Neurobiology of muscle fatigue

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ENOKA, ROGER M., AND DOUGLAS G. STUART. Neurobiology of muscle fatigue. J. Appl. Physiol. 72(5): 1631-1648, 1992.—Muscle fatigue encompasses a class of acute effects that impair motor performance. The mechanisms that can produce fatigue involve all elements of the motor system, from a failure of the formulation of the descending drive provided by supraspinal curvatures to a reduction in the activity of the contractile proteins. We propose four themes that provide a basis for the systematic evaluation of the neural and neuromuscular fatigue mechanisms: 1) task dependency to identify the conditions that activate the various mechanisms; 2) force-fatigability relationship to explore the interaction between the mechanisms that results in a hyperbolic relationship between force and endurance time; 3) muscle wisdom to examine the association among a concurrent decline in force, relaxation rate, and motor neuron discharge that results in an optimization of force; and 4) sense of effort to determine the role of perceived effort in the impairment of performance. On the basis of this perspective with an emphasis on neural mechanisms, we suggest a number of experiments to advance our understanding of the neurobiology of muscle fatigue.

task; force-fatigability relationship; muscle wisdom; sense of effort

ONE PROMINENT CHARACTERISTIC of the neuromuscular system is its adaptability. When it is subjected to a chronic stimulus, such as immobilization, training, or aging, it can adapt to the altered demands of usage. These adaptations can be extensive and have been shown to affect most aspects of the system, both morphological and functional. Similarly, the neuromuscular system can adapt to more acute challenges, such as those associated with sustained activity. One of the best known acute adaptations is a phenomenon that is referred to as muscle fatigue (hereafter referred to as fatigue). To advance our understanding of the adaptive responses that we call fatigue, it is important that we identify a set of principles, including a definition, that can provide the basis for subsequent studies. However, although the literature on fatigue is extensive, its interpretation is confounded by the diversity of definitions and by the variety of paradigms that have been used to study it. Our perspective is to consider fatigue as a phenomenon that had its origin in the study of human performance (for historical precedents see Refs. 5, 171, 177, 187, 190, 220). In this context, fatigue is a general concept intended to denote an acute impairment of performance that includes both an increase in the perceived effort necessary to exert a desired force and an eventual inability to produce this force (79; for other definitions see Refs. 3, 16, 69, 90). Because of its link to human performance and the multidisciplinary interest in the study of fatigue, it does not seem appropriate or necessary to attribute more precision to the definition of fatigue. Rather, the study of fatigue should focus on the mechanisms that can contribute to an acute impairment of performance.

Not surprisingly, the notion that the neuromuscular system can be stressed to the point of exhaustion has intrigued numerous investigators, particularly in recent years. From these studies on fatigue have emerged at least four themes (task dependency, force-fatigability relationship, muscle wisdom, and sense of effort) that seem to provide a reasonable basis for future neural and neuromuscular work in this area, especially studies for which the requisite techniques are already available. Although many studies have been undertaken in an attempt to identify a single fatigue factor, there seems to be little doubt that the concept of fatigue refers to a class of acute effects that can impair motor performance and not to a single mechanism that can, under all conditions, account for the decline in performance. These observations have led to the notion that the mechanisms underlying fatigue are task dependent. Furthermore the fatigue mechanisms appear to cascade so as to exhibit a hyperbolic
relationship between force and endurance time (force-fatigability relationship) and to exert interactive effects on each other. One prominent interaction, which is referred to as muscle wisdom, concerns the parallel changes (slowing) in the rate of muscle relaxation and the discharge rate of motor neurons that accompanies a loss of force during sustained maximum or strong isometric contractions. Another significant, but less appreciated, interaction that influences motor performance involves the psychophysical phenomenon of the sense of effort and the force that is exerted during a sustained task. These issues can provide a conceptual basis for many studies on muscle fatigue. The purpose of this review is to describe these four themes (task dependency, force-fatigability relationship, muscle wisdom, and sense of effort) and their utility as a focus for subsequent studies on muscle fatigue. A preliminary account of some of these themes has appeared previously (213).

Task Dependency

This theme embodies the concept that fatigue is not the consequence of a single omnipresent mechanism but, rather, that it can be induced by a variety of mechanisms. The term “task dependency” accounts for the role of the details of the task in determining the underlying mechanism(s) and sites associated with fatigue. When the details of the task vary significantly, it appears that the mechanisms underlying fatigue also vary. Furthermore, for a given task, it seems that the mechanisms contributing to fatigue can vary as the task proceeds. Task variables that can be manipulated by an investigator and influence the prevailing mechanism include the level of subject motivation, the neural strategy (pattern of muscle activation and motor command), the intensity and duration of the activity, the speed of a contraction, and the extent to which the activity is continuously sustained. These features of the task influence such fatigue mechanisms as the central nervous system (CNS) drive to motor neurons, the muscles and motor units that are activated (neural strategy), neuromuscular propagation, excitation-contraction coupling, the availability of metabolic substrates, the intracellular milieu, the contractile apparatus, and muscle blood flow. The following discussion of the task dependency theme is intended to demonstrate that these diverse mechanisms can, under specific conditions, induce fatigue; the purpose is neither to provide a comprehensive review of each topic nor to identify the boundary conditions associated with various tasks.

Central drive. One popular technique that has been used to identify the role of various mechanisms in fatigue has been to compare the force that can be elicited by supramaximal electrical stimulation (imposed activation by the experimenter) with the force that the human subject can exert by voluntary activation. This approach typically involves applying single shocks or a brief train of shocks to the nerve supplying the test muscle to determine whether the force that is exerted voluntarily can be supplemented by the imposed stimulation (76, 113). During a 60-s maximum voluntary contraction (MVC), Bigland-Ritchie et al. (21, 24) found that the force exerted by the adductor pollicis decreased by ~30–50% but that this decline in force could not be supplemented by the imposed electrical stimulation. Similarly, when subjects performed an intermittent (6-s contraction, 4-s rest) task with the quadriceps femoris muscle for which the target force was 50% MVC, Bigland-Ritchie et al. (19) found that the maximal voluntary and electrically elicited force declined in parallel so that at the endurance limit (mean time 4.4 min) both the MVC and the electrically elicited force were equal to the 50% MVC target force. These observations suggest that the decline in force (i.e., fatigue) under these conditions was not due to an inability to provide the necessary motor neuron activation.

However, there appear to be at least four exceptions to the general notion that humans are able to generate an adequate central drive during fatiguing activity. First, to observe a parallel decline in the voluntary and imposed electrically elicited force, it is necessary that the subjects be well motivated and practiced at the task (19, 21, 22, 24, 31, 97, 110, 169). A lack of motivation or practice presumably results in an inadequate CNS drive to the appropriate motor neurons. Second, it seems that it is difficult, even in motivated subjects, to maintain a maximal central drive for some muscles, even in an unfatigued state (69, 76, 124, 176). For example, Belanger and McComas (6) found that subjects could maximally activate the tibialis anterior, as assessed by the twitch superimposition test, but that 10 of 17 male and 4 of 11 female subjects could not maximally activate the plantarflexors muscle. This limitation seems to be enhanced during sustained activity. When Bigland-Ritchie et al. (19) had subjects perform the intermittent (6-s contraction, 4-s rest) task to the 50% MVC target force with the soleus, they found at the endurance limit (mean time 35 min) that the MVC force had declined to 50% of the initial value but that imposed electrical stimulation elicited a force that was 77% of the initial value. Similarly, Thomas et al. (217) reported that well-motivated subjects had difficulty maintaining an MVC for 5 min with the tibialis anterior, even though the subjects could momentarily increase the force with voluntary activation when they were asked to do so. Despite recent electrophysiological advances, it has not been possible to extend the observations of the 1960s (reviewed in Ref. 186) that revealed a differential strength of corticospinal connections to motor neurons innervating different muscles. For this reason, in part, it is unclear why some muscles, and not others, are prone to this type of failure. Third, subjects appear to have greater difficulty activating all the motor units innervating a muscle during repeated maximal concentric (shortening) contractions than during eccentric (lengthening) contractions (75, 215, 225). Furthermore, activation failure appears to vary with contraction speed and is greatest for low-speed concentric contractions (159a, 180a). This effect may be due to changes in central drive and neuromuscular propagation. Fourth, during a simulated 40-day ascent of Mt. Everest in a hypobaric chamber, some subjects were unable to generate a maximum CNS drive, as assessed by twitch superimposition, during a sustained MVC (104). These observations on unmotivated subjects, muscle-specific effects, eccentric contractions, and altitude suggest that fatigue can be caused by an inability to generate the necessary CNS drive.

