Spinal and Supraspinal Factors in Human Muscle Fatigue

S. C. GANDEVIA

*Prince of Wales Medical Research Institute, Prince of Wales Hospital
and University of New South Wales, Sydney, Australia*

Gandevia, S. C. Spinal and Supraspinal Factors in Human Muscle Fatigue. *Physiol Rev* 81: 1725–1789, 2001.— Muscle fatigue is an exercise-induced reduction in maximal voluntary muscle force. It may arise not only because of peripheral changes at the level of the muscle, but also because the central nervous system fails to drive the motoneurons adequately. Evidence for "central" fatigue and the neural mechanisms underlying it are reviewed, together with its terminology and the methods used to reveal it. Much data suggest that voluntary activation of human motoneurons and muscle fibers is suboptimal and thus maximal voluntary force is commonly less than true maximal force. Hence, maximal voluntary strength can often be below true maximal muscle force. The technique of twitch interpolation has helped to reveal the changes in drive to motoneurons during fatigue. Voluntary activation usually diminishes during maximal voluntary isometric tasks, that is central fatigue develops, and motor unit firing rates decline. Transcranial magnetic stimulation over the motor cortex during fatiguing exercise has revealed focal changes in cortical excitability and inhibitability based on electromyographic (EMG) recordings, and a decline in supraspinal "drive" based on force recordings. Some of the changes in motor cortical behavior can be dissociated from the development of this "supraspinal" fatigue. Central changes also occur at a spinal level due to the altered input from muscle spindle, tendon organ, and group III and IV muscle afferents innervating the fatiguing muscle. Some intrinsic adaptive properties of the motoneurons help to minimize fatigue. A number of other central changes occur during fatigue and affect, for example, proprioception, tremor, and postural control. Human muscle fatigue does not simply reside in the muscle.

The science of physiology, which, during the last hundred years has exclusively concerned itself with the study of animals, has been occupied during the last decade with problems which are more specifically concerned with the physiology of man. From the physiology of rest and of basal function we now increasingly turn to the study of man in an active role . . . in situations in which enormous demands are made upon the subjects' attention, will and adaptability.

N. Bernstein (1967)

The Co-ordination and Regulation of Movements

I. INTRODUCTION

If muscle is regarded as a motor, then the way it behaves depends not only on its intrinsic properties but also on the way that it is driven and the way feedback systems maintain its output. Feedback may operate locally at the level of the spinal motoneuron or at supraspinal levels. Just as many sites within the muscle cell control force, so many sites within the central nervous system (CNS) can modify the output of motoneurons. Modern reviews of muscle physiology often proceed on the premise that the limit to production of force by volition is at or within the muscle cell itself, or that if this is not so, deficiencies in drive to motoneurons are quantitatively small (e.g., Refs. 8, 90, 231, 235, 636, 665). As indicated in section IA, there is a history of controversy about central and peripheral factors in muscle fatigue.

Several factors have contributed to the delay in establishing the role of "central" factors in human muscle fatigue. First, it has simply been convenient to assume that the limits to muscle force established in reduced preparations of muscle devoid of effective neural input apply to a conscious human subject. Second, the methods to gauge central drive to muscle have not always been technically rigorous, so that findings obtained with them have been easily criticized or ignored. Third, although changes in the CNS during exercise can be measured, it has been more demanding to show that they cause a deficit in force production.

This review covers some of the changes that occur at the motoneuron pool and at supraspinal sites during human muscle fatigue. It highlights the occurrence and measurement of such changes and attempts to determine their functional importance.

A. Historical Perspective

Table 1 outlines major developments about "central" factors in human muscle fatigue. By the late 19th century it was clear that muscles were adapted for different tasks (e.g., red vs. white muscle) and that muscle performance could be limited by the muscle and also by the neural

machinery that drove it (216). Physiologists, including Fick, Fechner, Mosso, and Waller, recognized the steps that could define the extent to which the limitation was muscular. For example, in his influential book *Fatigue*, Alessandro Mosso (540) knew it would be cogent to compare voluntary performance with that reproduced by external electrical stimulation of the muscles. Unfortunately, his methods of stimulation were not sufficient for the task. Mosso and others adopted additional approaches, one of which relied on the variability of performance of a voluntary task requiring repeated submaximal isotonic contractions. If performance deviated from that expected, then Mosso inferred that the change, usually a deterioration, represented an influence of the CNS. Not only did prior physical exercise diminish performance but so did excessive mental "work" (usually measured in professorial colleagues who had lectured or examined medical students) (Fig. 1A). Mental excitement or agitation could improve voluntary endurance (463). The conclusion was that performance variations reflected central factors, which Mosso believed somehow directly altered peripheral function of the muscle. In analogous fashion, Waller, Lombard, and others noted that the excitability of muscles was sometimes preserved after apparent exhaustion: "that it (fatigue) is in part central is proved by the fact that when cerebral action has ceased to be effective . . . electrical stimulation of nerve or muscle is still provocative of contraction" (746) (for similar views see Refs. 463, 607). These propositions were dramatically revisited much later by Ikai and Steinhaus when they showed that the maximal voluntary strength of the elbow flexors could be increased by local cues such as firing a gun before maximal efforts (354) (Fig. 2). Hypnosis also altered performance, and epinephrine injection or ingestion of amphetamine enhanced strength (354).

A. V. Hill, in his book *Muscular Activity* (332), adopted the view subsequently accepted widely by exercise physiologists. Athletes were best for studies of the limits of voluntary performance because "with young athletic people one may be sure that they really have gone 'all out,' moderately certain of not killing them, and practically certain that their stoppage is due to oxygen-want and to lactic acid in their muscles. Quantitatively the phenomena of exhaustion may be widely different, qualitatively they are the same, in our athlete, in your normal man, in your dyspnoeic patient." Altough no direct evidence was presented to support this view about going "all out," Hill appreciated the difficulties if this assumption were not justifiable. "If one took a patient from the hospital and made him work till he could barely move, one could never be sure (a) that he had really driven himself to the limit—it requires an athlete to know how to exhaust himself; (b) that one would not kill him; and (c) what the cause of his stopping was."

If subjects did go all out, there was the worry derived

TABLE 1. *A list of conceptual and technical advances that are relevant to the contributions of the central nervous system to human muscle fatigue*

Year	Author	Reference No.	Description
1800s			Development of myographs and dynamometers
1904	Mosso	540	Attempt to compare fatigue in voluntary and electrically induced contractions, and to measure central fatigue using a variety of techniques
1926	Hill	332	Suggestion that athletes go "all out," with the end of exercise being due to "oxygen want"
1928	Reid	607	Electrically evoked isometric force showed "no marked difference" from maximal voluntary force
			Demonstration of combined central and peripheral fatigue at the "fatigue point"
1929	Adrian and Bronk	4	Increased force in human muscles produced by recruitment and rate coding of motor units
	Denny-Brown	177	Recognition that motor units were recruited differently in red and white muscles, e.g., soleus before gastrocnemii
1954	Merton	524	Development of twitch interpolation to assess proximal voluntary activation and to predict maximal evocable force in adductor pollicis
	Merton	524	Recognition that tetanic stimulation of adductor pollicis can produce a similar force to that in a maximal voluntary contraction
	Bigland and Lippold	60	
	Bigland and Lippold	60	Development of fine-wire intramuscular electrodes to attempt recordings of maximal voluntary firing rate of motor units
1955	Naess and Strorm-Mathisen	543	Fatigue in high-frequency electrically induced tetanus exceeds that in a voluntary contraction
1961	Ikai and Steinhaus	354	Demonstration that arousal, hypnotic suggestion and pharmacological interventions can affect voluntary strength and fatigue
1969	Marsden et al.	482 (see also Refs. 301, 375)	Fatigue in an electrically induced contraction almost matches that in a voluntary one when the stimulus frequency declines from 60 to 20 Hz over a minute: "artificial wisdom"
1971	Marsden et al.	483	Human motor units decline in rate during sustained maximal voluntary efforts of hand muscles
1978	Bigland-Ritchie et al.	67	Measurement of some low levels of voluntary activation in attempted maximal isometric contractions
1980	Edwards (chair)	140	Ciba Foundation Symposium: "Human Muscle Fatigue: Physiological Mechanisms"
1981	Belanger and McComas	45	Application of twitch interpolation to leg muscles and validation of technique
	Grimby et al.	301	
1982	Kernell and Monster	403	Detailed proposal that motoneuronal adaptation in the cat controls firing rate during sustained contractions
1983	Bigland-Ritchie et al.	65	Correlation of a decline in motor unit firing rate during sustained maximal voluntary contractions with the decline in speed of whole muscle
1986	Bigland-Ritchie et al.	76 (see also Ref. 767)	Evidence that a muscle reflex may reduce motor unit firing rates during muscle fatigue
1987	Duchateau and Hainaut	196	Immobilization associated with impaired ability to produce maximal voluntary force
1988	Garland et al.	276 (see also Refs. 274, 278)	Evidence that group III and IV afferents reduce motoneuronal output during muscle fatigue
	Hales and Gandevia	312	Amplifier designed to measure small force increments required for sensitive twitch interpolation
	Hayward et al.	320	Evidence that reflex from a fatigued muscle in the cat inhibits a synergist muscle
1990	Bongiovanni and Hagbarth	87	Vibration acting on muscle spindle endings can reflexly enhance force during a sustained maximal voluntary contraction
	Gandevia et al.	264 (see also Ref. 477)	Abolition of all muscle afferent feedback reduces maximal voluntary firing rates of human motoneurons
	National Heart, Lung, and Blood Institute Workshop	554	Formal definition of muscle fatigue that is suitable for respiratory and limb muscles
	Westing et al.	750	Superimposed tetanic stimulation increases maximal voluntary eccentric torque
1991	Lloyd et al.	459	Measurement of central fatigue during prolonged intermittent exercise
	Macefield et al.	474	Ensemble input from human muscle spindle endings declines during fatigue in sustained submaximal isometric contractions
1993	Brasil-Neto et al.	93 (see also Refs. 509, 777)	Prolonged reduction in responses to motor cortical stimulation when muscle relaxed after fatiguing exercise
	Nielsen et al.	556	Proposal that a high core temperature and not circulatory or metabolic factors produce task failure in a hot environment
1995	Mills and Thomson	535 (see also Refs. 510, 703)	Excitatory and inhibitory responses to motor cortical stimulation change during sustained maximal voluntary contractions
1996	Gandevia et al.	260	Central fatigue documented with motor cortical stimulation. Central fatigue dissociated from changes in motor cortical behavior during isometric muscle fatigue
	Herbert and Gandevia	327	Maximal voluntary activation of adductor pollicis is suboptimal as shown by peripheral nerve and motor cortical stimulation
	Loscher et al.	466, 467	Formal demonstration that electrical stimulation can still produce the required force with ankle plantarflexors when task failure occurs
1997	McKenzie et al.	511	Inspiratory resistive loading can produce task failure with little peripheral or central fatigue
1999	Pettorossi et al.	581	Evidence that groups III and IV muscle afferents inhibit the monosynaptic reflex during fatigue via a presynaptic mechanism in the rat
2000	Taylor et al.	705	Groups III and IV muscle afferents do not directly inhibit motoneurons or the motor cortex after fatigue

In such a list it is not possible to catalog all relevant studies. See text for further details.

