THE ORIGINS OF FATIGUE during exercise have intrigued scientists for well over a century and have proven to be a rich, but complex, area of investigation. Understanding fatigue and the consequent exercise limitation is not just an intellectual curiosity, but has far-reaching implications that traverse the broad spectrum of our communities. In chronically diseased or acutely ill patients, fatigue and exercise limitation can profoundly restrict daily activities and thus impair quality of life. In healthy individuals, fatigue can restrict performance in diverse occupational duties such as firefighting, the military, construction, and laboring, as well as limiting participation in recreational activities and sports. Most readers would link fatigue and exercise limitation to the grand stage of national and international sporting competition, adversely affecting elite athletic performance, with implications for medals, glory, and the sports industry. Fatigue and exercise limitation also impact on the young through to the aged, thus affecting all persons at multiple stages of our lives. It is therefore not surprising that investigation into the underlying causes of fatigue and exercise limitation has attracted special attention of scientists from clinical, basic, and applied science specializations.

Early investigations on fatigue mechanisms focused on metabolic fuel availability or accumulation of “waste products.” Prolonged exercise was thus considered to be limited by reduced muscle glycogen availability and/or hypoglycemia. Fatigue during intense exercise was typically portrayed as a consequence of phosphocreatine depletion and lactic acidosis. With evidence that action potential transmission across the neuromuscular junction was not impaired, fatigue was ascribed as largely occurring within the active muscles. Hence, the term “muscle fatigue” is now firmly entrenched within the general scientific vocabulary. This series of nine mini-reviews, all by experts in their respective fields, first demonstrate the tremendous recent advances in understanding the complex phenomenon known as fatigue. Second, these reviews clearly indicate that “fatigue” rather than “muscle fatigue” is much more appropriate for voluntary exercise, since fatigue limiting exercise involves mechanisms within the contracting peripheral or locomotive muscles and encompasses the respiratory muscles, muscle perfusion, other inactive skeletal muscle and organs regulating fuel, metabolite, or ionic homeostasis and, most importantly, within the central nervous system itself. Furthermore, fatigue can be understood not as a failure of regulation, “the bad guy,” but as a highly regulated strategy conserving cellular integrity, function and, indeed, survival. These state-of-the-art reviews reinforce the concept that understanding fatigue is integrative physiology at its finest. Each review integrates existing knowledge and importantly, includes a focus on new directions for the field, ensuring each is obligatory reading for all interested in fatigue and exercise.

The first six reviews focus on the mechanisms and importance of what have been labeled as peripheral muscle fatigue and central fatigue. The first two reviews have a cellular or “myo-site” focus of fatigue. Drs. Allen, Westerblad, and Lamb (1) review evidence for a failure of sarcoplasmic reticulum Ca$^{2+}$ release as a major causative factor in fatigue in muscle. The review draws heavily on elegant single-fiber experiments, which have used intact or mechanically skinned fibers and which clearly link insufficient Ca$^{2+}$ release to a reduction in force. They focus on the role of inorganic phosphate sequestration of Ca$^{2+}$ within the sarcoplasmic reticulum, rather than changes in action potential amplitude, as a primary factor responsible for the fatigue-induced decline in cytosolic Ca$^{2+}$ concentration and force. Drs. McKenna, Bangsbo, and Renaud (5) examine exercise effects on muscle ionic homeostasis and their essential role in fatigue, integrating findings from human exercise studies and in vitro studies of ionic effects on muscle function. Marked intracellular-interstitial perturbations in K$^+$ and Na$^+$ concentrations and impaired Na$^+$/K$^+$ pump activity are presented as causative factors in fatigue, via cellular membrane depolarization and inexcitability; whereas Cl$^-$ conductance changes oppose these effects. Hence regulation of each of these ions, and of the Na$^+$/K$^+$ pump, must be considered in understanding fatigue. The review by Drs. Secher, Seifert, and van Lieshout (8) goes to the top end, investigating the role of cerebral metabolism in fatigue. They show that exercise increases cerebral perfusion when perfusion is analyzed appropriately. Furthermore, arteriovenous studies across the brain indicate that glucose and lactate uptake are increased with exercise, but that cerebral oxygenation and cerebral metabolic ratio [O$_2$ uptake/(glucose and 1⁄2lactate uptake)] are in fact decreased. As a consequence, oxygenation of the brain is challenged during exercise and may be a vital factor in what has been defined as central fatigue.