Neural strategy. Related to the observation that an in-
adequate CNS drive may contribute to fatigue is the possibility that some tasks may permit a subject to alter the neural strategy (i.e., muscle activation patterns, motor commands) and hence influence the time course of fatigue (66, 82a, 130, 196). Clearly, changes in the muscle activation patterns are possible only with tasks that involve submaximal forces. Such was the case when Sjøgaard et al. (203) had subjects sustain an isometric knee extensor force at a target of 5% MVC for 1 h. On the basis of measurements of intramuscular pressure and electromyogram (EMG) for rectus femoris and vastus lateralis, they found that the subjects often switched the activity among the muscles that comprise the quadriceps femoris group while maintaining the target force for 1 h. Sjøgaard and colleagues (203, 204) suggested that the fatigue (12% decline in MVC force and increase in effort) associated with this task was due to a decrease in muscle cell excitability that was caused by a loss of K+ from the cells. It is possible, however, that these effects were minimized by the option the task afforded the subjects to vary the activity among the quadriceps femoris muscles. Although it has never been examined, the switching of activity during fatigue may occur within parts of a muscle, because we know that some muscles (e.g., biceps brachii, biceps femoris, sartorius, semimembranosus) consist of discrete compartments (219, 228). This seems most likely in muscles with distributed attachments, in which changes in the direction of the force vector can be associated with changes in motor unit activity (81).

Another, more speculative, example of a change in the muscle activation pattern is the possible rotation of motor units during fatiguing activity. Motor unit rotation would provide periods of inactivity that could be used for the replenishment of metabolic needs. The concept of orderly recruitment implies that once a motor unit has been recruited it will remain active as long as the force exerted by the muscle exceeds the threshold force of recruitment for the unit. Although most investigators accept this assumption, there were early suggestions that a muscle could minimize fatigue by rotating some of the active motor units (85, 201). Some evidence of this possibility was provided by Person (184) among the motor units of rectus femoris during an isometric knee extensor task. Furthermore, Enoka et al. (78) examined motor unit behavior during a ramp-and-hold task that was performed before and after a fatiguing contraction and found that some low-threshold motor units were not active after the fatiguing activity although the task was identical to that performed before the fatigue task. This variation in motor unit recruitment was interpreted as reflecting some degree of history-dependent flexibility in recruitment order among these motor units (see also Ref. 184), which is consistent with the concept of motor unit rotation. This possibility adds a new dimension to the strategies available to the motor system to accommodate demanding activity.

Associated with the fatigue-related flexibility in motor unit behavior (i.e., recruitment order, discharge rate, and discharge pattern), there is emerging evidence that the activation of a motor unit pool may vary with the relative magnitude of the muscle and load torques. When the muscle torque is less than the load torque, the active muscle shortens in what is referred to as a concentric contraction. Conversely, when the muscle torque is greater than the load torque, the active muscle shortens in what is referred to as an eccentric contraction. It seems that it is difficult to generate a maximal CNS drive to the motor unit pool under eccentric conditions, at least in comparison to that achieved in concentric conditions (75, 215, 225). Furthermore, when a contraction changes from the shortening (concentric) of active muscle to lengthening (eccentric), there can be a change in the motor units that contribute to the muscle force (178). More work is needed to determine the generality of these observations, the mechanisms underlying the variability in motor unit recruitment, and the susceptibility of these mechanisms to the effects of fatigue.

In addition to changes in muscle and motor unit activation patterns, fatigue-related changes in the neural strategy can include alterations in the motor command. These changes can affect both the quantity and the quality of the motor command. Clearly, when a subject is required to sustain a maximal force for a given duration, the subject does not have the option of increasing the magnitude of the motor command as the force declines. In contrast, when the task involves a submaximal contraction, the subject is able to increase the motor command to counteract the reduction in force due to peripheral (e.g., neuromuscular propagation, contractile apparatus) mechanisms. This strategy is used frequently during submaximal fatiguing contractions and is evident as an increase in the discharge rate of active motor units and the recruitment of additional units (17, 161). The actual expression of the increase in motor command, however, will vary among muscles because of differences in the upper limit of motor unit recruitment (144).

Although much less is known about the qualitative features of a motor command, it does appear that relatively minor changes in a task are accompanied by significantly different motor commands. For example, the motor command that elicits a one-legged isometric MVC (concurrent knee and hip extension) appears to be different from the command associated with a two-legged MVC. Rube and Secher (197) examined the fatigability of subjects during the performance of one- and two-legged MVCs before and after they completed a 5-wk training program with either the one- or two-legged task. The training resulted in a reduction in fatigability, but the effect was specific to the training task; that is, those subjects who trained with the two-legged MVC became less fatigable with this task and not with the one-legged task. Although both legs were trained with the two-legged task, the subjects were less fatigable only during the two-legged MVC and not when either leg was activated by itself. This observation suggests that the motor command for the two-legged MVC is sufficiently different from that for the one-legged MVC. Clearly, more work is needed on this issue to determine the specificity and adaptability of motor commands.

**Neuromuscular propagation.** In studies that have compared the voluntary and imposed electrically elicited force, the protocol has also often included measurements to determine whether neuromuscular propagation failure is associated with the decline in force. The most common
approach has been to measure the electrical response in the muscle (M wave) to the imposed electrical stimulation. The M wave consists of the synchronous sum of many muscle fiber action potentials that are elicited by the electrical stimulation. Because the M waves are always initiated by action potentials that begin in the motor axons at the level of mixed nerves or muscle nerves, changes in the M wave indicate alterations in neuromuscular propagation between the site of initiation (nerves) and the site of recording (muscle fibers). Despite the simplicity of this scheme, there remains a controversy over whether the M waves change with fatigue. Although some studies have reported that M waves do not decrease during a 60-s MVC (21, 24, 141, 145, 217), others have shown that the M waves do decrease with sustained activity (8, 158, 209, 232; A. J. Fuglevand, K. Zackowski, K. Huey, and R. M. Enoka, unpublished observations). This discrepancy may be partially due to differences in the tasks performed to induce fatigue. Low-force long-duration contractions have been shown to induce greater M-wave depression than high-force contractions (Fuglevand et al., unpublished observations).

