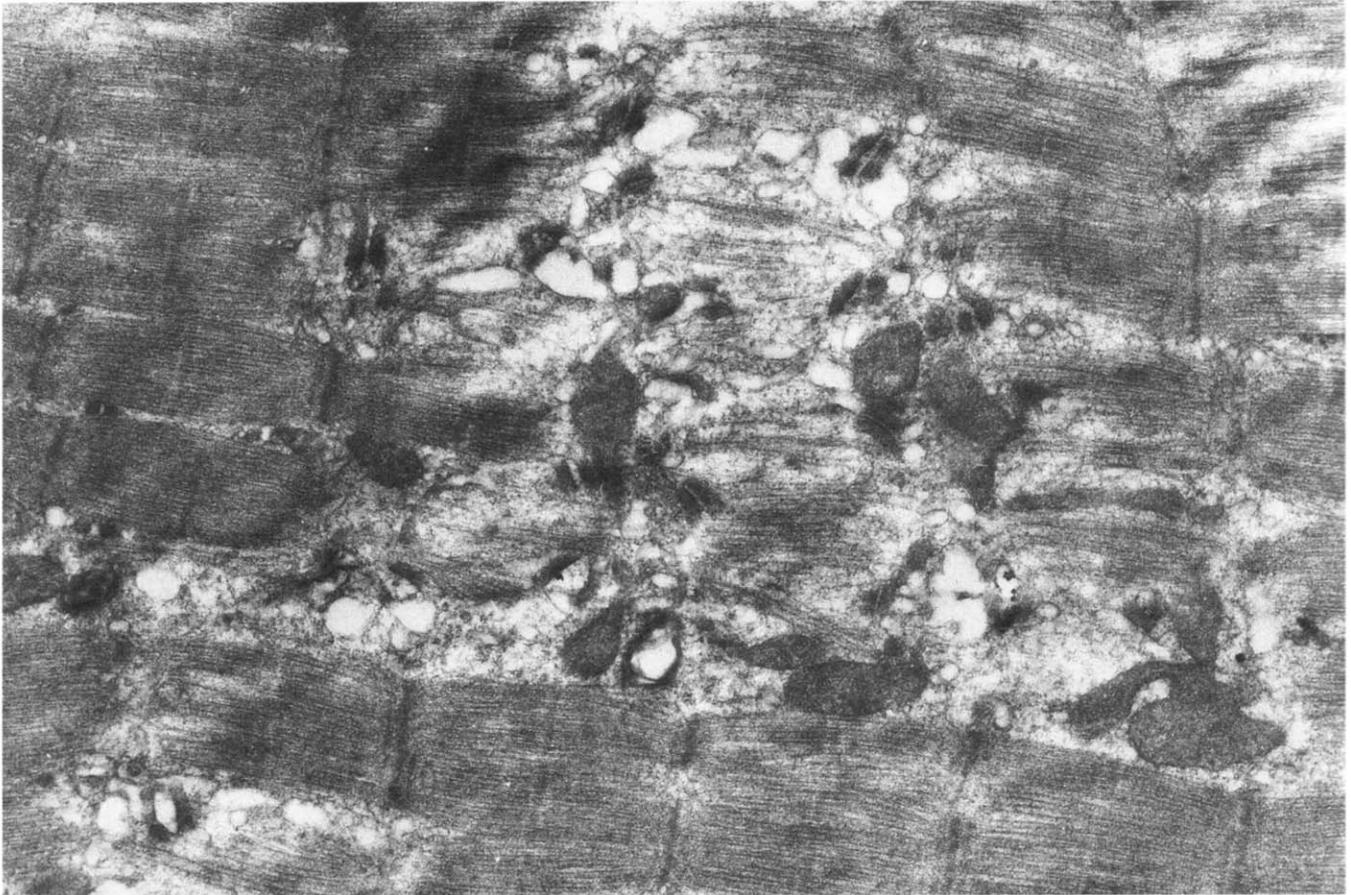


Fig. 6. *Macaca mulatta* biceps brachii after a 13-day spaceflight. Destruction of sarcomeres is visible, as are vacuolization of the sarcoplasmic reticulum and lysed products of the actin-myosin complex. Magnification $\times 15,000$.