A

Finger flexion movement

Midday
25th April 1890

Midday
26th April 1890
"after lecturing"

15 s

B

Finger flexion force

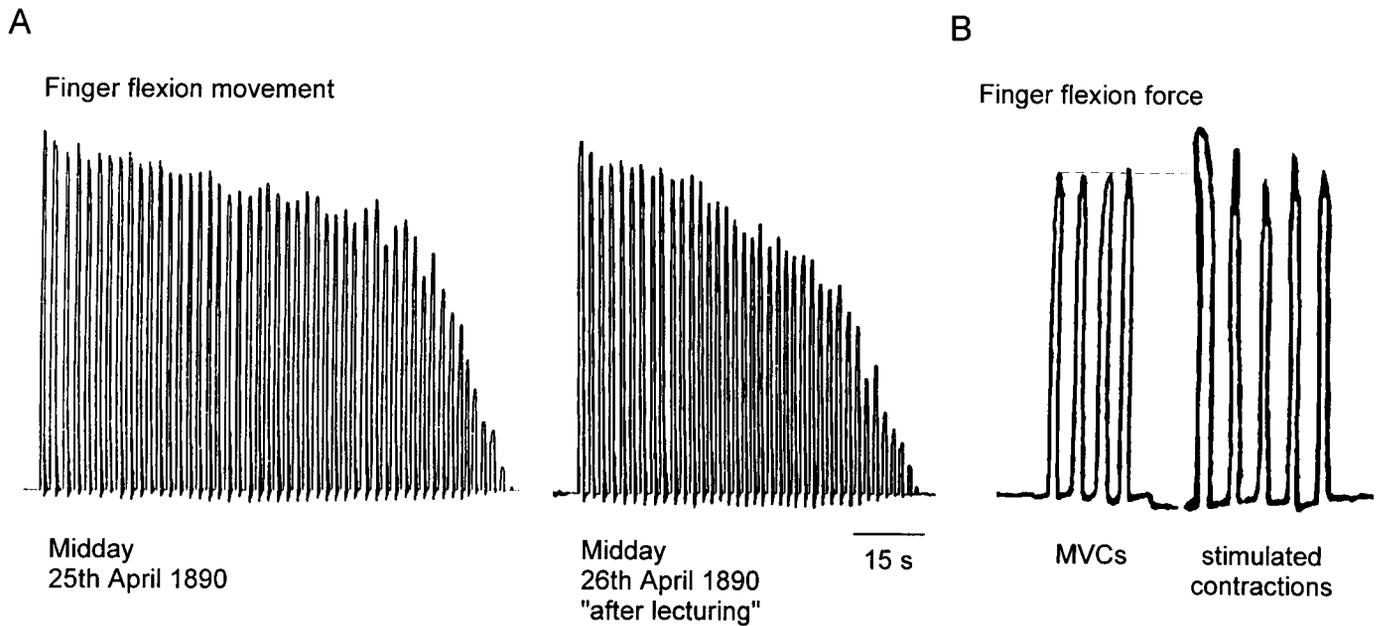MVCs   stimulated
            contractions

FIG. 1. Early studies of maximal voluntary activation and central fatigue. *A*: data obtained by Mosso (540) using his ergograph. Trace indicates the distance moved by the middle finger when lifting a weight of 3 kg each 2 s. Normal "fatigue tracing" and one obtained 24 h later "after lecturing" are shown. [Redrawn from Mosso (540).] *B*: Reid's comparison of a maximal voluntary contraction (MVC) of finger flexion and force produced by stimulation of the median nerve at the elbow (stimulus rate not specified) under isometric conditions. Artificial stimulation produced "as strong contraction as voluntary effort," although this is not clear in all the records (see horizontal dashed line), and Reid often found that large weights could be lifted by artificial electrical stimulation and not volition (see Fig. 4). [Redrawn from Reid (607).]

from clinical cases, that muscles would be torn, tendons ruptured, and bones broken. [We now know that unless there has been a pathological change in the tendon or bone, the strength of bone and tendon exceeds that of muscles (775).] Thus the common view was that the
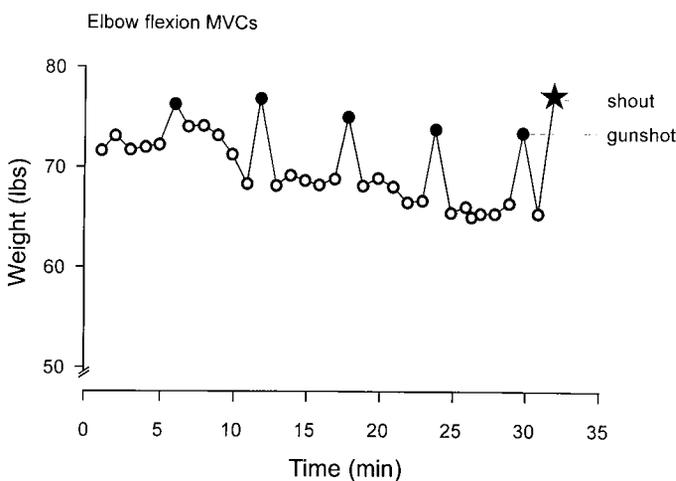

FIG. 2. Classical study of factors affecting maximal voluntary strength. Mean value for brief MVCs of elbow flexors made at 1-min intervals by 10 subjects. Control contractions (open circles), contractions preceded by an unexpected gunshot (solid circles), and a final contraction (star) in which the subject shouted are shown. [Redrawn from Ikai and Steinhaus (354).]

maximal contractile force was so high that "strength is kept in bounds by the inability of the higher centres to activate the muscles to the full" (528). This quandary prompted a milestone in 1954 when two reports appeared. Merton (524) and Bigland and Lippold (59) used electrical stimulation of the motor nerve to compare directly maximal force in a stimulated tetanus and during a maximal voluntary contraction (MVC). While supramaximal "artificial" stimulation of the nerve drives all motor units synchronously, unlike voluntary muscle contractions, this difference is not critical for the comparison provided that the stimulation frequency is high enough to produce a maximal tetanus.

Does the force produced by tetanic electrical stimulation exceed that produced by voluntary action? Both reports claimed that the two forces were similar, although the errors associated with the tests were not quantified and are not trivial (see sect. II). An earlier study by Reid (1928) had also reached this conclusion, although the raw records suggest that voluntary contractions did not quite match the force of an isometric tetanus (Fig. 1*B*). Using a special myograph that was said to measure the force produced only by adduction of the thumb, Merton compared the response to stimulation of the ulnar nerve above the wrist to the force of voluntary thumb adduction. Difficulties are that small changes in thumb position alter the forces produced by stimulation of the ulnar

nerve, and the forces produced by maximal voluntary efforts involve both intrinsic and unstimulated extrinsic hand muscles. In later studies of intrinsic hand muscles Ikai et al. (355) found that tetanic force produced by stimulation exceeded that produced voluntarily, but others have subsequently found that voluntary forces exceeded tetanic force (e.g., Refs. 164, 198, 328, 470) (see sect. II). Mindful of the many experimental difficulties, Merton later commented that his findings came about due to a "happy cancellation of errors" (484). It is unfortunate for muscle physiologists that few accessible nerve-muscle combinations allow isolated supramaximal electrical stimulation of all the motor axons that produce a simple force that is easily measured and mimicked perfectly by maximal voluntary effort.

Merton (524) provided additional insight when he showed that during a voluntary effort the force increment added by a stimulus to the ulnar nerve was inversely proportional to the level of initial force. No force increment appeared when voluntary force approached maximal values (Fig. 3A). Two conclusions were drawn: first, during a maximal effort "those muscle fibres whose motor nerve fibres are excited by the shock are contracting maximally," and second, the relation between voluntary force and the size of the interpolated twitch meant that absolute maximal force could be predicted by linear extrapolation. A corollary to the first conclusion was that during maximal effort, voluntary drive to the motoneurons was sufficient not only to recruit all stimulated motoneurons capable of exerting force, but also to drive them to frequencies that achieve full force. This contribu-

tion not only provided a method to investigate maximal voluntary performance, but it placed the limits for voluntary force back where physiologists thought they should be, within the muscle. The technique of twitch interpolation lay unused until the 1980s when Belanger and McComas (45) reassessed its assumptions and applicability for use in the plantar- and dorsiflexor muscles of the ankle. Independently, Grimby and colleagues (300, 301) used brief tetani superimposed on an isometric contraction of extensor digitorum brevis when they estimated optimal firing frequencies to minimize fatigue. Later a special amplifier was developed that improved the resolution of Merton's method 10-fold (312). Submaximal electrical stimulation superimposed during maximal voluntary eccentric contractions of knee extensors was later shown to increase ongoing torque by $\sim$20%, thereby establishing the usefulness of interpolated stimulation for demonstration of suboptimal drive during muscle lengthening (750).

Finally, Merton applied his twitch interpolation technique in fatigue to establish that "when strength fails electrical stimulation of the motor nerve cannot restore it" (524). He concluded that voluntary effort produced maximal force from muscles and continued to produce it even when peripheral fatigue developed. If the blood supply to the muscle was cut off with a blood pressure cuff after the MVC, then the twitch force did not recover. That is "there is no recovery of (voluntary) strength until the blood flow to the muscles is restored. If fatigue were a phenomenon of the central nervous system, it seems most improbable that recovery should be delayed by occluding the circulation to the arm" (525). The weight of
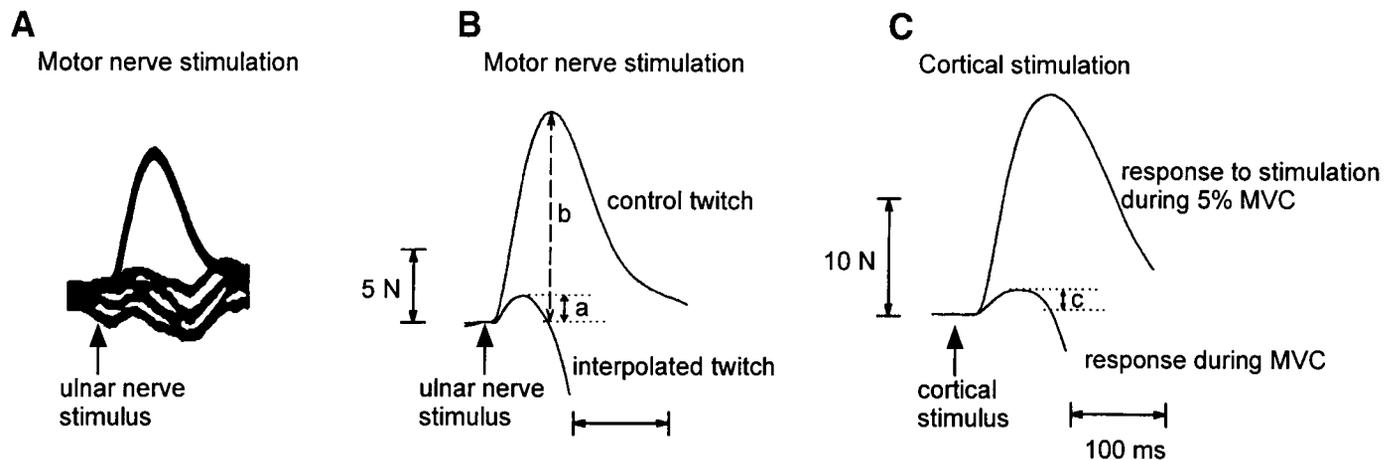

FIG. 3. Twitch interpolation of adductor pollicis muscle. *A*: traces from Merton's original study with vertical gain enhanced. Control twitch produced by supramaximal stimulation of the ulnar nerve and superimposed responses during attempted MVCs. Twitches aligned so that the time of the stimulus (arrow) is coincident, and baseline force before interpolated twitch has been subtracted. [Redrawn from Merton (524).] *B*: control twitch produced by supramaximal stimulation of the ulnar nerve (control twitch: *b*) and superimposed responses during attempted MVC (interpolated twitch: *a*). Voluntary activation (in percent) = 100 − 100(*a/b*). The reduction in force after the stimulus-induced force increment is due to nerve and muscle refractoriness, antidromic collision in motor axons, and spinal reflex effects of the stimulus. *C*: typical thumb twitches elicited by a transcranial magnetic shock to the motor cortex during a weak contraction at 5% MVC or during MVC. [*B* and *C* from Herbert et al. (326).]

these arguments seemed sufficient for his pronouncement that "anyone with a sphygmomanometer and an open mind can readily convince himself that the site of this fatigue is in the muscles themselves" (525).

If the muscle were the only significant limit to voluntary performance, at least for intrinsic muscles of the hand, then it was natural to check how the muscle was driven by the CNS. The surface electromyogram (EMG) provided an enticing way to examine the role of the CNS in muscle fatigue. Bigland and Lippold (59) had established in 1954 that the integrated surface EMG increased linearly with force (59). There is an obvious increase in the low-frequency content of the signal during fatigue, but this can be fully explained by changes in the compound muscle action potential (419, 534), and thus the ongoing signal provided no certain clue about central changes in motoneuron firing frequency. Changes in the frequency spectrum of the EMG accompany muscle fatigue, but they do not definitively cause it at a peripheral level, nor do they necessarily signify altered neural drive.

The amplitude of the EMG also seemed simple to interpret in terms of "neural drive" in fatigue, but the size and propagation velocity of the intracellular muscle fiber action potential, and possible compromise at the neuromuscular junction, affects the signal. Although the consensus is that blocking at the neuromuscular junction does not occur significantly with natural rates of motor unit firing (e.g., Refs. 61, 70, 247, 704), activity-induced changes in the single fiber potential, and activation of the muscle's electrogenic Na^+/K^+ pump to degrees which vary between fiber types and the degree of local ischemia seriously limit the surface EMG as a measure of voluntary activation of motoneurons.