One possible explanation for the decline in M waves could be a reduction in the excitability of the muscle fiber membranes. This could be accomplished by fatigue-induced accumulation of K+ and depletion of Na+ from the extracellular spaces. With electrical stimulation of isolated mouse muscle, Jones and colleagues (132) demonstrated that it is possible to mimic the rapid force decline with high-frequency imposed stimulation by reducing the Na+ concentration in the bathing medium. Similarly, muscle action potentials were diminished by increasing the extracellular concentration of K+ (131). Furthermore, Bezanilla et al. (13) demonstrated that manipulation of Na+ in the medium bathing single muscle fibers could prevent myofibrillar contraction, which they attributed to a failure of action potential propagation in the t-tubules. This effect, however, does not seem to be limited to high-frequency conditions, because although human subjects can sustain a 5% MVC for 1 h, this is accompanied by an extracellular accumulation of K+ (202) and fatigue-related significant increases in EMG amplitude and decreases in the mean frequency of the EMG power spectrum (135).

Excitation-contraction coupling. When the task is such that performance is not impaired by subject motivation, changes in the neural strategy, or reduction in the M waves, then the decline in force must be caused by other mechanisms. Bigland-Ritchie et al. (17) examined this condition with intermittent (6-s contraction, 4-s rest) submaximal (30% MVC) isometric contractions of the quadriceps femoris. During the first 30 min of the task, the MVC force and electrically elicited force declined in parallel to 50% of the initial value, yet there were no significant changes in muscle lactate, ATP, or phosphocreatine and the glycogen depletion was minimal and confined to the type I and IIA fibers. The decline in MVC force could not be explained by an inadequate central drive (M waves), acidosis, or lack of metabolic substrates. However, there was a disproportionate decrease in the electrically elicited twitch compared with the tonic (50-Hz) responses and MVC, which Bigland-Ritchie et al. interpreted as evidence of impaired excitation-contraction coupling. On the basis of this rationale, the decline in MVC force under these conditions was probably caused by a disruption of the link between activation of the muscle fiber membrane and the force exerted by the fibers.

Another widely accepted example of excitation-contraction coupling failure involves a standard test of motor unit fatigability (35). In this protocol, isolated single motor units are activated with 330-ms trains of stimuli (40 Hz) at a rate of once per second for 2 min (120 trains). When subjected to this regimen, some motor units [fast-twitch fatiguable (type FF)] fatigue and exhibit a marked decline in force while other motor units [fast-twitch fatigue resistant and slow-twitch (types FR and S)] do not fatigue. Although the type FF units can exert little force after 2 min, the EMG (compound muscle action potential) measured during the test shows little decrease below initial values (80, 115, 129). Because it has not yet been shown that 2 min of this stimulation can deplete the muscle fibers of metabolic substrates, cause marked alterations in the concentrations of various metabolites, or impair the contractile machinery, the fatigue is generally attributed to a mechanism related to excitation-contraction coupling (114, 115, 129).

Although a failure of excitation-contraction coupling has also been implicated in other experimental protocols (62, 65, 73, 129, 174), little is known about the relative contribution of the specific mechanisms. In a thorough review of the possible excitation-contraction coupling mechanisms, Fitts and Metzger (84) summarized the transformation of an action potential into cross-bridge activity as involving seven steps: 1) the sarcolemmal action potential, 2) t-tubular charge movement, 3) coupling of t-tubular charge movement with Ca2+ release from the sarcoplasmic reticulum, 4) Ca2+ release from the sarcoplasmic reticulum, 5) reuptake of Ca2+ by the sarcoplasmic reticulum, 6) Ca2+ binding to troponin, and 7) actomyosin hydrolysis of ATP and cross-bridge cycling. Changes in the intracellular milieu with fatigue seem to reduce the magnitude of the Ca2+ transient (step 4) (1, 28) and to impair the Ca2+-adenosinetriphosphatase-mediated Ca2+ uptake into the sarcoplasmic reticulum (step 5) (1, 57, 148, 224). The decline in the magnitude of the Ca2+ transient could be due to a decrease in the t-tubular charge movement (but this is unlikely) (15), inhibition of the coupling step, or impairment of the release process. Some evidence favors the latter mechanism and may involve an increased inactivation of the Ca2+ release channel and depletion of Ca2+ stores in the sarcoplasmic reticulum (28, 84, 222). Furthermore the observed decrease in the rate of Ca2+ reuptake into the sarcoplasmic reticulum may combine with an increased intracellular binding of Ca2+ to parvalbumin, troponin C, and the sarcoplasmic reticulum pump (224) to reduce the Ca2+ concentration gradient across the sarcoplasmic reticulum. The net effect of a reduction in the Ca2+ concentration gradient would be to diminish the flux of Ca2+ across the sarcoplasmic reticulum in response to t-tubular charge movement. However, the contribution of these mechanisms to muscle fatigue in vivo remains to be determined (84).
Despite the uncertainty concerning the relative contributions made by the specific mechanisms to the decline in force, the process of excitation-contraction coupling has been implicated in several reports on fatigue. A common strategy for assessing the impairment of excitation-contraction coupling has been to monitor the recovery from fatigue. In these experiments, the force loss due to impaired excitation-contraction coupling appears to be significant, to be most evident after contractions of long duration, and to recover slowly (30-60 min) (73, 148, 147, 172). Some evidence suggests that the depression in tetanic force after contractile activity may be due to an impairment in the coupling of the t-tubular charge movement to sarcoplasmic release of Ca\(^{2+}\) (222). In comparison, recovery of force loss due to metabolite-induced impairment of cross-bridge function seems to occur rapidly (~2 min) (147, 174, 198), as does recovery from impaired neuromuscular propagation (4–6 min) (Fuglevand et al., unpublished observations, 174). Furthermore, the mechanisms underlying the reduction in force appear to depend on the details of the task and can involve an impairment of several processes, including excitation-contraction coupling (Fuglevand et al., unpublished observations; 147, 174, 188). Experimental studies are required to define the task-dependent boundaries that activate the various mechanisms that cause a reduction in force, including an evaluation of the extent to which they are activated sequentially.

**Metabolic substrates.** As described by Edwards and Gibson (71), muscle force will decline when energy demands cannot be met by the rate of supply of ATP and the metabolites generated by contractile activity (e.g., ADP, P\(_i\), H\(^+\)) influence cross bridge activity or the supply of energy. Although the decline in force is not always associated with a depletion of metabolic substrates (17, 202), the extent of the dissociation seems to depend on the intensity of activity. Hermansen et al. (120) found that when subjects exercised (cycle ergometer) at a rate of 70–80% of maximal aerobic power, exhaustion coincided with glycogen depletion in the muscle fibers of lateralis indicated that intermittent stimulation was associated with an increase in ATP utilization. Bergström and Hultman (11) estimated that ~40% of the energy cost of a 1-s tetanus was attributable to the development and relaxation of force. These results indicate that under anaerobic conditions the force elicited with continuous stimulation is more economical than that produced with intermittent stimulation. However, when the test muscle (adductor pollicis) was not ischemic, Duchateau and Hainaut (65) found that the decline in the electrically elicited (30-Hz) force was similar with continuous and intermittent (1-s activation, 1-s rest) stimulation. From other experiments involving aerobic conditions and the use of reduced anesthetized animal preparations, there is evidence of a lower rate of cross-bridge formation during the steady-state phase of the tetanus than during its rising phase (33, 51, 153, 221). Therefore it appears that the energy cost of a task is influenced by whether the exerted force is intermittent or continuous and that this effect is modulated to some extent when the blood flow to the muscle is occluded.