been reported after spaceflight,^{8,62} even after as few as four days.⁶⁴ The vastus lateralis samples taken from astronauts before and after a seven-day Shuttle flight showed significant decreases in the number of fibers that reacted with antibodies against the slow isoforms of heavy chains of myosin.⁶³

However, changes in fiber-type ratio are not universal after gravitational unloading.^{39,43,65} In one study, suspending mature rats (as opposed to young rats) for two to six days produced no shifts in fiber-type composition of the soleus.⁶⁶ The authors of this study and others⁴³ hypothesize that the oft-observed shifts probably are not a true change in fiber-type ratio, but rather reflect a delay in the perinatal and postnatal transformation of fibers that is characteristic of development in rats and some other species. Moreover, some head-down bed-rest periods and a six-week unilateral leg suspension with humans also did not lead to consistent changes in fiber-type ratio.^{15-17,22}

Other studies in which rat muscle fibers were isolated and examined individually after spaceflight or hind-limb suspension revealed that contraction velocity increased, but the peak strength decreased.^{67,68} These changes, as a rule, were correlated with shifts in myosin-isoform patterns,⁶⁷ but were present in other fibers as well.⁶⁸

B. Changes in the Sarcotubular-Membrane System and Excitation-Contraction Coupling

The discovery that contractile properties changed in response to gravitational unloading stimulated interest in whether the sarcotubular-membrane system, which links the electrical and mechanical function of muscles, changes as well. A brief review of the nature of this link follows. First, the release of acetylcholine from axon terminals at the neuromuscular junction causes electrical activation of the skeletal muscle fibers through generating action potentials in the muscle cells. Action potentials are conducted into the interior of the fiber across the membrane of the transverse tubules, which are continuous with the sarcoplasm (the muscle-cell cytoplasm), thus causing the release of Ca^{2+} from the sarcoplasmic reticulum into the sarcoplasm. Calcium ions in the sarcoplasm bind to troponin, a component of the actin filament complex. The consequent displacement of tropomyosin allows the actin to bind to the myosin cross-bridges, thus stimulating muscle contraction. Muscles relax when the Ca^{2+} is actively transported out of the sarcoplasm and back into the sarcoplasmic reticulum.

Severe myopathies or acute eccentric mechanical loads are characterized by myofibrillar destruction and breaks in the sarcolemma, the plasma membrane of the muscle fiber.⁶⁹ One