The alternative to measures of global EMG during fatigue was to record the discharge of single motor units in voluntary contractions. Although the principle of motoneuron recruitment and frequency modulation had been known for decades (4), few had succeeded in recording unitary activity during sustained strong contractions due to the interference pattern caused by the discharge of many muscle fibers. Bigland and Lippold (59) recorded from adductor pollicis and abductor digiti minimi with a selective electrode based on two thin flexible wires (insulated to the tips) inserted into the muscle via a hypodermic needle. This method was subsequently adopted widely.

Motor units were believed to be recruited in a relatively stable order according to Henneman's size principle, from those with slow conduction velocity producing small forces to those with fast conduction velocity producing large forces (325) (for review see Refs. 78, 324). This principle links motoneuron properties (i.e., small size, long afterhyperpolarization, and low axonal conduction velocity) with properties of muscle fibers (small twitch force, long contraction time, slow fiber conduction

velocity, and low fatiguability). Although the distinctions between the various motor unit types may be more blurred in humans than experimental animals, this "size" principle of orderly recruitment appears to hold in humans, under most circumstances with isometric contractions (e.g., Refs. 181, 242, 537) (cf. Ref. 710), although some exceptions appear to occur during nonisometric contractions (e.g., Refs. 125, 342, 545) and fatigue (228), and for muscles with complex actions and different "task groups" of motor units (e.g., Refs. 615, 737) (for review see Refs. 153, 460). Functionally significant exceptions to the dominant principle of orderly recruitment have been hard to find. However, it must be conceded that different inputs to motoneuron pools, be they reflex (such as group Ia inputs, reciprocal inhibition, cutaneous inputs) or central (such as corticospinal inputs, recurrent inhibition, reticulospinal inputs), do not change the firing frequency of all motoneurons in the pool equally (e.g., Ref. 79) (for review see Refs. 78, 122, 324). For example, the corticospinal input in the cat will increase the firing of high-threshold motoneurons but decrease that of low-threshold motoneurons, thus altering the "gain" of the whole pool (402) and contributing to disrupt the order of motoneuron recruitment. An additional effect of the distribution of motor unit size and fatiguability across the pool is that during a sustained maximal contraction the decline in force will be dominated by fatigue in the large motor units, those recruited late in voluntary contractions. Furthermore, there is probably increased "spacing" between the thresholds of the motoneurons recruited close to maximal voluntary force (28), so that greater "effort" will be needed to generate the final part of the force in maximal efforts.

In 1971, Merton and colleagues (483) made another key observation on motor unit behavior: during a sustained maximal voluntary effort the firing rate of a single motor unit in first dorsal interosseous declined from ~60–80 Hz at the start to ~20 Hz after 30 s (Fig. 4) (483). The shortest initial interspike interval in their studies corresponded to a peak instantaneous frequency of ~150 Hz. They blocked the proximal ulnar nerve, a procedure which removed the major innervation of the muscle and made it easy to isolate the few motor units innervated by the median nerve. (The block also removes much homonymous and heteronymous muscle afferent feedback.) The decline in firing frequency was termed "muscular wisdom" because it matched the firing of the motoneuron to the altered contractile properties of the muscles (see sect. IIIB). It was already known that muscle relaxation slowed in repetitive contractions both in human muscles during strong voluntary efforts and in isolated mammalian muscles, a phenomenon now well characterized (e.g., Ref. 749), so that with the lower fusion frequencies lower firing rates might provide the same activation of the mus-

A

Single motor unit in adductor pollicis MVC

0-2 s

8-10 s

38-40 s

58-60 s
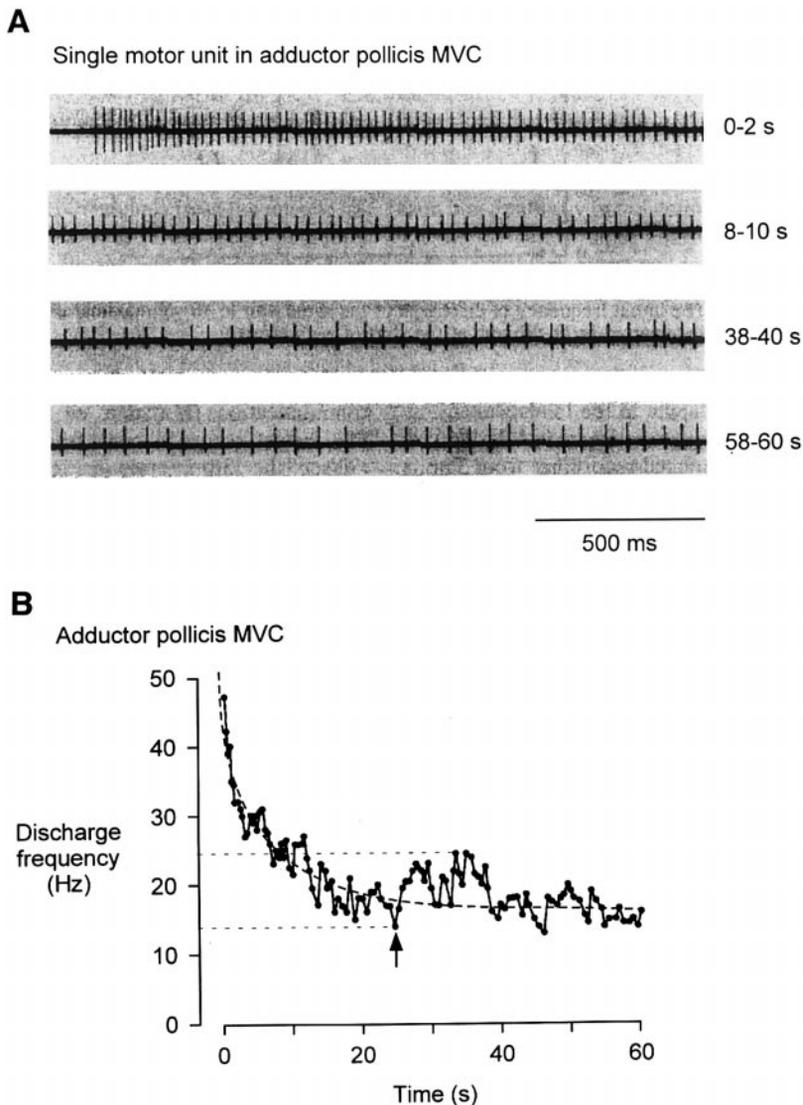
500 ms

B

Adductor pollicis MVC

FIG. 4. *A*: records from a single motor unit in adductor pollicis during MVC lasting 1 min. This unit was found after blocking the ulnar nerve at the elbow. Four 2-s sections were removed from the continuous record, covering the intervals 0–2, 8–10, 38–40, and 58–60 s. *B*: discharge frequency of the same unit during the MVC is shown as the reciprocal of the period occupied by 10 consecutive spikes. Points were plotted at the end of the 10-spike period. A curve has been fitted to the decline in rate. The highest initial peak firing rate was 150 Hz. Arrow and horizontal dashed lines mark a period when discharge rate almost doubled, evidence of prior submaximal voluntary drive. [Redrawn from Marsden et al. (484).]

cle. A direct association between the two phenomena was proposed by Bigland-Ritchie and co-workers (65, 76).

The decline in maximal voluntary firing rates with fatigue was subsequently confirmed (51, 66, 264, 289, 484, 707). The concept of muscular "wisdom" developed further because the greatest output from muscle (measured as force integrated over time) was generated by stimulation with a declining frequency which began at 50–100 Hz and leveled off at 15–20 Hz after about a minute (e.g., Refs. 301, 375, 483, 484). When rates were too high, failure at the neuromuscular junction and/or sarcolemma developed (e.g., Ref. 69). Meanwhile, other techniques were developed to record the firing of motor units during strong efforts with solid monopolar electrodes (66), fine-wire electrodes (313), and branched bipolar electrodes (227). Improved techniques arose to extract the firing of individual units from the multiunit EMG (e.g., Ref. 173). The major debate concerned the possibility that a reflex

arising in the contracting muscle causes the fall in motor unit firing rate.

To those familiar with stimulus rates required for tetanic fusion of mixed muscles of small laboratory animals, the firing rate of motor units in maximal voluntary efforts in humans appeared too low to produce maximal force (224). At least two factors are important: first, as shown elegantly by Rack and colleagues (450, 602), asynchronous stimulation of several groups of motor units produces higher forces than if they all discharge synchronously. However, the magnitude of this effect is not well established. Second, some of the natural variation in firing rate during voluntary contractions produces force more efficiently than regular trains of stimuli, and this may minimize fatigue, due to a series of "nonlinear" intrinsic muscle properties including catchlike behavior (in the cat, see for example Refs. 57, 123, 648, 776; in humans, see for example Refs. 80, 475, 711), twitch potentiation (e.g.,

Refs. 195, 280, 591), and nonlinear force summation (141, 175, 592). These factors produce hysteresis in the force-frequency relationship (e.g., Refs. 81, 284, 475, 571). Once units are recruited at a high firing rate, near-maximal force can be held with frequencies well below those initially required for fusion. Hence, a lower-than-expected firing rate in sustained voluntary efforts is not, on its own, sufficient to indicate that the muscle is not producing optimal force. The critical factor for muscle fatigue is whether the firing rates of motor units fall too much in voluntary efforts so that submaximal force is produced. Much evidence now supports this view.

This review emphasizes data obtained with isometric contractions because the neural mechanisms can be delineated more easily for them. Many of these are also relevant for concentric and eccentric contractions. After the introductory section, evidence is presented that neural drive is often insufficient to generate true maximal strength. Then, the development of central fatigue is considered along with the spinal and supraspinal mechanisms that are involved. Recent work using noninvasive stimulation of the motor cortex and corticospinal tracts is reviewed. The final section considers briefly other "central" aspects of muscular fatigue including possible neurotransmitter systems and task-related changes in performance.

B. Definitions and Background

The historical perspective focused on several key concepts and influential experiments related to the sufficiency of neural drive to muscles during maximal voluntary contractions. However, other aspects of neuromuscular control clearly change in exercise. These include the sensory accompaniments to the fatiguing task, the increasing tremor which can develop during exercise and persist afterwards, and the gradual recruitment of other muscles. These accompaniments are not contentious, but the mechanisms that produce them are not necessarily well understood (see sect. v*C*). Finally, when exercise is "open loop" (i.e., with no duration or distance etc., as a goal), the decision to terminate it is a voluntary act and thus can be influenced by cognitive processes.

With a seemingly simple word like "fatigue" it is tempting to assume that, while its meaning is not necessarily understood in the same way by the lay public and physiologists, there is at least agreement on its meaning among physiologists and clinicians. Not so. When applied to muscular exercise, fatigue can refer to "failure to maintain the required or expected force" (217) or failure to "continue working at a given exercise intensity" (90). On this view fatigue would occur suddenly, hence, the phrases to reach "the point" of fatigue or exhaustion. Although the absurdity of this position is obvious, it

would follow that fatigue in muscles (and its CNS accompaniments) begins only at the point of task failure when a subject exercises at a set rate to "exhaustion." This sort of definition was emphasized at the influential Ciba Foundation symposium on human muscle fatigue held in London in 1980 (140). In fact, the maximal force-generating capacity of muscles starts to decline once exercise commences so that fatigue really begins almost at the onset of the exercise and develops progressively before the muscles fail to perform the required task. Hence, a more realistic definition of fatigue is "any exercise-induced reduction in the ability to exert muscle force or power, regardless of whether or not the task can be sustained" (74). Because of the potential clinical significance of fatigue of respiratory muscles, a meeting of physicians formally defined muscle fatigue as "a loss in the capacity for developing force and/or velocity of a muscle, resulting from muscle activity under load and which is reversible by rest" (554). Finally, fatigue refers not only to a physiological or pathological state in which muscles perform below their expected maximum, but to a symptom reported by subjects in whom there may be no obvious defect in muscle performance. Indeed, it is the most common symptom in medical and psychiatric practice (331, 486).

Table 2 presents definitions. Because peripheral force-generating capacity usually declines early in exercise and because CNS changes occur before muscles fail to perform a task, the most useful definition of muscle fatigue must encompass, as given above, "any exercise-induced reduction in force generating capacity." Rest reverses it. This definition ignores competing intramuscular mechanisms that potentiate force during "fatiguing" exercise (e.g., Refs. 280, 591, 605, 732) and focuses on the net reduction in performance that ultimately develops. Fatigue can be assessed by measurement of maximal voluntary force, maximal voluntary shortening velocity, or power. Specific tests are required to determine the extent to which any reduction in voluntary capacity is centrally mediated (see sect. II). "Voluntary activation" refers to a notional level of "drive" to muscle fibers and motoneurons. This term is used loosely, often without distinction between drive to the motoneuron pool and that to the muscle. These drives are not the same: one recruits motoneurons and increases their firing, and the other relies on muscle fibers to translate the motoneuron firing into force. As applied to motoneurons, the term *voluntary activation* is sloppy because it does not specify the source of their excitation (from descending motor paths, reflex inputs, and from associated spinal circuitry). The "maximal evocable force" is that produced when the muscle is fully activated by volition or appropriate electrical stimulation and is the formal term for true maximal force.