As a complement to the study of energy supply and its role in fatigue, many investigators have examined the effects of the products of ATP hydrolysis on the decline in force. One early candidate for a prominent role in fatigue was lactic acid. However, the consensus now appears to be that an elevation of H\(^+\) concentration is more critical than lactate or the undissociated lactic acid (84). Furthermore, although H\(^+\) can inhibit glycolysis, this interaction does not appear to be a major mechanism underlying the decline in force (84). One fruitful approach to identifying the role of H\(^+\) in fatigue has been to reduce the intracellular pH in single intact muscle fibers by increasing the CO\(_2\) in the extracellular medium; the extent of the reduction in pH (7.0 to 6.6) is similar to that observed in humans during fatiguing contractions (147). On the basis of such studies, it appears that intracellular acidification results in a moderate decline in the number of attached cross bridges and a decrease in the force exerted by each cross bridge (68, 147). Qualitatively similar observations have been reported in studies on skinned muscle fibers (44, 50); however, there may be some differences between the two preparations in the magnitude of the H\(^+\)-induced decline in force (147).

Edman and Lou (68) suggested that although intracellular acidification is responsible for much of the altered mechanical performance of muscle with fatigue, the elevated H\(^+\) concentration does not provide a complete explanation of the changes. This reservation is based on the discrepancy in the stiffness of muscle fibers after intracellular acidification and fatiguing contractile activity. Probably, the other products of ATP hydrolysis (Mg-ADP and P\(_i\)) are able to modulate cross-bridge behavior. For example, an increase in the concentration of P\(_i\) has been shown to reduce maximum isometric force but not to affect the maximum speed of shortening (44, 50). Conversely, an increased concentration of Mg-ADP causes a
small increase in maximum isometric force and a modest decline in the maximum speed of shortening (50). Subsequent studies will undoubtedly address the interactive effects of changes in these products.

From these studies on the role of metabolism in fatigue, it seems reasonable to conclude, as with the other factors considered with this theme, that given the appropriate conditions an impairment of metabolism-related processes can contribute to the decline in force during fatiguing activity. Furthermore it appears that factors related to both the supply of energy and the accumulation of metabolites can contribute to this force reduction.

Summary. When the results from these various paradigms and protocols are considered together, it is apparent that the decline in force associated with fatigue can be caused by many different mechanisms. In fact, it appears that it is possible to design an experimental protocol for which any of the identified mechanisms can contribute to fatigue. Furthermore the data suggest that it is the details of the task that will largely determine the relative contribution of the different mechanisms to fatigue. There remains, however, a great deal of work to be done on this theme to identify the boundary conditions for each mechanism and to determine whether various reduced preparations appropriately mimic the function of an intact organism. Studies are needed to 1) identify the association between task variables and fatigue, 2) characterize the time course and interaction between the fatigue mechanisms within tasks (Fuglevand et al., unpublished observations; 147, 151, 174), 3) assess the generality of the observations for different motor systems (e.g., limb, respiratory, visual, speech), and 4) determine which mechanisms are important in human performance.

**Force-Fatigability Relationship**

Although some work has suggested that it is possible to sustain low-level isometric contractions indefinitely (193), most evidence indicates that activation of the neuromuscular system at any intensity will eventually elicit fatigue (203, 218). The greater the force exerted during a task, the more rapidly the muscle fatigues (9, 47, 151, 193). Although such a relationship might be anticipated, it does raise at least two interesting issues about the mechanisms underlying fatigue. First, on the basis of the rationale associated with task dependency, the observation of a generalized force-fatigability relationship suggests that the mechanisms causing fatigue interact in such a way that they scale with force. The multi-mechanism basis of the task dependency observations suggests that the force-fatigability relationship is not a simple extrapolation of motor unit force-fatigability relationships. Second, the tests that characterize motor unit fatigability (35, 107, 199) generally stress one, or perhaps two, fatigue mechanisms but not the complete set that span the force-fatigability relationship. Studies related to this theme need to address the role of the various fatigue mechanisms in defining the force-fatigability relationship.

Classical tests of muscle endurance, which involve a sustained isometric contraction, have typically revealed a hyperbolic relationship between force and endurance time. For example, when the jaw-closing muscles sustain an isometric force at various levels, the associated endurance times are inversely related to the magnitude of the force (47, 48, 143). Similarly, Bellemare and Grassino (9) found an inverse relationship between the magnitude of the transdiaphragmatic pressure during inspiration and the fatigue time constant (i.e., endurance time). Furthermore, when the duty cycle was increased (9, 150), which amounts to an increase in the work performed or the force-time integral for isometric contractions, the rate of fatigue increased (i.e., a decrease in endurance time). In a similar vein, when the duty cycle was held constant and the frequency of imposed stimulation was varied (15 or 30 Hz), Garland et al. (100) found that there was more fatigue when the force-time integral was greater. The rate of fatigue has also been reported to increase when the duty cycle was increased (65) or the duration of the cycle decreased (11), which suggests that the rate of energy utilization for intermittent contractions also influences the decline in force. Such observations suggest that the greater the force exerted, work done, or rate of work performance during a task, the greater the fatigue experienced by the muscle.

A central feature of the force-fatigability relationship seems to be its dependence on the absolute force exerted during the task. McKenzie and Gandevia (168) had subjects perform intermittent isometric contractions with either the elbow flexor or inspiratory muscles at two different muscle lengths: the optimal length and a shorter length that reduced the MVC force by 25%. Although the maximal absolute force was different at the two lengths, the subjects performed the intermittent task at the maximum voluntary force for each length. Fatigability was assessed as the decline in peak force after a series of 18 MVCs. Although the inspiratory muscles were less fatigued at the optimal length (final force: short length = 81% of initial; optimal length = 87%), the elbow flexor muscles were less fatigued at the shorter length (final force: short length = 61%; optimal length = 55%). Fitch and McComas (82) similarly found a greater fatigability (decline in electrically elicited torque) for tibialis anterior at its optimum length. These observations indicate for the limb muscles that although the relative force was the same at each length (i.e., for an MVC) and the muscles exhibited different amounts of fatigability, the absolute force was different and fatigability varied in direct proportion to the absolute force, as predicted by the force-fatigability relationship.

Although the force-fatigability relationship has appeared robust in a variety of experimental conditions, it appears that it is possible to alter the relationship by varying the rate and pattern of the imposed electrical stimulation. Although the rate of muscle activation has long been known to influence fatigability, it is now apparent that the pattern of activation can also have a significant effect on the decline in force. As expected for the generalized force-fatigability relationship, the rate and amount of force decline both increase with the frequency of electrical stimulation, both for whole muscles (23, 132) and for single motor units (199). This effect presumably involves a force-dependent sequential activation of the
mechanisms underlying fatigue (e.g., failure of neuromuscular propagation, excitation-contraction coupling) (23, 73, 199). However, when the imposed stimulation frequency is systematically reduced, there is less of a decline in whole muscle force (26, 130, 132). By simply changing the activation pattern, it is possible to significantly alter the force-fatigability relationship, so that from the same initial force there can be different amounts of fatigability. Presumably this effect is the result of a change in the dominant fatigue mechanism, such as a failure of action potential propagation with high-frequency stimulation and a failure of excitation-contraction coupling with low-frequency stimulation. The frequency-dependent change in the fatigue mechanism results in a change in the force-frequency relationship with fatigue, such as a decline in the force elicited with low but not high frequencies of stimulation (52, 73, 129, 199).

