

# This Week's Citation Classic®

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**Holloszy J O.** Biochemical adaptations in muscle: effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. *J. Biol. Chem.* 242:2278-82, 1967; and **Holloszy J O & Booth F W.** Biochemical adaptations to endurance exercise in muscle. *Annu. Rev. Physiol.* 38:273-91, 1976. [Dept. Preventive Medicine, Washington Univ. Sch. Medicine, St. Louis, MO]

The first paper reported that exercise training induces an increase in muscle mitochondria as reflected by increases in the levels of mitochondrial protein and respiratory enzymes. The second paper reviewed the research stimulated by this finding and presented a hypothesis regarding the physiological consequences of this adaptation. [The *SCI*® indicates that these papers have been cited in over 470 and 425 publications, respectively.]

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While in medical school and during my specialty training in internal medicine and metabolism, I became interested in the role of exercise in maintenance of health and functional capacity. Subsequently, while stationed at the University of Illinois by the US Public Health Service (USPHS), I was involved in studies of the effects of exercise on plasma lipids and cardiovascular function. During this research, I became fascinated by the remarkable increase in endurance that occurs with exercise training, and I decided to try to determine the biochemical basis for this adaptation. After leaving the USPHS I spent two years as a research fellow in biochemistry and then (in 1965) joined the Department of Preventive Medicine at Washington University, where I began my research on the biochemical adaptations of muscle to exercise.

Comparative studies had shown a good correlation between the ability of a muscle to perform prolonged exercise and its content of respiratory enzymes. This relationship suggested the hypotheses, which I set out to test, that the mitochondrial content of a muscle is influenced by its habitual level of contractile activity and that an exercise-induced increase in muscle mitochondria plays a major role in the increase in endurance with training. These hypotheses have proved to be correct. Perhaps the most difficult aspect of this study was learning how to train rats to become marathon runners. My finding that endurance exercise training increases the respiratory capacity of skeletal muscle, which provided the stimulus for much of the basic research in exercise physiology during the past 20 years, was soon confirmed and extended to other species, including humans.

My 1967 *Journal of Biological Chemistry* paper is frequently cited because it stimulated a new area of research that has three components. The first involved a detailed characterization of the biochemical adaptations of skeletal muscle to endurance exercise. The second dealt with the physiological consequences of these exercise-induced adaptations. The third area of research stimulated by these two papers relates to the mechanisms by which exercise induces the adaptive increase in muscle mitochondria. Studies of this question have shown that exercise results in an increase in the rate of synthesis of a number of mitochondrial enzymes.<sup>1,2</sup>

In our 1976 paper in the *Annual Review of Physiology* we reviewed the research in this area and proposed a hypothesis regarding the mechanisms by which the exercise-induced increase in muscle mitochondria could account for the slower utilization of glycogen, the increased oxidation of fat, and the reduced production of lactate during exercise in the trained as compared to the untrained state. This hypothesis was recently shown to be correct.<sup>3,4</sup> This paper has been frequently cited because it provides a biochemical explanation for some of the physiological consequences of endurance exercise training.

1. Booth F W & Holloszy J O. Cytochrome c turnover in rat skeletal muscles. *J. Biol. Chem.* 252:416-9, 1977.
2. Morrison P R, Montgomery J A, Wong T S & Booth F W. Cytochrome c protein-synthesis rates and mRNA contents during atrophy and recovery in skeletal muscle. *Biochemical J.* 241:257-63, 1987.
3. Constable S H, Favier R J, McLane J A, Fell R D, Chen M & Holloszy J O. Energy metabolism in contracting rat skeletal muscle: adaptations to exercise training. *Amer. J. Physiol.* 253:C316-22, 1987.
4. Dudley G A, Tullson P C & Terjung R L. Influence of mitochondrial content on sensitivity of respiratory control. *J. Biol. Chem.* 262:9109-14, 1987.