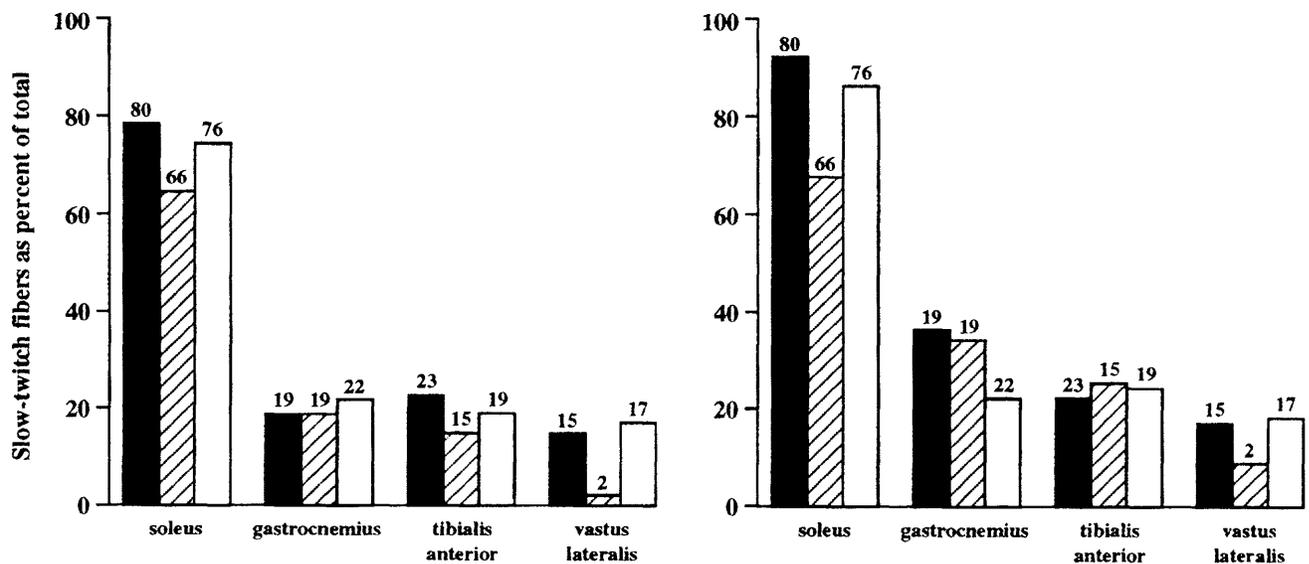


Fig. 7. Relative proportions of slow-twitch fibers in muscles of two monkeys before and after flight on a biosatellite. Black bars, before flight; hatched bars, after flight; clear bars, ground control animals.

group used a lanthanum tracer to assess whether spaceflight or microgravity simulations could induce breaks in the sarcolemma; this technique can reveal breaks of 2 nm or less.¹⁹ No membrane damage was found in the gastrocnemius of humans who had undergone 1 to 3 days of dry immersion; however, early signs of myofibrillar damage were present as early as 24 hours of immersion.¹⁹ Lanthanum-colloid particles did penetrate into fibers of the biceps brachii and gastrocnemius medialis in monkeys flown on Kosmos-2229. However, the muscle samples in this instance were taken three to four days after landing, and thus these results may have reflected readaptation to gravity rather than microgravity effects.⁵¹

The possibility that muscle-cell membranes could become more permeable to macromolecules during spaceflight is supported indirectly by observations that blood concentrations of muscle enzymes are greater several hours after flight than before.⁷⁰ Bed-rested subjects also produced greater amounts of muscle proteins in blood plasma after a loading test than they did before bed rest.⁷¹

Gravitational unloading by means of hind-limb suspension seems to induce substantial changes in the excitation-contraction system. By the 15th day of suspension, the volume of the sarcoplasmic reticulum, the accumulation of calcium ions in the fibers, and the rate of their release and reuptake all were increased.^{72,73} These changes probably reflect the gradual replacement of slow-fiber Ca-ATPase isoforms with those characteristic of fast fibers in the sarcoplasmic reticulum.⁷⁴ Assessment of the temporal characteristics of contraction in isolated fibers revealed that gravitational unloading seemed to suppress the sensitivity of the myofibrillar apparatus to intracellular calcium concentrations.⁷³

Another way of assessing the effect of gravitational unloading on the excitation-contraction system involved examining the reaction of isolated muscle fibers to external calcium

solutions.⁴ Slow-twitch (type I) fibers were isolated from rats that had undergone hind-limb suspension and rats that had not. In the control group, the fatigue induced by a rapid series of tetanic contractions was significantly accelerated in a low-calcium solution. Fibers from the suspended group, in contrast, showed a large drop in the *amplitude* of tetanic contractions in the low-calcium solution. These results were taken to indicate that gravitational unloading increased the sensitivity to external calcium, and stabilized that sensitivity to calcium ions at a level lower than normal. According to this interpretation, extracellular calcium under normal circumstances would accumulate on the inside of the sarcolemma, where it may inhibit the function of calcium-ion sensors. This accumulation would not take place in decalcified medium. If unloading causes an increase in the volume of the sarcoplasmic reticulum, then large quantities of Ca^{2+} probably have already accumulated therein. The release of these ions during the contraction, then, would be so great that it inhibits the sensor function even if no calcium were to enter from outside the cell.

In summary, then, changes in the contractile properties of muscles induced by gravitational unloading may be associated not only with changes in the volume and composition of contractile structures, but also with disruption of the structure and function of the sarcolemma excitation-contraction system.

C. Skeletal-Muscle Energy Supplies

Both muscle contraction and relaxation require energy in the form of adenosine triphosphate (ATP). Thus, the energy supplied to skeletal muscles also plays an important role in muscle function, particularly with regard to muscle endurance, which is known to be reduced by exposure to microgravity.