In addition to these whole muscle experiments, a pattern effect has been demonstrated at the level of the motor unit with only subtle changes in the activation pattern (12). In these experiments, which are an extension of work on the catchlike property of single motor units (36; 206; 231), Stuart and colleagues (12) compared the fatigability of type FF motor units with two stimulus regimens: one that comprised a constant submaximal frequency and another that rearranged the stimuli to optimize the force but retain the same average frequency. Repetitive activation with the optimized stimulus regimen resulted in a greater initial force and less fatigability, which contradicts the expectation based on the generalized force-fatigability relationship. It remains to be shown whether this observation reflects a change in the dominant fatigue mechanism or less stress on the prevailing mechanism(s).

Although chronic adaptations associated with alterations of the normal patterns of usage can change the fatigability of muscle, there are no systematic studies on the effects on the force-fatigability relationship. While endurance training is known to decrease fatigability (61, 138), it appears that the muscle atrophy associated with various reduced-use regimens does not cause the muscle to become more fatigable, but instead the muscle may become less fatigable (89, 111, 122a, 173, 178a, 192, 212). This reciprocal change in force and fatigability is consistent with the force-fatigability relationship. However, the dissociation between changes in maximum force and fatigability may be due to the selective impairment of high-threshold fatigable motor units following a reduced-use protocol (65a). A potentially informative experimental strategy would be to characterize the force-fatigability relationship and the time course of changes in muscles that had undergone various chronic perturbations with the intent of identifying the adaptability of the various mechanisms that underlie fatigability.

Summary. A generalized force-fatigability relationship seems to be valid for most, but not all, experimental conditions that have been examined. According to this relationship, the greater the force exerted by a muscle, or a motor unit, during a given task, the more the muscle will fatigue. Presumably the mechanisms underlying fatigue vary with the level of the force that is exerted. Studies are needed that 1) systematically explore the force-fatigability relationship, 2) characterize local regions of the force-fatigability domain where the relationship is nonmonotonic, 3) identify the mechanisms that predominate at various levels of force, 4) assess the interactions between the fatigue mechanisms that produce the hyperbolic relationship between force and endurance time, and 5) use the force-fatigability relationship as a probe to examine adaptations in the motor system that are associated with short-term changes in the activation pattern and chronic perturbations such as long-term activation patterns, immobilization, exercise training, and aging.

**Muscle Wisdom**

As fatigue proceeds in conscious humans during both MVCs and imposed contractions (electrical stimulation with a selected pattern), there is a progressive decrease in the rate of relaxation in whole muscle (21, 72, 126), single motor units (35, 64, 107, 188, 216), and single muscle fibers (1, 147); a reduction in motor neuron discharge rate and in the frequency of activation necessary to elicit the maximum force (20, 61); and, for a given submaximal frequency, a greater degree of fusion in the force (110, 132, 158). For example, the original work (Fig. 1A) demonstrated that the decline in force during a 60-s MVC of adductor pollicis could be mimicked by a reduction in the stimulus frequency (60 to 20 Hz) used for the electrically elicited force (132). Furthermore, Binder-Macleod and colleagues (25, 26) showed that the force elicited in quadriceps femoris with imposed variable-frequency (60- to 30-Hz) electrical stimulation decreased less than that with a constant-frequency (60-Hz) protocol, which suggests that the reduction of the stimulus frequency serves to optimize the submaximal force (Fig. 1B). Similarly, Bottomer and Cope (32) found that to sustain a submaximal force (25% of maximum) it was necessary to reduce the stimulation rate of fast-twitch motor units. This association of a concurrent decline in force, relaxation rate, and motor neuron discharge rate has been referred to as...
Immediately after a period of stimulation and then to the right after fatigue; a, after fatigue). Functional significance of this adaptation is that although maximum force declines with fatigue, a submaximal stimulus frequency-force relationship will elicit a greater proportion of current (normalized) maximal force when relationship is shifted to the left. (Adapted from Fitts et al. (83).) B: stimulus frequency-force relationship is not shifted to the left for human quadriceps femoris, and at some frequencies of stimulation relationship is shifted to the right, exhibiting low-frequency fatigue, (i.e., before fatigue, i.e., after fatigue). These data represent shift in relationship when fatigue was induced by electrical stimulation of quadriceps femoris. The same result was found when fatigue was induced by voluntary activation of muscle (27). These data indicate that effect of fatigue on stimulus frequency-force relationship is unresolved. (Adapted from Binder-Macleod and McDermont (27).)

“muscle wisdom” (157, 158). The functional significance of muscle wisdom is that it optimizes the force and ensures an economical activation of fatiguing muscle by the CNS.

The ability to replicate the decline in MVC force by reducing the stimulus frequency has been hypothesized to result from a leftward shift of the stimulus frequency-force relationship (Fig. 2A). The basis of this rationale is that if the time course of the twitch increases, then the activation rate can decline and it is still possible to achieve the same degree of fusion of the twitch responses. Bigland-Ritchie et al. (21) proposed, albeit on the basis of limited data (their Fig. 4), that fatigue causes a leftward shift in the normalized stimulus frequency-force relationship because of changes in the time course of the twitch with fatigue. Accordingly, Fitts et al. (83) reported that the optimal frequency for the frog semitendinosus muscle decreased from 150 to 60 Hz after 5 min of electrical stimulation (Fig. 2A). However, other experimental observations on both motor units (199, 216) and whole muscles (10, 27) showed that the stimulus frequency-force relationship normalized to the maximum force does not always move to the left with fatigue (Fig. 2B; see also Ref. 52). Rather, depending on the fatigue regimen, the relationship may move to the right for some stimulus frequencies (Fig. 2B).

At the motor unit level, in both conscious humans (216) and experimental animals (188), the stimulus frequency-force relationship seems to move in opposite directions as a function of motor unit type. Powers and Binder (188) found that the stimulus frequency-force relationship for type FR motor units moved to the left immediately after a period of stimulation and then to the right after ~30 min of recovery. In contrast, the stimulus frequency-force relationship for type FF motor units simply moved to the right. Because the activation of muscle is known to influence processes that both potentiate and diminish force (Fuglevand et al., unpublished observations; 103, 108, 129, 142, 179, 189), Thomas et al. (216) make the reasonable suggestion that the differences among motor units in the shift of the stimulus frequency-force relationship depend on the balance between the time courses of fatigability and potentiation for each unit. Because whole muscle responses represent the weighted average of the constituent motor unit responses, this variability among motor units raises the issue of how various tasks influence the direction of the shift in the stimulus frequency-force relationship for the whole muscle.

Most of the evidence on the activation patterns associated with muscle wisdom has been derived from studies of whole muscle and populations of motor units (18, 105). Largely because of technical limitations, much less is known about the contribution of single motor units to this phenomenon. Because muscle wisdom has been mimicked by reducing the stimulus frequency, it was anticipated that evidence of a fatigue-related decline in motor unit discharge would be forthcoming. Although some investigators (30, 94, 110, 158) reported an expected decline in the discharge rate of single motor units during maximal and submaximal sustained contractions, others have observed either no reduction in discharge rate (161) or a variety of discharge patterns in single motor units, including an increase in discharge rate (31, 63, 102, 105, 161, 182) during sustained submaximal contractions. Consequently, although the net discharge (based on measurements for populations of motor units) appears to decline with sustained activity, there can be substantial variability at the level of individual motor units.

On the basis of the population responses, therefore, it seems that the muscle wisdom theme is associated with a concurrent decline in force, relaxation rate, and motor neuron discharge rate that optimizes muscle force and ensures the economical activation of fatiguing muscle by the CNS. Although the prolongation of the twitch and the increased sluggishness of the muscle may be appropriate for isometric conditions, they do not seem optimal for rhythmic activities, such as locomotion. The slower relaxation of muscle will increase the energy consumed by a muscle as it works against antagonist muscles. This requisite coactivation will increase the energy cost of a task and will result in a decrease in the net torque exerted about a joint for a given level of muscle activation. Clearly the muscle wisdom theme needs to be extended to dynamic conditions to determine whether the adaptations parallel those observed under isometric conditions.