During exercise the failure to maintain the initial maximal force depends on "peripheral" fatigue occurring distal

TABLE 2. *Definition of key terms in alphabetical order*

Central fatigue	A progressive reduction in voluntary activation of muscle during exercise.
Maximal evocable force	Maximal force that can be produced by a muscle or muscle group; it would occur when twitches interpolated during a maximal voluntary contraction add no more force.
Maximal voluntary contraction	A maximal contraction that a subject accepts as maximal and that is produced with appropriate continuous feedback of achievement.
Muscle fatigue	Any exercise-induced reduction in the ability of a muscle to generate force or power; it has peripheral and central causes.
Peripheral fatigue	Fatigue produced by changes at or distal to the neuromuscular junction.
Supraspinal fatigue	Fatigue produced by failure to generate output from the motor cortex; a subset of central fatigue.
Task failure	Cessation of a bout of exercise. This may be accompanied by peripheral fatigue, central fatigue, or both.
Twitch interpolation	A method to measure voluntary activation in which one (or more) stimulus is delivered to the motor axons innervating the muscle during a voluntary effort.
Voluntary activation	Level of voluntary drive during an effort. Unless qualified, the term does not differentiate between drive to the motoneuron pool and that to the muscle. Maximal voluntary activation can be measured using twitch interpolation during a maximal voluntary contraction.

to the point of nerve stimulation and on "central" fatigue resulting from a failure to activate the muscle voluntarily. This arbitrarily includes branch-point failure and failure at the neuromuscular junction in the "peripheral" component. That component of overall muscle fatigue dependent on a progressive failure to drive motoneurons (and muscle fibers) voluntarily is termed "central fatigue." It is a progressive reduction in voluntary activation during exercise. Part of this central fatigue is "supraspinal fatigue" because motor cortical output becomes less than optimal (see sect. IV). Eventually, there is "task failure" when the exercise can no longer be continued. This point is often termed "exhaustion" by exercise physiologists. Surprisingly, the neural mechanisms underlying task failure have received little attention from electrophysiologists who are capable of stimulating the neuromuscular apparatus to check the validity of Waller's original claim that exercise stops when effective muscle contraction is still possible (607). Some recent studies have confirmed this (466, 467, 511). An early and a recent example of central fatigue with premature task failure are shown in Figure 5.

It is not possible to specify all the sites within the CNS at which contributions to voluntary activation, central fatigue, and supraspinal fatigue occur. The traditional model for considering muscle performance traces a causative "chain" from high levels within the CNS via descending paths to the motoneuron and then via motor axons to the neuromuscular junction, the sarcolemma, t tubules, and ultimately the actin and myosin interactions (Fig. 6A). A common, but unintended (and illogical), assumption in such a model is that any change at a link in the chain will affect force production. To continue this analogy, the chain is as "weak" as any of its links so that, theoretically, evolution might have ensured that all were equally strong. This does not hold because, for example, in normal subjects during voluntary tasks, events at the muscle cell and at supraspinal levels provide definite limits, while conduction block in (say) motor axons and failure at the neuromuscular junction do not. Of course, diseases and lesions

(e.g., myesthenia gravis and spinal cord injury) damage preferentially particular links in the chain.

Just as it has been important to determine whether activity-induced changes in processes within muscle cells cause fatigue, one must be equally careful to determine whether more "proximal" changes cause, or merely, accompany fatigue. For example, the surface EMG, a direct result of motoneuronal activity, changes during and after exercise, but the changes do not necessarily alter force production (see sect. III). The critical links in the "chain" of Figure 6A operate across the full range of exercise, from when many muscle groups contract, as in cycling or running, to "laboratory" exercise of one muscle or muscle group. The latter form of exercise makes it easier to measure accurately supraspinal and motoneuronal drives with electrophysiological techniques.

II. EVIDENCE THAT VOLUNTARY ACTIVATION IS SUBMAXIMAL IN "MAXIMAL" EFFORTS

If, in maximal voluntary efforts, the CNS fails to generate maximal evocable force, then a "reserve" exists that could theoretically be called on in exceptional circumstances. Maximal voluntary force would usually be limited by the subject's capacity to activate motor units. The term *limit* here does not imply that there are no other limits; the force generated by the recruited motor units is also a limit. Two possibilities exist if there is no reserve at the start of maximal exercise: voluntary activation remains maximal during exercise (with a purely peripheral limit to performance), or central fatigue develops. Three possibilities exist if voluntary activation is initially submaximal: it may increase (and thus draw on the reserve), stay the same, or decrease with exercise. Of the five possible outcomes in maximal tasks, in only one (full initial activation with no central fatigue) is the performance limited solely by the muscle.

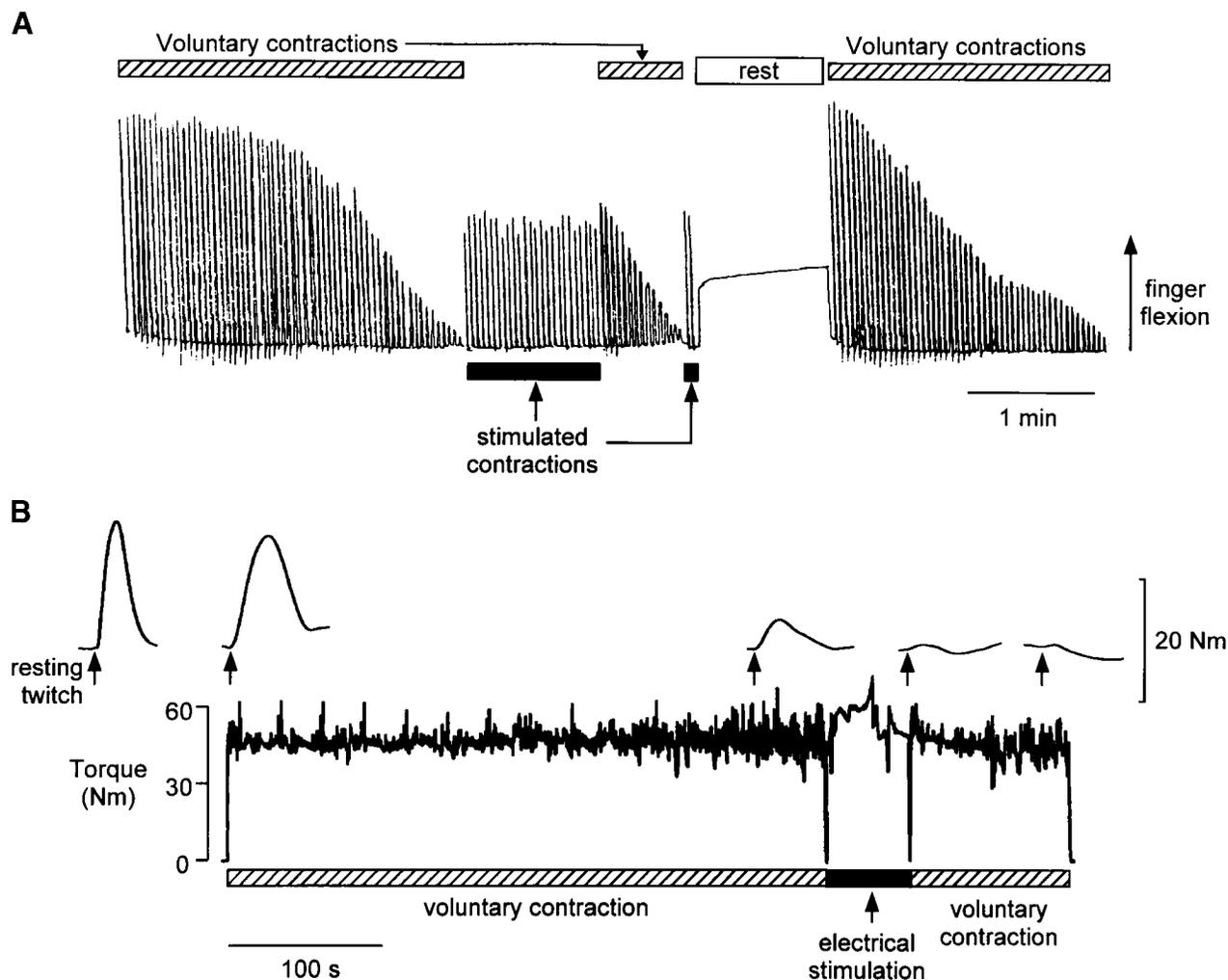The isometric force trace itself suggests that maximal

A

B

FIG. 5. Examples of task failure in repeated isotonic contractions and in a sustained submaximal MVC. *A*: data for maximal isotonic contractions of the flexors of the middle finger (3 kg at 24/min). When the weight could barely be lifted voluntarily (i.e., task failure), it was lifted during median nerve stimulation. Complete rest (open bar) for a minute allowed recovery from both peripheral and central fatigue. It restored voluntary force more readily than repeated tetani (solid bar) that allowed only central fatigue to recover. [Redrawn from Reid (607).] *B*: torque during sustained contraction of ankle plantar flexors at 30% MVC in which the subject tried to maintain the target force as long as possible. After the first voluntary contraction (at 410 s), the triceps surae muscles were electrically stimulated for 1 min, and the subject was then able to maintain the target torque voluntarily. *Top traces* show the resting control twitch response and superimposed twitch responses at 7, 396, 473, and 573 s. Arrows indicate timing of interpolated stimuli. Note the increment in force produced with the stimulus interpolated before the end of the main voluntary contraction. At this stage, voluntary activation was not maximal. [Redrawn from Loscher et al. (466).]

voluntary force is less than the maximal evocable force or true maximum. Many myographic recordings show fluctuations in force that are not (or would not be) present in contractions produced by nerve stimulation. Provided the fluctuations are not dominated by variable input from antagonist muscles (which is unlikely, see Refs. 9, 161), or the action of remote muscles stabilizing the proximal skeleton, they reflect changes in output from the agonist motoneuron pool. The magnitude of the fluctuations would then set a lower boundary to the variation in voluntary drive during a contraction.

Many other observations allow inferences about whether muscles are activated maximally by volition.

These range from claims of feats of superhuman strength and endurance to the beneficial effects of various ergogenic substances. Claims of the former type require extraordinary documentation and remain unsubstantiated, whereas the latter are beyond the current scope. Some of the influential observations and techniques are considered below. Included are observations made during training, comparison of unilateral and bilateral contractions, and the technique of twitch interpolation.