Muscles at rest obtain most of their energy from the aerobic respiration of fatty acids. Aerobic energy is provided to muscles by three peripheral “subcomponents”: the capillaries, which supply blood to the muscles; the myoglobin molecules, oxygen carriers that act in the extracellular-intracellular diffusion space; and the mitochondria, which generate the high-energy bonds in phosphagenic molecules through oxidation. Although type I (slow) fibers have a greater capacity for aerobic respiration, and type II fibers for anaerobic respiration, type II fibers also can respire aerobically.

1. Capillaries and Blood Supply to the Muscles

The muscle capillary system is structured as follows.^{75,76} The precapillary vessel is perpendicular to the axis of the fiber, and branches into capillaries that are parallel to the axis. The number of capillaries on a fiber can change only if new capillaries appear, or if old ones branch or are lost. However, capillary density (number of capillaries per cross-sectional area of tissue) also reflects the thickness of the fibers. The amount of tissue served per capillary is one of the most important indicators of the effectiveness of the vascularization of a working muscle.⁷⁶

Almost all types of gravitational unloading seem to increase capillary density in muscle. Spaceflights lasting 7 to 14 days,^{6,38,39} hind-limb or whole-body suspension of rats,^{6,35} unilateral lower-limb suspension of humans,²² and head-down tilt hypokinesia in primates¹⁸ all lead to increased capillary density, even though the number of capillaries per fiber can be unchanged or diminished. This effect is associated primarily with fiber atrophy, the extent of which apparently is greater than the decrease in number of capillaries.

In contrast to the capillary-density measurements, studies of blood-flow volume in resting and working muscles after gravitational unloading have generated contradictory results. Two groups of investigators^{77,78} used microspheres to test blood flow rate in the soleus before vs after hind-limb suspension. One group⁷⁷ found flow rate to be unchanged after suspension both at rest and during submaximal exercise; the other⁷⁸ found blood flow at rest to be 50% less after suspension than before. Impedance plethysmography revealed inconsistent changes in blood flow in humans before and after 20 days of bed rest.⁷⁹ However, another impedance-plethysmography study revealed that hypokinesia produced elevations in the peak blood flow after standard static loading in humans.⁸⁰ This latter result may have been associated with increased capillary density in the muscles.

2. Diffusion Distance and Muscle-Fiber Dimensions

The distance that oxygen molecules and energy substrates must travel between the capillary and the mitochondria can be divided into the extracellular and intracellular spaces. In the traditional view, diffusion across the intracellular distance is the limiting factor for getting oxygen and energy substrates to the mitochondria.⁷⁵ Atrophy of muscle fibers induced by gravi-

tational unloading shrinks the diffusion distance, since the extent of atrophy typically exceeds the decrease in capillary number (see above). The conditions for oxygen transport are probably improved during this process.

3. Oxidative and Glycolytic Potential of Muscle Fibers

The oxidative potential of muscles refers to their capacity for oxidative phosphorylation, i.e., for generating energy through the aerobic oxidation of energy substrates. Oxidative potential typically is assessed by measuring the maximum oxygen consumption of perfused muscles, isolated fibers, or isolated mitochondria; the activity of the enzymes of aerobic oxidation; and the density of mitochondria per unit volume of muscle.^{28,81} Under normal conditions, these markers are closely correlated with each other and are considered interchangeable.⁸¹ However, the oxidative potential does not reflect the actual aerobic-energy production in the working muscle, but rather represents the maximum capacity of the mitochondria.²⁸

Mitochondria are distributed heterogeneously within each fiber; most are present in the fiber periphery, just under the sarcolemma, and fewer are present between the myofibrils, toward the center of the fiber.⁸² Caution is required in evaluating suspension-induced changes in the oxidative activity of individual fibers, since these changes depend greatly on the evaluation method and the particular muscle and fiber type being considered.