Sensory feedback hypothesis. In principle, the muscle wisdom-associated change in motor neuron discharge with sustained activation should be mediated by some combination of afferent feedback from peripheral sources, adaptation in the discharge rate of segmental interneurons and motor neurons, and changes in descending commands from suprasegmental centers. Sayers forth proposed that “in fatigue the active units usually decrease in frequency . . . [which] might be due to afferent impulses sent from the fatigued muscle to the spinal medulla . . . This view appears to be supported by the results of the ischaemia experiments” (Ref. 201, p. 46). Bigland-Ritchie et al. similarly suggested that “during fatigue, motoneurone firing rates may be regulated by a
peripheral reflex originating in response to fatigue-induced changes within the muscle” (Ref. 18, p. 451), which has been referred to as the sensory feedback hypothesis (213).

Although some indirect evidence has implicated small-diameter afferents (group III/IV) in the reflex inhibition of motor neurons during fatigue (99, 101), the discharge of many slowly conducting group III/IV mechanoreceptor afferents declines during the initial phase of fatigue (117, 118). Alternatively, because motor units do not exhibit a decline in discharge rate during sustained activity until recovery from anesthetic block is complete, which suggests that small-diameter axons are involved, Bon giovanni and Hagbarth (30) proposed that the decline in discharge rate from a high initial value depends on disfacilitation (i.e., a reduction in fusimotor-driven feedback from muscle spindles; see also Ref. 229). Subsequently, direct evidence in favor of this possibility was reported by Macefield et al. (156), who found that the discharge of most muscle spindle afferents decreased by ~50% during sustained submaximal isometric contraction of the human dorsiflexor muscles. These observations suggest that the fatigue-related decline in motor unit discharge does include a peripheral component (94), but the relative roles and time courses of reflex inhibition mediated by small-diameter afferents and disfacilitation of the motor neuron pool are unresolved. One possibility is that “a decline in motoneurone firing rate during the first 5–10 s of a maximal voluntary contraction may reflect the reduction in muscle spindle input and increase in presynaptic inhibition, while metabolic effects exerted reflexly through small-diameter afferents contribute more later in the contraction” (90).

At present, there are conflicting observations on the effects of fatigue on the sensitivity of large-diameter proprioceptive afferents and their spinal reflex efficacy. Initial results on the sensitivity of muscle spindle afferents in anesthetized reduced animals are generally in agreement, with fatigue shown to enhance the responsiveness of group Ia and II afferents to single motor unit contractions (46, 77, 233; cf. 190). However, evidence from conscious humans indicates that fatigue results in a decline of fusimotor drive to muscle spindles (30) as well as other mechanisms that may contribute to a reduction in spindle discharge during sustained isometric contractions (156). The effects of fatigue on the group Ib tendon organ afferent are also uncertain. In studies on reduced animals, there is evidence of little (208) or no (109) change in tendon organ responsiveness, whereas there appears to be a reduction in group Ib responsiveness to whole muscle stretch (128) and a reduction in contraction-induced group Ib autogenic inhibition in motor neurons (233). There is similar uncertainty concerning the spinal reflex efficacy of this sensory input. Some evidence suggests that fatigue enhances the efficacy of short- and long-latency reflex EMG and motor neuron responses to brief muscle perturbations (55, 139, 227), but these results appear to be contrary to other reports (54, 112, 127). Studies are needed that examine the effects of type-identified motor units on afferent fibers during fatigue in reduced animals (77) and conscious humans (226); the interactions among proprioceptive feedback, recurrent inhibition, and motor neuron adaptation in experimental animals (229); and analysis of spinal reflex transmission in interneuronal pathways in the conscious human, with use of recently developed techniques (86).

In the formulation of the sensory feedback hypothesis, it was also emphasized that “The decline in motoneurone discharge rates seen during fatigue of a sustained m.v.c. may result primarily from changes in central motoneurone excitability; the time course of frequency changes is quite similar to that reported by Kurnell and colleagues for changes in the discharge rates of cat single motoneurons in response to constant current injection” (Ref. 18, p. 458). Kurnell and Monster (137, 138) certainly provided convincing evidence that the intracellular injection of a sustained depolarizing current elicits, in the presence of an after-hyperpolarization in the action potential, a progressive reduction in the discharge rate of motor neurons in a deeply anesthetized adult cat. This adaptation, which has been termed late adaptation, is more prominent in larger motor neurons and, for the same cell, it is more pronounced at higher initial discharge rates (137, 183, 205). It is important to emphasize, however, that these results were obtained in deeply anesthetized cats, whereas the sensory feedback hypothesis is based on the voluntary contractions of humans. It has been argued that the afterhyperpolarization and its obligatory late adaptation are unlikely features of motor neuron discharge during voluntary contractions (205, 206). On the basis of these various results, there is a need for substantially more work on discharge rate adaptation and its association to the sensory feedback hypothesis. The change in motor neuron discharge during fatigue undoubtedly involves an interaction between intrinsic motor neuron properties and synthetically mediated effects associated with muscle activation (i.e., as attributable to descending command signals, interneuronal pattern generation, and sensory feedback).

Despite the uncertainty of the mechanisms underlying the change in motor unit discharge during fatigue, they undoubtedly exert a powerful effect on the activity of the motor neuron pool. When a human subject sustains a submaximal force to exhaustion, the whole muscle EMG increases, yet motor unit discharge appears to decline (18, 102, 185). Consequently, the increase in EMG is generally attributed to an increase in the recruitment of motor units. This means that, for a given excitatory drive to the motor neuron pool during fatigue, there is a dissociation between the recruitment and discharge rate of motor units. In contrast, increases in muscle force during nonfatigue conditions are accomplished by concurrent increases in motor unit recruitment and discharge rate (214). Fatigue-inducing activity, therefore, must activate some influential processes, either related to intrinsic motor neuron properties or synthetically mediated effects, that permit an excitatory drive to recruit motor units yet for discharge rate to decline. Furthermore, these effects seem to be capable of influencing nonfatigued synergist muscles (116).

Although most attention has focused on potential roles of intrinsic motor neuron properties and synthetically mediated effects in the decline of motor unit discharge, a
contribution from a reduction in central drive cannot be excluded. Formulation of the sensory feedback hypothesis was based on observations of a decline in the discharge of motor unit populations in biceps brachii during sustained MVCs (18, 201, 230). Because the subjects were highly motivated and practiced at the task and on the basis of the twitch superimposition technique, it was assumed that central drive was maximal throughout the task. Subsequently, Garland and McComas (101) demonstrated a reduction in the excitability of soleus motor neurons (H reflex) in response to an imposed (electrical) intermittent stimulation regimen that induced fatigue. Although this evidence implicates a peripheral reflex mechanism in the diminution of motor unit discharge, it does not eliminate a role for a decline in the central drive. Along these lines, Maton (160) recorded from cells in area 4 of the motor cortex of monkeys as they exerted repetitive isometric elbow-flexion torques (duration 2–10 s). On the basis of spike-triggered averaging, the cortical cells were shown to be associated with the EMG of the muscles that cross the elbow joint. Maton examined the change in cortical cell discharge and the EMG power spectrum from the 1st to the 20th repetition. As with the motor unit studies, cortical cell discharge was found to decrease, remain constant, or increase as the EMG power spectrum changed. This suggests that motor neuron discharge may also be modulated by descending signals during fatiguing contractions.