Many approaches rely on measurements of MVCs, and unless steps are taken to maximize motivation, the contribution of "supraspinal" factors will be magnified. Therefore, when interpreting experimental findings, one

A

Planning of willed movements

Motor cortical & other corticospinal outputs

Other supraspinal & propriospinal outputs

α and γ motor neurons

motor axons

neuromuscular junction & sarcolemma

excitation-contraction coupling

cross-bridge force ATP hydrolysis

blood flow, O_2 & energy sources

Input from group I, II, III & IV muscle & other afferents

B

Descending corticospinal, propriospinal & other drives

group III & IV

spindle group II

group Ib

group Ia

α MN

presynaptic inhibition

range of group I-IV reflex inputs

γ MN

Renshaw cell
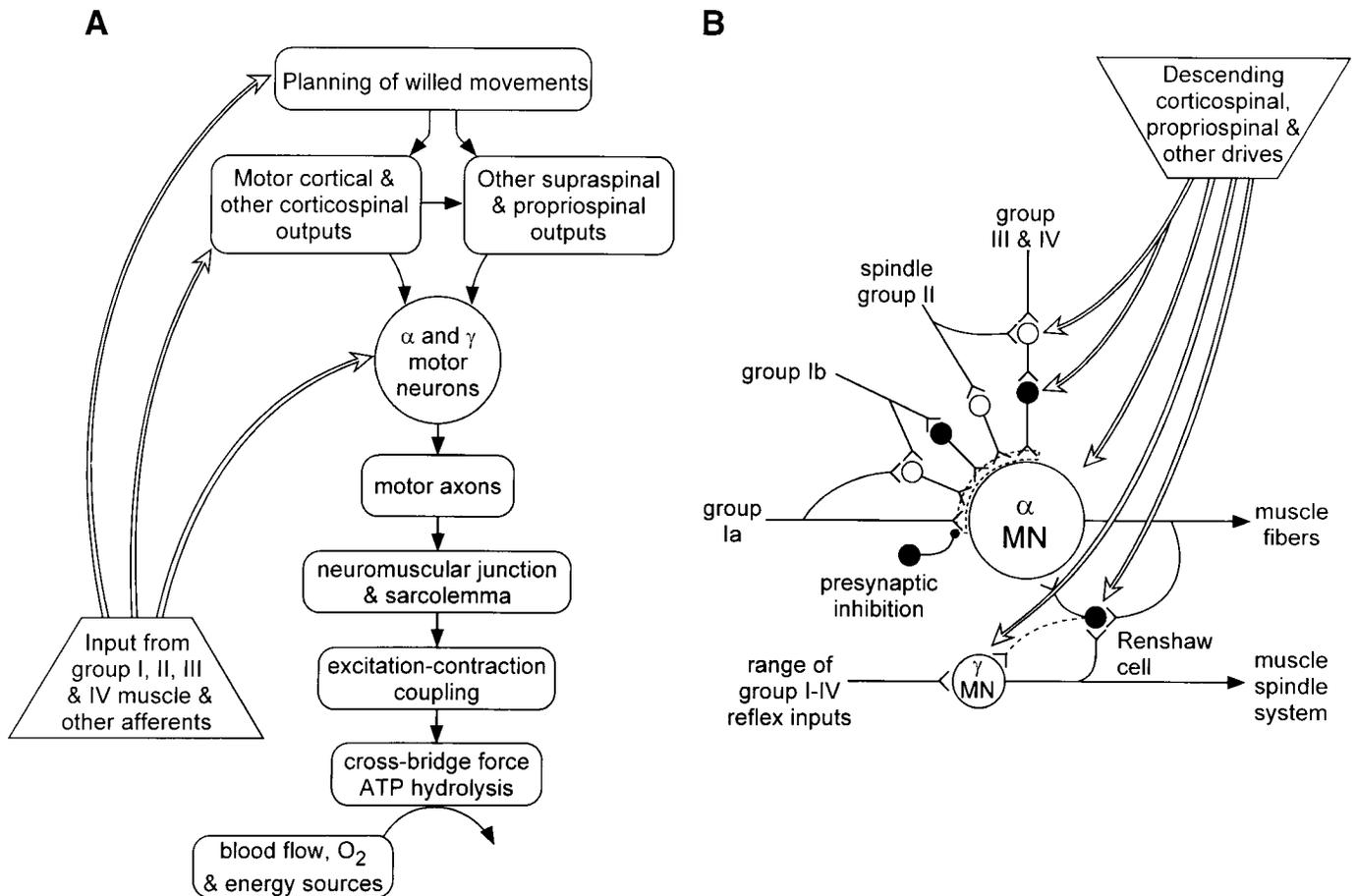
muscle fibers

muscle spindle system

FIG. 6. Steps involved in voluntary force production and factors acting at motoneuronal level. *A*: diagrammatic representation of the "chain" involved in voluntary contractions. A major source of feedback, that from the muscle, is shown acting at three levels in the central nervous system. Other sources of feedback that also act at these levels are not shown. *B*: summary of inputs to α- and γ-motoneurons for an agonist muscle. Cells with solid circles are inhibitory. Dotted curved region at premotoneuronal terminals denotes presynaptic inhibition acting selectively on the afferent paths to motoneurons.

should check the following six experimental details. Failure to disclose these methodological details is as unhelpful as failure to perform them.

1) All maximal efforts should be accompanied by some instruction and practice.

2) Feedback of performance should be given during the efforts (e.g., clear visual display) rather than delayed until after them.

3) Appropriate standardized verbal encouragement should be given (e.g., Refs. 58, 514), preferably by the investigators and others, rather than an audio tape.

4) Subjects must be allowed to reject efforts that they do not regard as "maximal," although with care, this occurs rarely.

5) In studies that involve repeated testing within a session, or studies in patient groups additional precautions are needed. The gain of any real-time visual feedback should be varied so that the subject or patient is not necessarily aware of the magnitude of any decline in performance, the aim being to *maximize* performance without necessarily providing a calibrated indicator of it.

6) With repeated testing over many sessions, weeks, or months, provision of rewards should be considered (326).

These various critical procedures are often ignored. Without attention to such details it is inevitable that voluntary activation will be variable and that it will be submaximal from the outset of the exercise.

A. Training for Strength

Voluntary muscle strength increases with training, but the mechanisms are controversial (for review, see Refs. 90, 223, 225; see also Refs. 503, 507, 539, 637, 638), and there is much intersubject variation (330). Strength may be assessed under controlled conditions such as isometric or concentric isokinetic contractions, or less

controlled conditions such as measurement of the largest weights that can be lifted. If the rate of increase in voluntary strength exceeds that attributable to a change in the muscle, then some of the improvement must have occurred in the CNS, either through learning or altered patterns of muscle and motor unit recruitment. This means that in the untrained state, voluntary activation must have been insufficient to produce maximal evocable force, with training improving voluntary activation, at least in the tested task. Thus any increase in force with training can be split into peripheral and central adaptations, with the latter often termed the "neural training effect."

An early study by Scripture et al. in the 1890s (661) illustrates the issues: subjects squeezed a mercury sphygmomanometer "as strongly as possible." The height attained by the mercury was noted. Over the first 2 wk, maximal performance increased steadily by ~70% for the right hand, but it also increased ~40% on the left hand which was tested on only the first and last day. The increase in strength on the side contralateral to training involved learning a useful strategy that could be applied on either side (see also Ref. 161). The earliest phase of strength training involves learning the right pattern of muscle activation, and once learned it can be applied, for example, on the contralateral side. Such learning has a degree of specificity for the precise voluntary task, for example, the angle at which it was undertaken (e.g., Refs. 273, 409, 451) or its velocity (42). The methodological requirements for measurement of maximal voluntary force may explain why not all studies find rapid and highly specific training effects.

To attempt accurate conclusions about the extent of peripheral and central contributions to increased voluntary muscle strength after training, many investigators have relied on measures that might parallel either central drive (e.g., the EMG) or peripheral force (e.g., muscle cross-sectional area and tetanic force). While application of these approaches has often revealed some neural training effect, the arguments are not always straightforward nor the methods watertight. Some relevant arguments are considered below. The final position is that while results from some methods have been overinterpreted, much evidence favors the view that voluntary activation is a key limiting factor in force production before training.

1. Changes in the electromyogram

The EMG increases within days or weeks of training. This occurs for various training protocols using isometric, concentric, and other forms of contraction, and it may precede purely peripheral adaptations in the muscles (e.g., Refs. 164, 308–311, 415, 539, 547). The simple explanation is that with training more motor units are recruited or are firing faster. However, local peripheral factors also change the surface-recorded EMG. These include, first, a change in the amplitude of the single fiber action potential (due to a change in fiber size, membrane potential, or sarcolemmal function). Second, the recorded potential may change due to altered electrical conductivity between the electrodes and around the muscle fibers. These factors can be partially controlled by measurement of the compound muscle action potential produced by supramaximal nerve stimulation (M_{max}). Increased voluntary EMG after dynamic training of a hand muscle was observed (194) in the absence of a change in the maximal muscle action potential, but others found a parallel increase in voluntary EMG and M_{max} after quadriceps training (611). Many factors including changes in fiber type, intramuscular ionic concentrations, and sodium-potassium pump content will alter the muscle fiber action potential (e.g., Ref. 665). Third, the contribution of far-field EMG sources to the signal may change due to altered drive to synergist or antagonist muscles. Intramuscular recordings from these muscles would be instructive here.

If the above factors are controlled, then a real change in the surface EMG after training will reflect a change in the neural drive to the muscle. However, the translation of a real increase in surface EMG into force also needs scrutiny. For example, an increase in the number of doublet discharges (i.e., discharges with interspike intervals of ~5 ms) (38, 178) during the sustained phase of a maximal task may not increase force, whereas doublets during the initial concentric phase of a task will increase the shortening velocity and rate of force production. Initial doublets may minimize later force declines (75) (cf. Ref. 475). The propensity to fire doublets is probably largely regulated at the motoneuron. The contraction times of the motor units may shorten due to training, and thus fusion would need a higher rate of discharge. Then, increased surface EMG would not necessarily signify an enhanced ability to extract muscle force. Thus, in terms of both the peripheral EMG signal and the force-EMG relationship, an increase in the surface EMG is not an invariant index of an increase in voluntary activation after training. This consideration should be extended to measurements of reflexes after training (e.g., Refs. 536, 639).

In a few studies single motor units have been studied after training. With months of practice, the ability to sustain the discharge of high-threshold motor units in the toe extensors improved and central fatigue declined (301). Both observations point to an ability to improve the neural drive to muscle in a strong contraction. After 12 wk of dynamic training of ankle dorsiflexor muscles, whole muscle contraction time was unchanged, but the MVC and speed of ballistic contractions increased (729). The percentage of doublet discharges increased sixfold (from 5 to 30% of the units), and the maximal firing rates at the onset of ballistic efforts increased. Less direct evidence suggests that the maximal rate of force development is usu-

ally limited by the ability to deliver asynchronous motor unit discharges with short initial interspike intervals (see Refs. 484, 532).

2. Changes in muscle cross-sectional area

Increases in maximal voluntary force after training have been compared with increases in cross-sectional area of muscle. The anatomical cross-sectional area of muscles apparently does not increase as much as maximal voluntary strength (e.g., Refs. 353, 369, 376, 472, 547). In a review, Booth and Thomason (90) estimated that cross-sectional area increases by 0.1%/day with strength training, whereas an estimate across studies reveals that voluntary force typically increases by ~1%/day. If the training period is brief, this suggests that voluntary activation was incomplete before training (90). However, not all studies confirm this disproportionate change, and the argument is indirect (e.g., Refs. 376, 494, 547). It assumes that measures of anatomical cross-sectional area are a valid measure of the force-generating capacity, a property which depends on physiological cross-sectional area and specific tension. Physiological cross-sectional areas are two to eight times the anatomical cross-sectional areas in leg muscles (252). Ideally, corrections should be included for changes in muscle fibre type, specific tension, changes in architecture of both muscle fibers and tendon, changes in length-tension properties of muscle fibers, and changes in nonmyofibrillar components of the muscle cross section (e.g., Refs. 390, 493, 494; cf. Ref. 166). It is difficult to estimate the cumulative effects of the necessary corrections. Any could cause large errors in the assumed proportionality between a muscle's apparent cross-sectional area and the force at the tendon.

3. Changes in evoked muscle force

Because the response to nerve stimulation bypasses volition, such responses have been checked before and after training. Maximal voluntary force has been reported to rise more than the increase in tetanic force in a number of studies (e.g., Refs. 164, 506, 547, 772). Data from a typical study are shown in Figure 7. Force evoked by artificial stimulation is not the same as that produced volitionally in more ways than just the lack of intervention of the will. As is critically important during sustained efforts, voluntary contractions use natural motor unit firing patterns that may enhance force rises and reduce force declines. However, voluntary contraction also allows full use of synergist muscles and those responsible for stabilization of proximal joints. These are not usually included in the artificial stimulation. If trick movements require attention in evaluation of patients with nerve lesions, the same caution must apply to those neurologically intact performing strength tests.