In rats, the specific activity of Krebs-cycle enzymes and three-dimensional density of mitochondria were either unchanged or increased after 7- to 28-day suspension^{3,45,83} or spaceflight^{8,37,84,85} in both type I and II fibers; the rate of oxidation of fatty acids decreased.^{37,85,86} However, other investigations revealed decreases in the density of mitochondria (per volume) after suspension, and mismatches between changes in mitochondrial ultrastructure and enzymes during suspension.⁸⁷ Still another group found that suspending rats did not change the activity of succinate dehydrogenase in type I fibers, but decreased it in type II fibers, in “fast-twitch muscles.”⁸⁸ In monkeys, mitochondrial volume density in the deep parts of the triceps brachii and biceps brachii was unchanged after the Kosmos-2229 mission.⁵⁸ Neither we⁵¹ nor Bodine-Fowler⁴³ found significant changes in oxidative-enzyme activity in monkeys after flights on Kosmos-2229 or -2044. However, the distribution of mitochondria within the fiber shifted such that more mitochondria—and thus greater oxidative-enzyme activity—were present in the center of the fiber, and fewer were near the sarcolemma.^{45,93}

To summarize, oxidative potential may decrease in proportion to the decrease in fiber size, but the specific volume of mitochondria does not seem to change accordingly. However, both spaceflight and suspension seem to decrease the oxidative potential of muscle.^{35,89,90} This decrease may be associated with larger interstitial spaces within the muscle.^{91,92} Another possibility is that the fiber-type shift

(to fewer oxidative, slow type I fibers and more anaerobic, fast type II fibers) affects the oxidative potential of the entire muscle.

Results obtained from humans after head-down bed rest have been somewhat different. In one study, visual inspection of histochemical slides suggested that 49 days of hypokinesia had induced some decrease in oxidative-enzyme activity.¹⁴ Another 30-day study revealed decreases in citrate synthase (oxaloacetate transacetase) activity of 39% in the soleus and 18% in the vastus lateralis.¹⁷ During a 370-day head-down bed-rest period,¹⁵ succinate dehydrogenase activity began to decrease markedly in type II fibers in the gastrocnemius lateralis on day 60, and then returned to baseline values on day 120. The activity of this enzyme was reduced consistently in type I fibers throughout the first 120 days of bed rest. Subsequently, after the subjects began exercising during the remainder of the bed-rest period, oxidative potential first returned to baseline values, but then began to decline after day 240, reaching 75–77% of baseline values by day 300. On day 365, oxidative activity had stabilized at 82–85% of baseline. Changes in both types of fibers at this time were quite similar.

From these results, we hypothesize that decreased endurance after spaceflight or its simulations probably does not result from changes in the peripheral transport of oxygen or substrate. Rather, we suspect that poor endurance is due to decreases in the oxidative potential of the entire muscle as a result of shifts in the proportion of fiber types (toward predominance of fast-twitch fibers), or perhaps to other factors. Alternatively, the supply of energy could be satisfactory, but its utilization by the contractile apparatus could be inadequate. (Contraction power diminishes after spaceflight or its simulations, either because of atrophy or because of other mechanisms.)

Slow fibers in rats have demonstrated increases in glycolytic potential (activity of α -glycerophosphate dehydrogenase and lactate dehydrogenase) in response to gravitational unloading by hind-limb suspension^{8,85} or by spaceflight.^{8,94} Analogous changes were detected in primate soleus after the Kosmos-2229 mission.³³ Changes in the activity of glycolytic enzymes are thought by some⁸ to result from their functional dependence on myosin-isoform ratio and thus on myofibrillar ATPase activity.⁸ However, α -glycerophosphate dehydrogenase activity increased in both fiber types in the Kosmos monkeys.³³ In our opinion, any increased glycolytic potential of muscles in microgravity probably results from greater participation of anaerobic respiration and carbohydrate metabolism in the energy-supply processes.⁹⁵

III. Physiological Mechanisms Underlying Muscle Adaptation to Microgravity

A. Contractile Activity

Contractile activity in muscles decreases markedly in response to microgravity conditions; tonic activity virtually dis-

appears, and dynamic activity is substantially modified. This decrease in contractile activity has been considered the primary reason for the structural and metabolic changes that microgravity produces in muscles. Similarities between experimental decreases in motor activity on Earth and microgravity usually are cited to support this point of view. Atrophy and some other effects of gravitational unloading also can be prevented in some circumstances through the physical loading provided by exercise, particularly during head-down bed rest. Physical loading and electrical stimulation have compensated significantly for the development of muscle atrophy both in humans^{14,15,96} and in animals.^{97–102}