Summary. Although the adaptability of motor unit discharge seems to be well established at the level of whole muscle, there is less certainty about whether all motor units contribute to this effect, and the relative significance of the mechanisms (sensory feedback, spinal neuron adaptations, descending modulation) that control the change in motor unit behavior remains to be determined. Studies are needed (1) to examine the discharge behavior of single motor units in various fatiguing tasks, including dynamic conditions, 2) characterize fatigue-related changes in the efficacy of spinal reflex pathways, 3) quantify fatigue-induced changes in the transducing properties of various afferent species, 4) determine the functional significance of spinal neuron adaptation and its potential relation to more peripheral mechanisms of discharge rate adaptation, and 5) assess the role of descending modulation of motor neuron discharge during fatiguing activity.

Sense of Effort

Whenever a human subject is asked to sustain a submaximal force for an extended period of time, such as holding a heavy briefcase while waiting for a bus, the first hint that this task cannot be accomplished indefinitely is not an inability to exert the necessary force but, rather, a perception that it is necessary to increase the effort associated with the task (93, 133, 162, 165, 166). It is even possible, especially with some clinical conditions, for an individual to report an effort-related fatigue but with no impairment of the ability to exert force (152, 211). The effort associated with performing a task is assessed by requiring subjects to match forces. It seems that subjects’ judgments are based on the effort required to generate a force rather than the absolute magnitude of the force that is exerted. This judgment is referred to as the sense of effort and is distinct from the force sensation associated with a contraction. Because increased effort and force failure are associated with an impairment of motor performance, they are both regarded as essential features of fatigue. Accordingly, any physiological process that contributes to either of these features can be described as a fatigue mechanism.

Corollary discharge. Three lines of experimental evidence suggest that the sense of effort appears to be strongly influenced, if not totally dependent, on centrally generated corticofugal motor commands that give rise to corollary discharges (2, 39, 123, 167). Corollary discharges are defined here as “the internal actions of motor commands” (167) and possibly of the high-level neuronal processing associated with the formulation of such commands (S. Gandevia, personal communication; 152). From this perspective, the sense of effort is a sensation derived from the component of the corticopetal component of the corollary discharge that projects to the primary somatosensory cortex.

As reviewed by McColosky et al. (167), the evidence for a role for corollary discharge in the sense of effort is based on an analysis of perturbations to the system at three different levels of the neuraxis. First, when the force that a muscle can exert is experimentally reduced (e.g., by fatigue, with curarization, by cutaneous-derived inhibition of motor neurons, or by their reciprocal inhibition elicited by vibration of the antagonist muscle), the perceived effort for a task increases in association with the more substantial motor command that the subject must generate to achieve the target force (42, 95, 96, 104, 166). Second, when the excitability of a motor neuron pool is experimentally heightened (e.g., vibration of a muscle to elicit an excitatory spindle discharge), there can be a decrease in the necessary motor command and in the perceived effort (166). Other investigators, however, reported the converse observation that vibration of the muscle tendon consistently increases force sensation during a muscle contraction (38, 134), which suggests that intramuscular receptors are able to influence the perception of muscle tension (37, 39). Third, intracranial lesions due to simple motor strokes can result in muscle weakness that requires an increase in centrally generated commands to achieve normal activation of spinal motor neurons. Even when these lesions produce only motor deficits with no clinically detectable loss of peripheral sensation, there is an increase in perceived effort (91, 92, 96).

Psychophysical experiments have demonstrated the independence of perceived effort and force failure during sustained activity. When subjects were asked to support a weight with one hand for 10 min, they were able to do so but, with a matching contraction performed by the contralateral hand, indicated that the perceived effort increased during the task (166). Similar observations have been reported for intermittent (brief rest periods) submaximal and maximal contractions (39). In these studies, subjects are required to estimate the force during the fatiguing contraction with the contralateral limb, and investigators infer, on the basis of the increase in the per-
**FIG. 3.** Relationship between muscle force and perceived effort. A: mean values for 5 subjects and 2 muscles (●, adductor pollicis; ○, quadriceps femoris). Perceived effort increases as an exponential function of muscle force. Decreased steepness of curve indicates reduced discriminative capability for sense of effort. (Adapted from Baanister [4].) B: modeling studies (88, 119) suggested a sigmoidal relationship between excitatory drive to a motor neuron pool (input) and force (output). This comparison suggests that sense of effort is not a simple linear interpretation of excitatory drive to a motor neuron pool.

Perceived amplitude of the matching force, that the subjects were estimating effort. Some studies have found that during a constant-force task the perceived effort increases as a power function of duration and that for different tasks the perceived effort increases as a power function of the target force (4, 34a, 91, 167, 177a, 210). Similarly, when the effort associated with a handgrip contraction was held constant, the decline in force was characterized by an exponential function (41, 134a). Others, however, have found a linear relationship between the matching force and time during constant-force contractions (93, 133, 166).

The shape of the perceived effort-force relationship (Fig. 3A) implies a reduced discriminative capability for the perceived effort at low forces. Interestingly, the relationship between perceived effort and force is opposite to that predicted from modeling studies (88, 119). These models have produced a sigmoidal relationship between the excitatory drive to the motor neuron pool and the force exerted by muscle (Fig. 3B). According to this relationship, the requisite increase in excitatory drive necessary to increase force by 10% is greater at high force levels. In contrast, the perceived effort increases more for a 10% increase in force at low forces (Fig. 3A). This difference suggests a nonlinear transformation, as can be achieved with neuronal networks, between the excitatory drive to a motor neuron pool and perceived effort.

Although the sense of effort appears to be derived from corollary discharge, this association is probably influenced by humoral factors circulating in the cerebrospinal fluid. This expectation is based on observations of the effect of various pharmacological agents on endurance capability. For example, the administration of amphetamine increases the time of swimming rats to reach exhaustion (14). Furthermore the pretreatment of running rats with 6-hydroxydopamine, a neurotoxin that destroys catecholaminergic fibers, decreased the time to reach exhaustion (121). Such observations have led investigators to conclude that epinephrine (122) and the neurotransmitter 5-hydroxytryptamine (29, 43) may play a role in central fatigue. If endurance time is influenced by such agents, then it seems likely that the sense of effort would also be affected. This possibility awaits investigation.

**Systems issues.** Despite the significance of perceived effort as it relates to fatigue experienced by humans, little is known about the sense of effort and fatigue. There are at least four avenues that invite systematic investigation at the systems level of inquiry. First, the relationship between the sense of effort and the magnitude of force reduction during fatiguing contractions should be quantified for different muscle groups and motor tasks. It is unclear whether this relationship would be affected by the motor system (e.g., respiratory vs. jaw vs. limb), muscle mass (hand vs. leg), muscle function (flexors vs. extensors, single joint vs. multi-joint), or degree of direct cortical control (hand and forearm vs. leg). Furthermore, because force failure is known to be task dependent, it is necessary to determine the influence of motor task on the relationship between the sense of effort and force reduction. This would involve an evaluation of the effects of subject motivation, the intensity and duration of the activity, and the extent to which the activity is continuously sustained.

Second, there is a need to examine the effects of fatigue in experimental paradigms that have been used previously to demonstrate the importance of sensory feedback in seemingly simple low-force tasks; jaw control in intact and deafferented monkeys (106); postural control in intact humans after ischemic deafferentation of the legs (60, 163); and thumb, wrist, and arm movements of humans with selected sensory neuropathies (159, 195, 200). The relationship of this literature to the perception of force during fatiguing contractions has not yet been considered. For example, sensory updating may still be required for such perceptions, even with the availability of the sense of effort.