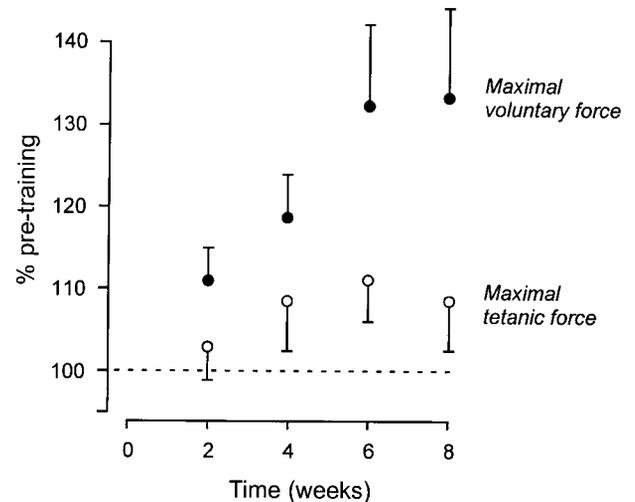Factors needing careful control for evoked force

FIG. 7. Training can induce a greater increase in maximal voluntary isometric force than force produced by electrical stimulation. MVC of first dorsal interosseous (solid circles) is compared with the tetanic force produced by electrical stimulation over the motor point (open circles). Maximal tetanic force increased by 11% after 8 wk of strength training (80 MVCs/day), but maximal voluntary force increased more, by 33%. Forces have been normalized to their initial pretraining values. Values are group mean data ± SE. [Redrawn from Davies et al. (164).]

measures include the following: the degree of potentiation (especially of the twitch), the duration of the tetanus (peak forces may not be reached in short tetani), the maximal frequency of stimulation, and the unintended stimulation of antagonists. For example, ulnar stimulation activates both abductors and adductors of the fingers, and common peroneal nerve stimulation activates ankle plantarflexors as well as dorsiflexors. In many studies, the frequency and level of stimulation are limited by the tolerance of the subject. Mosso (540) long ago reported his unwillingness to inflict a painful current and he "had not the heart to use it, in spite of the devotion" of his subjects. Supramaximal stimuli that avoid antagonists are best. Tetani at submaximal intensities will not necessarily test the motor units used in training because weak stimuli preferentially excite large motor axons (with high thresholds for voluntary activation). Furthermore, if submaximal intensities are used, different motor units will be activated in different trials due to intrinsic and extrinsic variations in axonal threshold. Fortunately, the limit imposed by painful stimulation is less when stimuli are delivered *during* strong contractions, as with twitch interpolation, presumably because sensory "gating" at cortical and subcortical levels makes the same stimulus much more bearable.

4. Imagined training

If imagination of exercise improves voluntary strength, then voluntary activation had to be submaximal before "training," and it was improved by mental re-

hearsal. Yue and Cole (773) evaluated the effect of 4 wk of imagined training on the MVC of abductor digiti minimi, an intrinsic hand muscle. This muscle was selected because it is rarely used in large sustained efforts. Voluntary strength increased by 22% in those undertaking imagined training and 30% in those training with real contractions (statistically equivalent increases), while there was no increase in a control group. Twitch force of abduction produced by ulnar nerve stimulation and the force of voluntary toe extension were unchanged in all groups. Voluntary strength increased with both real and imagined training on the contralateral nontrained side by ~10%. Voluntary EMG (normalized to the maximal compound muscle action potential M_{max}) increased with real training, but not imagined training, and it did not increase on the contralateral side. Because the increases in voluntary abduction force were poorly correlated with the force of flexion of the little finger, they are unlikely to reflect hypertrophy of abductor digiti minimi produced by imagined training. This study provides unequivocal evidence that voluntary efforts of the tested muscle did not produce maximal evocable force before training.

An attempt to reproduce this effect for the elbow flexor muscles failed (326). Imagined training for 8 wk produced only a small increase in force. Maximal voluntary activation measured with twitch interpolation was high before the training (~96%) and did not increase after it. This finding has been noted for quadriceps (316; see also Ref. 376), although the sensitivity of the measures was lower. The findings suggest that any increase in force that accompanies training for these muscle groups reflects changes in the muscle. Subjects undergoing real training increased strength significantly more (18%) than those performing no training (6.5%) or imagined training (6.8%). There is no obvious technical reason for the discrepancy in the two studies. However, a likely explanation is that maximal voluntary activation is lower for some intrinsic hand muscles than for elbow flexors (327). Hence, a greater central reserve, accessible by real or imagined training, exists for intrinsic hand muscles.

B. Unilateral and Bilateral Contractions

Support for the view that voluntary activation is limited also comes from studies of unilateral and bilateral contractions. If, as commonly reported, the MVC during bilateral contractions is less than the sum of the forces produced in unilateral MVCs, then voluntary activation in the bilateral task is deficient (e.g., Refs. 341, 423, 663, 733, 734). Training, familiarization, and the actual task may reduce this bilateral "deficit" (341, 629, 663; cf. Refs. 632, 653). The ratio of the bilateral maximal force to the summed forces from each side may be as low as 75%, but is usually ~90%. Because measurements of force and

EMG do not necessarily give concordant results for the size of the deficit (e.g., Refs. 341, 653), biomechanical constraints in the bilateral task (especially contraction of remote stabilizing muscles) must be relevant. However, neural factors are involved. For example, direct interhemispheric connections and subcortical pathways can contribute to mediate an inhibitory interaction among homologous muscles (e.g., Refs. 188, 282).

Two recent studies have examined in detail the behavior of muscles activated in bilateral MVCs. In one, the voluntary activation of adductor pollicis was studied during simultaneous contralateral contractions of the homologous hand muscle or of the contralateral elbow flexors (327). Bilateral maximal contractions of the elbow flexors were not performed due to the difficulty in stabilization of the subject (cf. Ref. 565). Voluntary activation of the thumb adductors was ~90% (based on twitch interpolation) and unchanged when the subject produced maximal force by elbow flexion on the contralateral side. However, it diminished slightly, but significantly (by ~1.5%), when both thumb adductors contracted simultaneously, and, as would be expected, maximal force showed a similar difference. Furthermore, voluntary activation changed in parallel for both muscles in simultaneous maximal efforts (Fig. 8). This positive correlation between voluntary activation on the two sides did not occur for simultaneous efforts of the thumb adductor and elbow flexors. It is as if supraspinal drive changes together for the muscle pair, rather than activation on one side being at the expense of that on the other side. When unilateral and bilateral con-
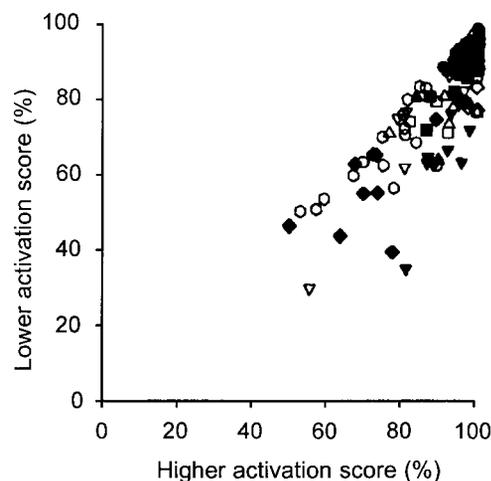

FIG. 8. Bilateral contraction of adductor pollicis assessed with twitch interpolation. Voluntary activation was measured in MVCs of thumb adduction on the left and right sides using twitch interpolation with supramaximal stimulation of the ulnar nerve at the wrist. The higher measure of maximal voluntary activation is plotted against the lower one achieved concurrently in opposite limb. The level of voluntary drive was highly positively correlated on the two sides when subjects simultaneously contracted the thumb adductors bilaterally in MVCs. Data are from contractions in all subjects with each symbol representing one subject. [From Herbert et al. (326).]

tractions of the quadriceps were performed with measures of force, surface EMG, motor unit firing rates, and voluntary activation, there was no support for a significant deficit in bilateral performance (361). There were no confounding effects due to cocontraction of antagonist muscles.

In summary, although a deficit in force production may exist for bilateral contractions of some homologous muscles, the effect can be relatively small. Moment-to-moment performance of homologous muscles may be correlated due to variations in supraspinal drive.

C. Twitch Interpolation and Voluntary Activation

As indicated in section IA, the technique of twitch interpolation seemed to measure voluntary activation of muscle. Merton (524) reported that the increment in force produced by a supramaximal stimulus to the ulnar nerve supplying adductor pollicis diminished linearly as voluntary force increased and that at maximal voluntary effort no additional force was evoked (524). The proportional decline with increasing central drive has been confirmed in animal studies with twitches interpolated to the diaphragm during increasing central respiratory drive, but the linear decline was only examined over a small range because the highest neural activation that could be obtained was well submaximal (186, 233). Merton's original claims can now be assessed in detail.

1. Maximal efforts

Usually voluntary activation is derived by the formula: voluntary activation = $100(1 - T_{interpolated}/T_{control})$, where $T_{interpolated}$ is the size of the interpolated twitch and $T_{control}$ is the size of a control twitch produced by identical nerve stimulation in a relaxed potentiated muscle. If evoked forces are measured at high gain with the voluntary force offset using a special amplifier (312), then small force increments can frequently be measured in response to single stimuli delivered during attempted MVCs. With this conventional formula, voluntary activation could exceed 100% if interpolated twitches had negative values. This is physiologically unreasonable, and MVCs with a rapidly declining baseline are best discounted (for discussion, see Ref. 328).

With Merton's original system, force increments of ~5% of the resting twitch could not be easily resolved, whereas modern systems can resolve below 1% of the twitch (261), which may be below 0.1% of the MVC. Figure 3 enhances the resolution of Merton's system and contrasts it with that in a recent study of the same muscle (327). Voluntary activation was not usually complete for MVCs of thumb adduction tested with supramaximal stimulation of the ulnar nerve. A similar conclusion was reached using motor cortical stimulation, although the measures of voluntary activation with

the two forms of stimulation are not comparable (see sect. IV). Twitch interpolation is ideally suited to estimate voluntary activation when all muscles contributing force are stimulated. As indicated below this situation occurs rarely (if ever). Thus it does not apply for thumb adduction, although the adductor pollicis does provide the majority of the torque (681).

Twitch interpolation has now been applied in various ways for examination of maximal voluntary activation in a range of muscles, including abdominal muscles (269, 697), abductor digiti minimi (266), adductor pollicis (51, 65, 66, 69, 72, 215, 327, 524, 672), ankle plantarflexors (45), biceps brachii (9, 10, 13, 14, 22, 51, 179, 192, 260, 266, 327, 459, 514, 551, 564, 633, 702), brachioradialis (13), diaphragm (14, 48, 49, 201, 267–269, 431, 511, 514, 516, 530, 674), extensor digitorum brevis (300), first dorsal interosseous (712), masseter (471), quadriceps femoris (e.g., Refs. 103, 104, 283, 316, 349, 361, 376, 438, 553, 562, 610, 616, 621, 632–634, 690, 695, 722, 743), soleus (51), tibialis anterior (44–46, 266, 397–399, 712), and triceps brachii (709). In many studies insensitive forms of twitch interpolation have propped up the view that voluntary activation is "maximal" and therefore that measures of voluntary force (motor unit firing rates) are also roughly "maximal." However, other studies have found definite evidence that additional stimulation produces more force than can be achieved with volition. Furthermore, a realistic model incorporating measured muscle properties and motor unit firing rates confirms even at maximal voluntary force small superimposed twitches should be evident (Fig. 9A) (328).

