The Space Shuttle Program provided a wealth of valuable information regarding the adaptations of skeletal muscle to weightlessness. Studies conducted during the Extended Duration Orbiter Medical Project (EDOMP) represented ground breaking work on the effects of spaceflight on muscle form and function from applied human research to cellular adaptations. Results from detailed supplementary objective (DSO) 477 demonstrated that muscle strength losses could occur rapidly in response to short-duration spaceflight. The effects of spaceflight-induced unloading were primarily restricted to postural muscles such as those of the back as well as the knee extensors. DSO 606 provided evidence from MRI that the observed strength losses were partially accounted for by a reduction in the size of the individual muscles. Muscle biopsy studies conducted during DSO 475 were able to show muscle atrophy in individual muscle fibers from the quadriceps muscles. Reduced quadriceps muscle size and strength was also observed during the 17-d Life and Microgravity Spacelab mission aboard STS-78. Multiple maximal strength tests were conducted in flight on the calf muscles and it has been hypothesized that these high force contractions may have acted as a countermeasure. Muscle fiber mechanics were studied on calf muscle samples pre- and postflight. While some responses were crewmember specific, the general trend was that muscle fiber force production dropped and shortening velocity increased. The increased shortening velocity helped to maintain muscle fiber power. Numerous rodent studies performed during Shuttle missions suggest that many of the effects reported in Shuttle crewmembers could be due to lesions in the cellular signaling pathways that stimulate protein synthesis as well as an increase in the mechanisms that up-regulate protein breakdown. The results have important implications regarding the overall health and performance capabilities of future crewmembers that will venture beyond low-Earth orbit.

**Learning Objective:** Overview of the Space Shuttle Program regarding adaptive changes in skeletal muscle function and performance, including what was learned from research and what was implemented for countermeasures.

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