Continuing the focus on the central nervous system, Drs. Taylor and Gandevia (9) review the supraspinal and spinal mechanisms contributing to fatigue during both maximal and submaximal voluntary contractions. They summarize results

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from elegant experiments in human volunteers that use twitch interpolation and transcranial magnetic stimulation to probe the relative importance of central and peripheral fatigue mechanisms. While maximal contractions have been studied the most, and it is technically challenging to study submaximal contractions, there is evidence of central fatigue in both types of muscle activation. Returning to the muscle, Dr. Fitts (4) examines the role of cross-bridge cycling in the development of fatigue. There are numerous metabolic factors with the potential to impair cross-bridge interactions and they are well discussed. The role of acidosis has been debated over the years and new results suggest an inhibitory effect of increased [H⁺] on muscle fiber shortening velocity and power production (4). The past decade has seen an explosion of interest in reactive oxygen species (ROS) and their impact on skeletal muscle function. Drs. Ferriera and Reid’s review (3) identifies increased ROS production in contracting muscles as a cause of fatigue in a variety of experimental models. The intracellular target proteins are not fully resolved, but likely include tropomyosin, myosin, actin, Ca²⁺-ATPase, and Na⁺-K⁺-ATPase, with thiol oxidation strongly implicated as a key player. In a new twist, they address the important question of whether antioxidants can delay fatigue, by primarily focusing on studies using the non-specific antioxidant N-acetylcysteine (NAC) and with impact on the abundant intracellular antioxidant glutathione. They demonstrate that NAC is efficacious in both exercising humans and in vitro preparations.

The final three reviews examine applied integrative aspects of fatigue, covering hyperthermia (6), arterial oxygenation (2), and respiratory muscle function during exercise (7). Dr. Nybo (6) heats up the debate as he eloquently outlines the importance of hyperthermia-induced fatigue, contrasting mechanisms of exercise limitation during intense and prolonged exercise in humans. Cardiovascular limitations to high-intensity exercise performance with hyperthermia are apparent, with declines in cardiac output, muscle blood flow, and oxygen uptake. Hyperthermia during prolonged exercise is associated with a reduction in central activation, or central fatigue, which is progressive rather than an all-or-none phenomenon. Interestingly, Nybo also challenges the concept of a “critical core temperature” at which exercise cessation must occur in voluntary exercise. Convective oxygen transport has long been known to be a critical determinant of maximal oxygen uptake and exercise performance. Drs. Amman and Calbet (2) review the effects of oxygen availability on fatigue development and exercise performance, concluding that a reduction in oxygen supply exacerbates the development of fatigue via direct effects on both muscular performance and central nervous system motor activation and via inhibitory feedback from those muscles affected by reduced oxygen delivery. Finally, Drs. Romer and Polkey (7) provide an overview of the role of respiratory muscles in exercise limitation. Long considered the loyal servant of the cardiovascular and musculoskeletal systems during exercise, there is clear evidence that in certain exercise conditions, respiratory muscle fatigue occurs and can limit arterial oxygenation, with consequent effects on muscular and nervous system function (see Ref. 2). Furthermore, reflexes arising from fatigued respiratory muscles act to limit blood blow to active limb muscle, but in so doing enhance limb muscle fatigue and reduce exercise tolerance. These latter reviews elegantly demonstrate the critical interdependence between central and peripheral mechanisms in the development of fatigue and exercise limitation.

So how then do we understand this complex phenomenon known as fatigue? Clearly, fatigue during exercise can be viewed as a cascade of events occurring at multi-organ, multi-cellular, and at multi-molecular levels. The challenge for scientists is to understand how these mechanisms work together. The implications are profound as fatigue is important in exercise limitation, affects the whole of the community, and thus impacts on human health, economics, and sporting endeavors. Finally, all reviews include topics for future research, ensuring this series will have broad appeal and continuing impact.

REFERENCES