Few studies using twitch interpolation have compared voluntary activation during maximal efforts of different muscles. Belanger and McComas (45) found that ankle plantarflexors could not be activated as fully as ankle dorsiflexors in attempted MVCs. This difficulty in voluntary activation of plantarflexors (particularly soleus) has been confirmed by others using twitch interpolation (63) and is familiar to electromyographers who coax activity from this muscle in patients. Thus voluntary activation varies between muscles. Corticospinal connections may offer a partial explanation for the muscles acting around the ankle because the predominant initial effect of cortical stimulation on soleus motoneurons is inhibition (e.g., Refs. 98, 154). Maximal voluntary activation of an intrinsic hand muscle (adductor pollicis) is lower than that for the elbow flexors when tested in the same session in the same subjects (329). Similarly, voluntary activation of the diaphragm in maximal inspiratory tasks is also slightly lower than that of the elbow flexors (14). Maximal activation of elbow flexor muscles with radial innervation is less than that of those with musculocutaneous innervation with the forearm supinated (13). Twitch interpolation has revealed that voluntary activation of some muscles is often well submaximal in at-
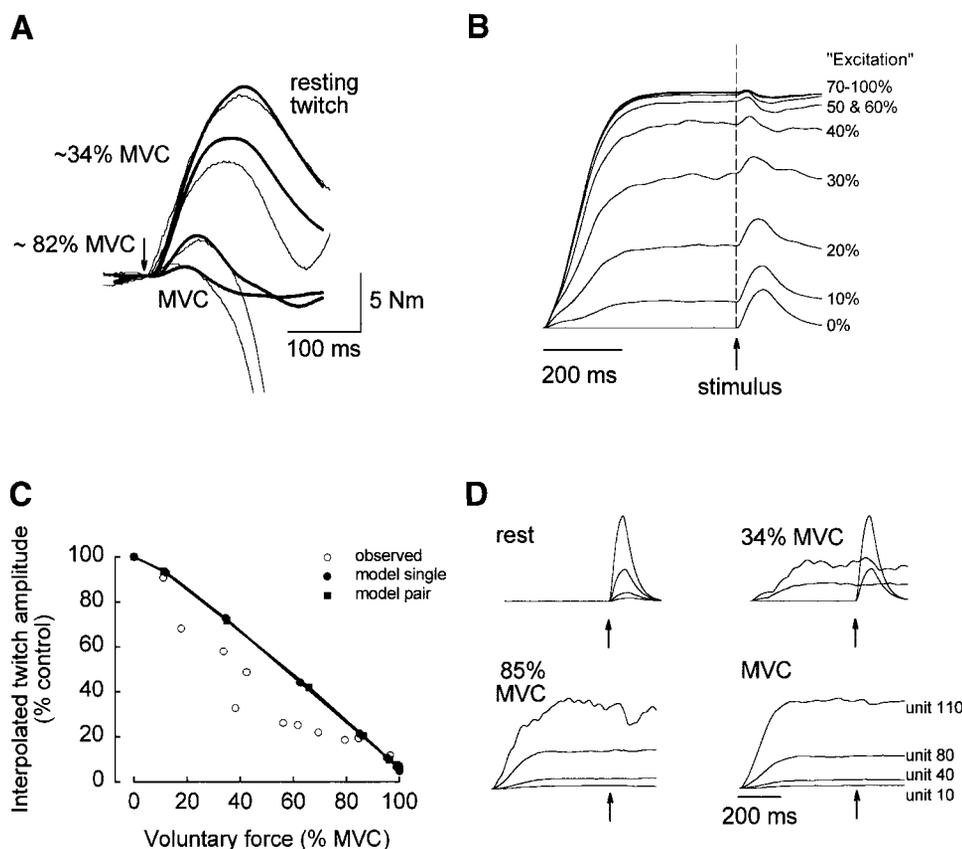
FIG. 9. Real and simulated twitch interpolation for adductor pollicis. *A*: simulated and experimental interpolated twitches of adductor pollicis. Twitches obtained at rest and during contractions to ~34, ~82, and 100% MVC. Twitches are aligned with onset of force (shown by arrow) and baseline force preceding the stimulus subtracted. Thick line shows simulated data, and thin lines show experimental data. Note that the twitch was nearly but not fully extinguished during the "maximal" contractions. *B*: simulated force responses to stimuli interpolated at varying levels of "excitation" of the motoneuron pool. Force responses of the whole muscle when excited from 0 to 100% of maximal excitation are shown. Stimulus is delivered at the arrow. Note the small force increments at excitations which correspond to maximal observed motor unit firing rates. *C*: amplitude of interpolated twitches (expressed as a percentage of resting twitch amplitude) at contraction intensities of 0–100% MVC. Experimental data are shown, as well as simulations with single and paired interpolated stimuli. *D:* force response of the 10th, 40th, 80th, and 110th motor units (with units numbered in order of size) at rest and at 34, 85, and 100% MVC. Stimuli were delivered at the arrows. Force scale differs between panels. Note the importance of high-threshold motor units in generation of the interpolated twitches. [From Herbert and Gandevia (328).]

tempted maximal voluntary efforts, for example, in the jaw closers (471) and the abdominal muscles (269, 697). No muscle appears blessed with truly optimal drive during maximal isometric efforts. Given the variety of muscles tested (proximal, distal, truncal, upper limb, and lower limb), this conclusion suggests that no central or peripheral specialization of a muscle protects it from some failure of voluntary activation.

How should voluntary activation in MVCs be reported? The median of trials in a subject provides the best measure of central tendency as the data are usually not distributed normally, with voluntary activation being constrained to values at or below 100%. Results from subjects tested repeatedly are shown in Figure 10. An alternative is to average the evoked responses from acceptable trials, but the average is unduly influenced by single trials with poor activation (266).

2. Methodological issues and submaximal efforts

Another way in which data obtained from twitch interpolation have been used to infer that voluntary activation produces submaximal force is to extrapolate the relationship between the size of the superimposed twitch and the voluntary force at which it was obtained. The use of twitch interpolation to predict maximal voluntary force was first noted by Merton (524) and has been applied by others for the diaphragm (e.g., Refs. 48, 49, 269), quadriceps (e.g., Refs. 43, 562, 633), elbow flexors (e.g., Refs. 179, 192), and jaw closers (471). Unfortunately, many experimental errors and physiological realities conspire to make it difficult to define a simple linear function between a force increment to superimposed nerve stimulation and the absolute level of "drive" to the muscle or its motoneurons. These are summarized in Figure 11.
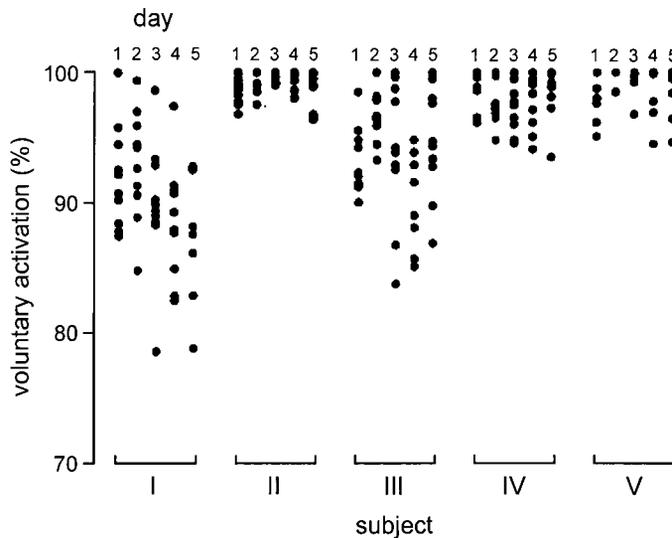
FIG. 10. Reliability of measures of maximal voluntary activation measured with twitch interpolation for elbow flexor muscles. Data shown for each MVC were performed by 5 subjects studied on 5 separate days. Voluntary drive was reproducible but differed significantly between subjects. [From Allen et al. (9). Copyright 1995 John Wiley & Sons, Inc.]

They include failure to use a fully potentiated twitch, a compliant myograph (e.g., Ref. 465), antidromic collision and axonal refractoriness (328), nonlinearities between firing frequency and force, recruitment of synergists (13), and use of a stimulus that inadvertently activates antagonist muscles (22, 108) or is submaximal.

The common equation for voluntary activation has some predictable consequences. First, the value of activation depends on the size of the control twitch. Given that a motor unit recruited in an MVC will be potentiated, the control twitch should also be potentiated. In practice, the control twitch is produced a short time (<5 s) after the maximal effort. The assumption that the degree of potentiation (combined with any fatigue from the MVC) is equivalent for the interpolated and the control twitch has not been formally tested. Second, when fatigue develops, it preferentially drops the forces produced with isolated single twitches (and at low frequencies, so-called "low-frequency" fatigue), an effect ascribed to impaired excitation-contraction coupling (e.g., Refs. 152, 215). This means that voluntary activation may erroneously appear to deteriorate; a practical solution is to use paired stimuli that show a decline in force with fatigue that parallels the decline in maximal voluntary force. Third, if it is to be used quantitatively, the technique relies on stimulation of the same motor axons in the twitch and during the contraction. This cannot be reliably ensured unless supramaximal stimuli are delivered. With repeated contractions and fatigue, motor axons are hyperpolarized so that fewer are recruited with the same stimulus intensity (55, 723).

A natural modification of "twitch" interpolation was

to increase the size of the "signal" by delivery of more than one stimulus (either a pair, or a brief tetanus, Fig. 9C) (267, 301, 328, 552, 692; see also Ref. 329; cf. Ref. 43). Superficially this is attractive and, at least for paired stimuli (10-ms interval), the induced errors are trivial when analyzed in a detailed model (328). However, as the number of stimuli and duration of stimulation increase, there are unwanted consequences due to antidromic activation of motoneurons and Renshaw cells, plus reflex effects on synergists and remote muscles. When applied to some elbow flexor muscles at high voluntary force (>80% MVC), superimposed pulse trains do not always produce a predictably larger force, perhaps due to an inhibitory reflex involving synergists. For quadriceps, superimposed submaximal tetanic stimulation increased the signal, but this was more than offset by an increase in the "noise" of the background force (552). Even though sub-
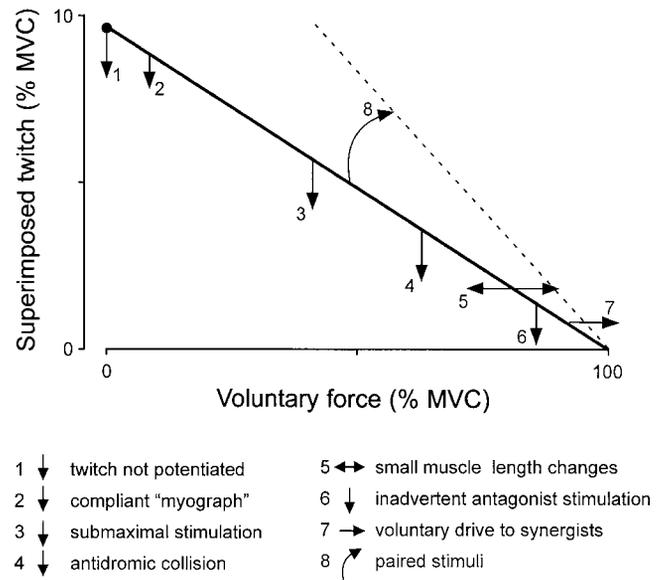

FIG. 11. Factors affecting the relationship between the size of an interpolated muscle twitch to a single stimulus and the level of voluntary isometric force. The inverse relationship between voluntary force and the size of the superimposed twitch can be markedly distorted by experimental factors. It is drawn as a simple linear relation (see Ref. 328), with the twitch contraction of the muscle being 10% of the maximal voluntary force. Thus the initial twitch force will be lower than it should if the muscle twitch is not potentiated and if the myograph and connections to it are not stiff at low forces. Additional factors that reduce the twitch force during stronger contractions include antidromic collision (and muscle/nerve refractoriness). The size of superimposed twitches will also be reduced if any antagonist muscles are inadvertently stimulated. Other factors that can influence the precise shape of the relationship include the recruitment of additional synergists (not in direct proportion to the agonist) and failure to prevent small changes in length of the tested muscles. The dotted line shows the increase in slope of the relation when paired stimuli are used. The distortions can be accentuated when many muscles evoke the voluntary force and the test stimulus is submaximal. The arrow indicates the direction of change and not its magnitude. Most of the distortions occur across the full range of voluntary forces. The figure emphasizes that many factors can distort the relationship between voluntary force and the superimposed twitch (i.e., voluntary activation).

maximal tetanic stimulation fails to activate all relevant axons for quantitative twitch interpolation, an evoked force increment is nonetheless unequivocal evidence of a failure of voluntary drive.

At least for some muscles, the relationship between the response to the interpolated stimulus and voluntary force seems nonlinear at high forces. Maximal voluntary forces are produced that are higher than predicted from linear extrapolation of data obtained at lower forces. An inference is that maximal evocable force greatly exceeds that observed or predicted by linear extrapolation if twitch interpolation becomes insensitive as a measure of voluntary activation at high voluntary forces. Recent experimental and modeling studies have addressed this issue.

Single, pairs, and sets of four stimuli were applied to biceps brachii during graded voluntary contraction of the elbow flexors in a protocol that minimized the effects of potentiation (13). The size of the evoked twitch(es) in biceps/brachialis decreased in proportion to the voluntary force until ~80% MVC where the slope became less steep. At least two factors were shown to contribute to this nonlinearity. First, based on twitch interpolation of radially innervated elbow flexors, these synergists were not activated proportionately, being less well activated at high voluntary forces than biceps brachii. Second, despite a near rigid myograph and attempts to fix the shoulder, it was impossible to eliminate some initial shortening and then lengthening of the elbow flexor muscles. The adjective *isometric*, frequently used to describe such contractions, is somewhat unsatisfactory; not only do sarcomeres shorten and thereby lengthen tendons, but whole end-to-end length is not maintained. It was concluded that factors other than voluntary activation of biceps contributed to the nonlinear behavior at high voluntary forces. A third technical factor is that if excessive currents are used to stimulate biceps and brachialis, the weaker antagonist elbow extensor muscles inadvertently contract (22, 108). This would truncate the diminishing twitches of the elbow flexors and result in abolition of a force increment at submaximal voluntary forces.

One study that shows a markedly concave relationship between interpolated force increment and voluntary force used a large interelectrode distance such that stimulation of elbow extensors would be favored (192). It is notable that in the comparatively few studies in which a single muscle has been studied with single supramaximal stimuli, the linear relation predicted by Merton holds reasonably well (266, 524, 633; see also Ref. 471). A detailed model of twitch interpolation for adductor pollicis predicts the near-linear decline in size of interpolated responses (328). Together, the data suggest that for single muscle groups tested rigorously, the extrapolation method can predict maximal evocable forces and that these are not greatly in excess of those observed experi-

mentally. The latter conclusion is supported by the results of motor cortical stimulation (see sect. IV). The model has also been useful because it has highlighted the nonlinear relationship between excitation of the motoneuron pool and its force output. At high levels of "voluntary" drive, even small degrees of central fatigue represent rather larger reductions in net motoneuronal excitation.