Differences in the extent of muscle atrophy displayed by different muscles and different fiber types, logically enough, result from differential decreases in their contractile activity in response to gravitational unloading. This point was confirmed indirectly in an experiment that involved giving hind-limb-suspended rats tetrodotoxin, a neurotoxin that blocks action potentials from being transmitted from the somatic motoneurons to the muscle.¹⁰³ The degree of atrophy in the tetrodotoxin-treated, suspended rats was increased (relative to that in rats that were only suspended), but only in “fast” fibers. These results were interpreted as meaning that the activity of fast fibers (in contrast to slow fibers) does not cease completely during suspension, which leads to “incomplete” atrophy of fibers of this type.

The transformation of slow fibers into fast in response to gravitational unloading can be reversed, either by prolonged electrical stimulation¹⁰⁴ or by peroral administration of the creatine analog β -guanidinopropionic acid. The latter induces a chronic deficit in high-energy phosphate compounds, and thus simulates the metabolic consequences of chronic loading to an extent impossible with actual physical training.¹⁰⁵ These reverse-transformations suggest that accumulation of undergraded high-energy compounds (as a result of fiber disuse) may stimulate the transformation of the myosin phenotype.

Decreases in skeletal-muscle fiber contractile activity also may be accompanied by structural-functional changes in motoneurons. This supposition was confirmed by signs of partial denervation of muscles in animals (after biosatellite flights) and in humans (after hypokinesia), as well as by changes in structural and metabolic aspects of motoneuron bodies in the anterior horn of the spine in rats after biosatellite flights.^{106–108} Disruption of innervation in itself could also be a source of atrophy and other changes in muscle fibers. However, muscle atrophy was only moderate in cats that had undergone spinal transection.¹¹⁰

Some findings, however, make unambiguous explanations of the mechanisms underlying contractile changes difficult. First, muscles do not atrophy during normal daily activities, even though most muscle fibers remain inactive. Limiting physical activity in itself does not always lead to atrophy of skeletal muscles, although it can interfere with growth.¹⁰⁹ Moreover, exercise cannot completely prevent the atrophy and fiber transformation induced by gravitational unloading. For example, the combination of electrical stimulation and dynamic

(isotonic) loads did not prevent fiber-type ratios from shifting in hind-limb-suspended rats, but isometric loads did.¹⁰⁴ Thus, microgravity's effects on muscle structure may result from a combination of factors that depend on the mechanical or tonic activity generated by motoneurons¹¹¹ as well as other factors that are not associated with contractile activity.

B. Afferent Gravitational Stimuli

The plasticity with which muscles adapt to microgravity may well depend on the nature of the afferent information that converges at the motoneurons. For example, limb deafferentation in rats is known to induce atrophy in both slow- and fast-twitch muscles.¹¹² On the other hand, providing even moderate support (i.e., some degree of weight loading) during microgravity or its analogues can limit the extent of atrophy. Allowing suspended rats to walk for 10-minute periods six times a day decreased the extent of atrophy in the soleus by 50%.^{34,113} In another rat experiment, supporting one hind limb during a 14-day head-down suspension prevented soleus atrophy, but did not prevent a decrease in citrate synthase activity.¹¹⁴ Rats aboard a biosatellite that were centrifuged to mimic 1-g conditions exhibited few of the microgravity effects observed in an on-board control group that was not centrifuged, despite otherwise identical conditions for physical activity.¹¹⁵ Intermittent centrifugation was found to protect about 90% of the mass of the soleus in hind-limb-suspended rats on Earth as well.¹¹⁶

In summary, changes in the nature of supporting afferentation in weightlessness may help to trigger muscle adaptation. The effects of this factor must be mediated by tonic activity of the small (slow) motoneurons and the corresponding activity of muscle fibers.