Third, the role of corollary discharge and kinesthesia has recently been extended to include judgments about the timing of muscle contractions (167) and the control of fine manipulation (98). The perception that is formed is presumably task dependent; it could be critical in tasks that require the cooperative activation of separate muscle groups for high-speed movements in which sensory feedback is not available to the control system. Studies on the effect of fatigue on timing judgments could provide insight into both the types of motor performance most sensitive to the adaptations that underlie fatigue and the mechanisms by which corollary discharge may mediate this perception. The implication of a role for corollary discharge in fine manipulative tasks (98) underscores the precision of perceptions based on corollary discharge. Indeed, Gandevia and Rothwell were able to conclude that “motor commands can be precisely monitored and fractionated for individual intrinsic muscles of the human hand without recourse to afferent feedback” (Ref. 98, p. 1117). It would be of interest to determine whether this discriminative capability was impaired by fatigue.

Finally, virtually no information is available on the relationship between the sense of effort and the readiness potential (Bereitschaftspotential) (140), which is a
negative-going signal that is averaged from scalp electroencephalogram recordings and thought to originate in cerebral cortical structures during the planning of voluntary (particularly novel) movement. However, a preliminary report has shown that muscle fatigue is accompanied by an increased readiness potential, suggesting that “isometric hand contractions with fatigued muscles involve a greater degree of cortical activation or in other terms, the engagement must be higher when working with fatigued muscles” (87). An extension of this finding would be valuable to determine whether fatigue has a greater effect on the early bilateral component of the readiness potential than on the later unilateral component. This would be of interest, because the early component has recently been shown to be primarily generated by the supplementary motor area and the latter by the primary motor area (58). This assessment was based on the concurrent measurement of the readiness potential, the magnetoencephalogram, and regional blood flow. This combination of measurements could potentially provide a noninvasive method of determining the role of various cerebral structures in fatigue.

Cellular issues. It may be possible to explore the cellular basis of the sense of effort. A substantial database exists on the impulse traffic between suprasegmental and segmental centers during the elaboration of movement, as recorded in conscious primates trained to perform a variety of motor tasks. The data consist of the activity of single cells recorded from a number of suprasegmental structures and then related to the kinematic and kinetic details of the movement. This approach, pioneered by Evarts in the 1960s, has provided a means to determine the relative roles of the cerebral cortex, basal ganglia, and cerebellum in the control of movement. This work includes the demonstration of corticopetal input from primary sensory afferents during movement, but not of corollary discharges from lower spinal centers, as has been achieved in primate visual centers and the spinal centers of other species [electric fish, cat (7, 154)]. It now seems appropriate to extend Evarts' technique to population analyses (104a) in the study of suprasegmental aspects of muscle fatigue to address the following questions. 1) Can a neuronal basis for corollary discharge at various levels of the neuraxis be established in the conscious primate? 2) What is the temporal relationship between changes in corollary discharge and force failure during fatigue? 3) Does fatigue influence the association between corticopetal input driven by corollary discharge and the timing of muscle contractions? 4) Is corollary discharge during fatigue influenced by peripheral afferent feedback? Studies that address such issues should contribute to our understanding of the cellular basis of the sense of effort.

Clinical issues. Although muscle fatigue is a prominent symptom in a wide variety of diseases of the CNS and the peripheral neuromuscular system, there are no recent systematic accounts of its prevalence in the clinical literature. This situation is changing at the peripheral neuromuscular level of clinical inquiry, where electrophysiology, muscle biopsy biochemistry, and nuclear magnetic resonance have all contributed to recent advances in our understanding of the mechanisms underlying clinically relevant fatigue. These mechanisms include adaptations in neuromuscular transmission, muscle membrane excitation-contraction coupling, intracellular metabolic changes, and substrate depletion (70, 149, 176, 181, 194). For the role of CNS pathophysiology in fatigue, however, progress has been far slower due to problems of definition, inattention to the potential value of psychophysical tests, and lack of control data (56). Nonetheless, well-established techniques that are now in regular clinical use (74, 176) can be used to study suprasegmental aspects of clinical fatigue. For example, Stokes, Edwards and colleagues (211) used these techniques to examine patients with “effort syndromes,” a term loosely used to describe a variety of syndromes that include an increased sense of effort during activities of daily living. Their patient sample was shown to have central, rather than peripheral, neuromuscular impairments. Similarly, in patients suffering from the “chronic fatigue syndrome,” there is recent evidence that the abnormality was expressed “above the level of the motor cortex” and “the executive pathways for movement” (152). These studies underscore the need for advanced psychophysical testing and therapy for such patients and suggest that the sense of effort may entail at least two components: one associated with the impairment of performance and another of “higher” pathophysiological origin, wherein the perceived effort does not relate directly to motor performance.

Summary. Although changes in the perceived effort associated with a task represent an important component of fatigue, little is known about the behavioral and neurophysiological basis of this sensation. However, the psychophysical and neurophysiological techniques to study the sense of effort are currently available, and there is a demonstrated clinical need for systematic studies in this area. Studies are needed to 1) quantify the relationship between the sense of effort and the decline in force for different muscle groups and tasks, 2) examine the effects of fatigue on tasks for which sensory feedback is known to be important, 3) assess the effects of fatigue on timing judgments and the means by which corollary discharge may mediate this perception, 4) characterize the relationship between the sense of effort and the readiness potential, 5) use established electrophysiological population-analysis techniques to explore the cellular basis of the sense of effort, and 6) extend psychophysical procedures to study the sense of effort in clinical populations.

Conclusions

Fatigue is a concept that encompasses a class of acute effects that impair motor performance. We have identified four themes that provide a basis for the systematic study of fatigue.

1) Task dependency. The specific mechanisms that cause fatigue in a given condition are determined by the details of the task performed by the individual; these mechanisms can include the CNS drive to motor neurons, the muscles and motor units that are activated, neuromuscular propagation, excitation-contraction cou
pling, the availability of metabolic substrates, the intracellular milieu, the contractile apparatus, and muscle blood flow. Task variables that can influence the prevailing mechanism include the level of motivation of the subject, the intensity and duration of the activity, and the extent to which the activity is continuously sustained (isometric vs. dynamic). Studies are needed that identify the boundary conditions and interactions between these mechanisms during human performance.

2) Force-fatigability relationship. For most, but not all, experimental conditions, the greater the force exerted by a muscle or motor unit for a given task, the more the muscle will fatigue. This suggests that the mechanisms underlying fatigue scale with the force that is exerted. There is a need to systematically explore the force-fatigability domain for a variety of muscles and tasks to determine the global nature of the relationship and to identify local regions where the relationship is nonmonotonic.

3) Muscle wisdom. One set of adaptations that has been associated with sustained activity includes a concurrent decline in force, relaxation rate, and motor neuron discharge. This association has been termed “muscle wisdom,” because it optimizes the force and ensures an economical activation of fatiguing muscle by the CNS. The mechanisms underlying muscle wisdom remain to be identified.

4) Sense of effort. The perceived effort associated with a task, which represents an important component of fatigue, is derived from centrally generated motor commands (and perhaps their formulation) that give rise to corollary discharges. Little is known about the interaction between changes in the sense of effort and force failure in fatigue, although the techniques to study the sense of effort are available and a clinical need for information on this topic has been demonstrated.

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