C. Muscle Length

The absence of gravity in space evidently affects the resting length of muscles. Passive stretch can decrease the degree of atrophy and change the protein synthesis-lysis balance in the soleus of suspended rats.^{117,118} This "anti-atrophy" effect from passive stretch occasionally is as strong as that from physical exercise.¹⁰² Stretching the extensor of the talocrural (ankle) joint in rabbits during a 15-day hind-limb suspension period prevented both fiber atrophy and myofibrillar damage in the soleus.¹¹⁹ Eccentric contractions induced with intramuscular electrodes attenuated atrophy in the soleus of suspended rats.¹⁰¹

The protective effect of stretching may be a consequence of reflexive activation of motoneurons, or perhaps a direct effect on the muscle. Several observations seem to support the latter alternative. First, atrophy could be attenuated somewhat in isolated spinal motoneurons of cats by passive stretch of the calf extensor muscles.¹²⁰ Mechanical stretching in a culture of chicken muscle cells decreased the level of glucocorticoid-induced atrophy.¹²¹ Finally, the effect of gravitational unloading was intensified somewhat by passive *shortening* of

muscles independent of fluctuations in the electrical activity of the contracted muscle.¹²²

Thus, the protective, "anti-atrophy" effect of passive stretch could be a direct mechanical effect, possibly via accumulation of the products of myofibril destruction (which would stimulate protein synthesis), or instead might reflect reflex support of tonic activity in the muscle fiber.

D. Hormonal Factors

Reductions in the concentrations of anabolic hormones, increases in the concentrations of glucocorticoids, or increases in tissue sensitivity to the latter, also might produce some of the structural and metabolic effects of microgravity. For example, blocking corticosteroid receptors in suspended rats prevented type I fibers from being transformed into type II fibers.¹²³ However, removing the adrenal glands did not prevent suspension-induced atrophy, even though cortisol is known to enhance atrophy in the soleus and the extensor digitorum longus.¹²⁴ Glucocorticoid-induced atrophy, which primarily affects type II (fast) fibers, thus seems to differ from microgravity-induced or disuse atrophy.¹²⁵

For rats, consuming a high-protein diet during a 21-day hind-limb suspension both prevented the transformation of fibers and decreased the amount of triiodothyronine in blood.¹²⁶ Decreases in thyroid-hormone concentrations may enhance the dominance of type I (slow) fibers, as evidenced by transformation of fast fibers to slow in hypothyroidism. However, the results from this study suggest that triiodothyronine also would decrease in suspended rats if they were fed normal amounts of protein, even though fibers in these animals would change from slow to fast.

As for anabolic hormones, daily doses of growth hormone had no effect on the development of atrophy in the soleus of rats flown on the Space Shuttle,⁶⁴ although a testosterone derivative did attenuate loss of muscle mass in rats that were suspended for 6 weeks.¹²⁷

These results suggest that hormonal factors may not be crucial in the development of microgravity-induced atrophy. However, the participation of hormonal mechanisms cannot be ruled out as a component of a larger chain of adaptive events.

E. Blood Supply to the Muscles

Some investigators have proposed that changes in the blood supply to the muscles contributes to the atrophy of skeletal muscles in microgravity.⁷⁸ This concept was developed from the observation that infrared radiation applied to the soleus of suspended rats both increased the rate of blood flow and prevented atrophy.⁷⁸ However, another group found that torbaphillin, a xanthine vasodilator that facilitates capillary growth, had no effect on the degree of fiber atrophy.¹²⁸ No consensus has been reached at present regarding the potential role of blood supply in the development of skeletal-muscle atrophy in microgravity.

IV. Summary and Conclusions

In conclusion, exposure to the unique circumstances of microgravity is thought to trigger a sequence of events that themselves confer direct and indirect effects on human skeletal-muscle function. First, the absence of "support" (weight loading) in microgravity could suppress or reduce the transmission of afferent information to the motoneurons. The ensuing reduction in motoneuron background activity could lead to muscle atony, which itself could lead to myofibrillar restructuring, atrophy, and fibrillar transformation. Next, passive shortening of muscles probably leads directly to inhibition of protein synthesis, and could decrease the amount of proprioceptive information that reaches the motoneurons. This in turn would affect muscle tone. Finally, neurogenic, myogenic, or humoral factors independent of impulse activity could control the size and phenotype of muscle fibers on Earth. Changes in these factors in microgravity thus could affect the structure and metabolism of muscle fibers.

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