Finally, an alternative to interpolation of stimuli during the maximal contractions to measure voluntary drive is comparison of the decline in maximal voluntary force with that in the force of brief tetanic stimulation delivered at rest. The results of this approach must be interpreted cautiously (e.g., Refs. 61, 742). When submaximal stimuli are given during rest periods between contractions, the increase in motor axonal threshold produced by prior activity will ensure that a smaller number of motor axons (and thus muscle fibers) are stimulated, while reduced voluntary activation will mean that the stimulated high-threshold units have contracted less, a fortuitous cancellation of errors that could minimize any discrepancy and act to preserve the ratio of tetanic to voluntary force. Another problem is that tetanic nerve or intramuscular stimulation can reflexly (and variably) add force to the contraction produced by submaximally driven motor axons (121, 148, 291, 436). The phenomenon has been under recognized with tetanic stimulation of some human muscles. Indeed, such an effect is probably evident in the rising tetanic forces produced at rest as depicted in Figure 14 and may reflect nonlinear (plateaulike) properties of motoneurons. These superadded "reflex" effects can exceed 20% MVC (148).

3. Nonisometric contractions

Many of the methods described earlier in this section can give information about voluntary activation during concentric and eccentric contractions. Twitch interpolation is technically more demanding when muscle length is changing. Interpolated trains of stimuli to quadriceps evoked small tetani that were not detectable during shortening contractions as low as 50% MVC (41; cf. Refs. 362, 553). A recently devised myograph and analysis has allowed small torque increments to be detected with reasonable sensitivity using single stimuli during maximal concentric contractions of elbow flexors (to 300°/s) (263). As with isometric contractions, voluntary activation was high but variable between subjects, and it could remain high as peripheral fatigue supervened (cf. Ref. 553). Even this method is unlikely to permit measurement of voluntary activation during the fastest concentric contractions. During eccentric contractions drive is more interesting because of the increased contractile force achievable during lengthening. Mounting evidence points to inadequate motoneuronal activation during maximal voluntary eccentric contractions, possibly due to the reflex inhibition

at a motoneuronal and premotoneuronal level (199, 553, 664, 750). Golgi tendon organs will be potently driven by the active muscle lengthening (e.g., Refs. 7, 597). Paradoxically, however, with maximal lengthening contractions the reflex support from muscle spindles should be very high because of the combined effects of strong fusimotor drive and muscle stretch (7, 115).

4. *Voluntary activation in pathological conditions*

Conditions that impair maximal voluntary activation of motoneurons will usually produce an abnormal reduction in strength, i.e., weakness (for review see Ref. 505). Twitch interpolation has revealed the expected impairment in voluntary drive in conditions when there is a corticospinal lesion, such as stroke (550), spinal cord injury (709), and multiple sclerosis (400, 610, 672), with a lesser impairment in amyotrophic lateral sclerosis. There is a small but stable reduction in maximal voluntary activation in many patients with prior polio, a finding which could not be explained by altered muscle contraction dynamics (10, 11, 40; cf. Ref. 670). It may result from diminished descending drive and fusimotor-mediated spindle excitation. Joint pathology, even if acute, has long been known to reduce voluntary strength (172, 741, 765). This reflects reduced voluntary drive (e.g., Refs. 349, 350, 633), due to spinal reflex inhibition and supraspinal factors, and depression of the H-reflex has been reported (e.g., Refs. 396, 684). Chronic cardiac failure impairs drive to limb muscles, perhaps secondary to diminished use (317) (see sect. v), whereas voluntary drive to the diaphragm seems well preserved in chronic airflow limitation (549) but is variable in asthma (14). Voluntary activation is significantly lower and more variable in obese compared with nonobese males (82). An interesting use for twitch interpolation has been in patients with chronic fatigue, myalgia, and effort syndromes (e.g., Refs. 283, 360, 399, 459, 519, 533, 634, 690). Results for voluntary activation and central fatigue in these studies have varied presumably due to rather small numbers of subjects and heterogeneity of the patient groups. Twitch interpolation may be also suitable for detection of malingering (438, 504), although poor activation alone is not a specific finding.

Finally, the links between learning (or training) and voluntary drive may be exemplified by conditions in which high motoneuronal firing rates must produce excessive fatigue, such as myesthenia gravis, or conditions in which the contractile properties of the muscle change. Although not quantified formally, patients with myasthenia appear to have learned the benefit of using submaximal firing rates to prevent of blocking at the neuromuscular junction (663), as a way to aid long- not short-term performance. Myopathic disorders should produce high levels of drive (unpublished observations) (cf. Ref. 499). A similar adaptation may regulate maximal voluntary activation when chronic pathological or physiological changes occur in dynamics of muscle contraction. Indeed, there would be little benefit in changing motoneuron and muscle fiber properties unless motoneurons were driven appropriately. Modeling shows that small changes in twitch dynamics will alter the relation between voluntary activation of motoneurons and maximal evocable force (328; cf. Ref. 611). Although hardly pathological, the changes with aging show the interaction between motoneuron firing properties and voluntary activation: the degree of contractile slowing with age is counterbalanced by a slowing of firing rates so that voluntary activation in isometric efforts can remain high (150, 179, 731; cf. Ref. 316). Other factors differentially increase the irregularity of motor unit firing in nonisometric contractions in the elderly (433).

D. Conclusions

It is widely believed that training increases neural drive to muscles. This is evidence that drive is initially submaximal. However, the evidence comes from observation of changes in EMG, stimulated force, and the effects of imagined training. These findings can be difficult to interpret because of technical limitations, whereas others, such as the effect of imagined training, have not been sufficiently replicated. Further evidence of failure of voluntary activation derives from bilateral contractions. However, this bilateral deficit can be small and is open to alternative interpretations. Strong evidence of failure of neural drive comes from studies employing twitch interpolation or superimposed tetanic electrical stimulation during maximal efforts. Such studies provide unambiguous evidence of failure of voluntary drive across many muscle groups. For technical and theoretical reasons, there is some controversy about whether twitch interpolation can provide quantitative measures of the degree of failure of voluntary activation of motoneurons.

Six specific criteria are given to optimize performance in tests of maximal voluntary isometric contractions (e.g., provision of feedback, etc).

To assess maximal voluntary activation, it would theoretically be best to measure the instantaneous net current driving motoneurons and to compare it with that required to generate maximal evocable force. This is not possible in human studies. However, although manual muscle testing depends on the skill and experience of the examiner, sensitive isometric myographs together with standardized procedures for instruction, practice, verbal encouragement, and force feedback permit reproducible measures of voluntary strength. Twitch interpolation with single stimuli can measure maximal voluntary activation, although for each muscle and stimulus type, critical methodological issues must be addressed. Use of the technique

to predict maximal voluntary force by extrapolation is theoretically justifiable. However, in practice, the confidence intervals on extrapolated estimates can be appreciable because several experimental factors, particularly the use of submaximal stimulation and muscle actions with several synergists, lead to extrapolations of maximal force that are larger than observed in practice or predicted on theoretical grounds.

III. DEVELOPMENT OF CENTRAL FATIGUE

A. Central Fatigue During Isometric Contractions

As argued in section II, voluntary activation may not be optimal during brief maximal efforts but a key question is how this changes during sustained or repeated contractions. At least for sustained MVCs, the motor unit firing rates decline, initially rapidly, and reach a plateau after about 30 s (Figs. 4 and 12). The maximal rates vary for different subjects and muscles, being particularly low for soleus (e.g., Refs. 51, 64, 77). During maximal isometric efforts, the firing rates decline, and this has been documented for a range of upper and lower limb muscles (e.g., Refs. 65, 264, 300, 579, 767). The rate of this decline may vary between muscles, perhaps due to the preponderant type of motoneuron (e.g., "slow" vs. "fast"). In one toe extensor muscle, the decline in firing rate appears minimal (476).

The reduced discharge frequency of spinal motoneurons will reduce force unless muscle speed has slowed in a parallel fashion for each slowed unit. In addition, some motor units probably stop firing altogether (197, 276, 302, 579). While muscle relaxation time (and sometimes also contraction time) usually lengthen during sustained or intermittent MVCs (e.g., Refs. 64, 65, 214, 288, 347), twitch interpolation has revealed that voluntary activation becomes progressively lower. Central fatigue has been documented in several muscle groups for sustained and intermittent MVCs including elbow flexors (e.g., Refs. 11, 12, 260, 459), ankle plantarflexors (391), ankle dorsiflexors (712), and quadriceps (61, 68) (see also Refs. 104, 767). In some muscles such as the jaw closers, endurance is often limited by pain (142).

Central fatigue with isometric contractions of limb muscles occurs in subjects regardless of whether the initial level of voluntary activation is low or high. However, the decline in voluntary activation during isometric MVCs does not occur smoothly, and its time course is better defined with data from several subjects or (less practically) several contractions (Fig. 13). Another indicator of a central failure of voluntary activation can occur when an initially submaximal isometric contraction (30% MVC) is held until it can no longer be continued (Fig. 4). Before termination of the task, twitch interpolation reveals that voluntary drive is not complete for ankle plantarflexors (466, 467) or first dorsal interosseous (783). Task failure could have been delayed if central fatigue had not intervened.

Development of central fatigue can also be inferred from the increasingly obvious fluctuations in force and variations in motor unit firing rates as the voluntary force declines (Figs. 4B and 14). Such fluctuations require greater energy expenditure by the muscle than a smooth
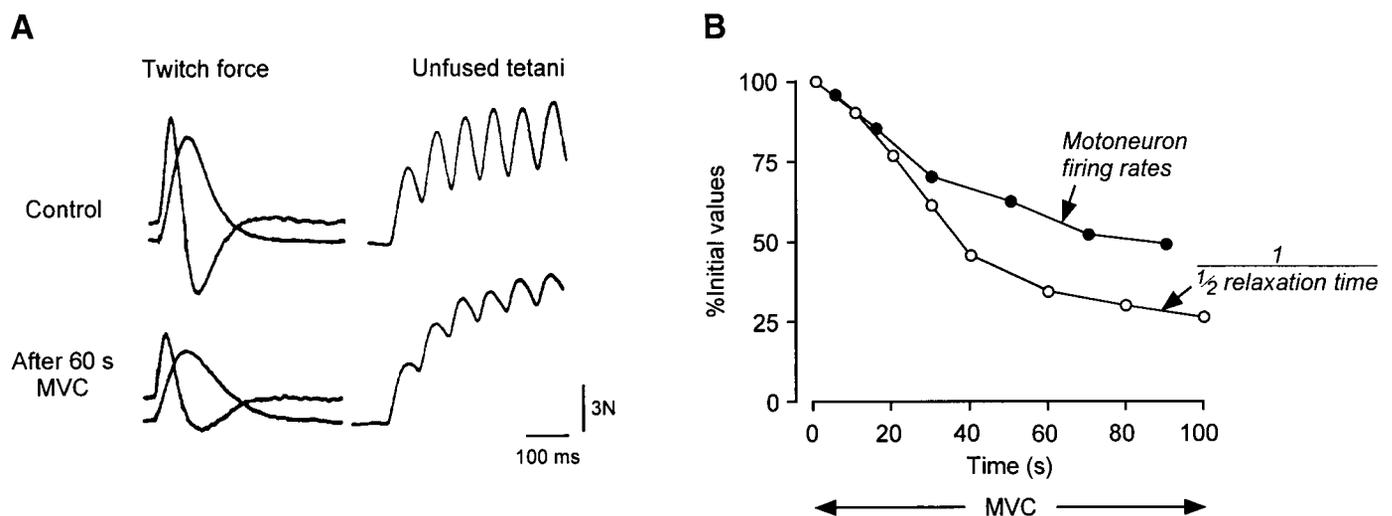

FIG. 12. Associated change in whole muscle twitch dynamics and maximal discharge frequencies during a sustained MVC of adductor pollicis. A: an example of altered relaxation time after a 1-min MVC. Twitch force (and differentiated force) and the "ripple" with a 7-Hz tetanus are reduced after the MVC. B: the decline in motor unit firing rate during a sustained MVC. Data are pooled over 10- and 20-s duration. The increase in the relaxation time with fatigue is shown as a decline in the inverse of the half-relaxation time. [Redrawn from Bigland-Ritchie and Woods (74).]
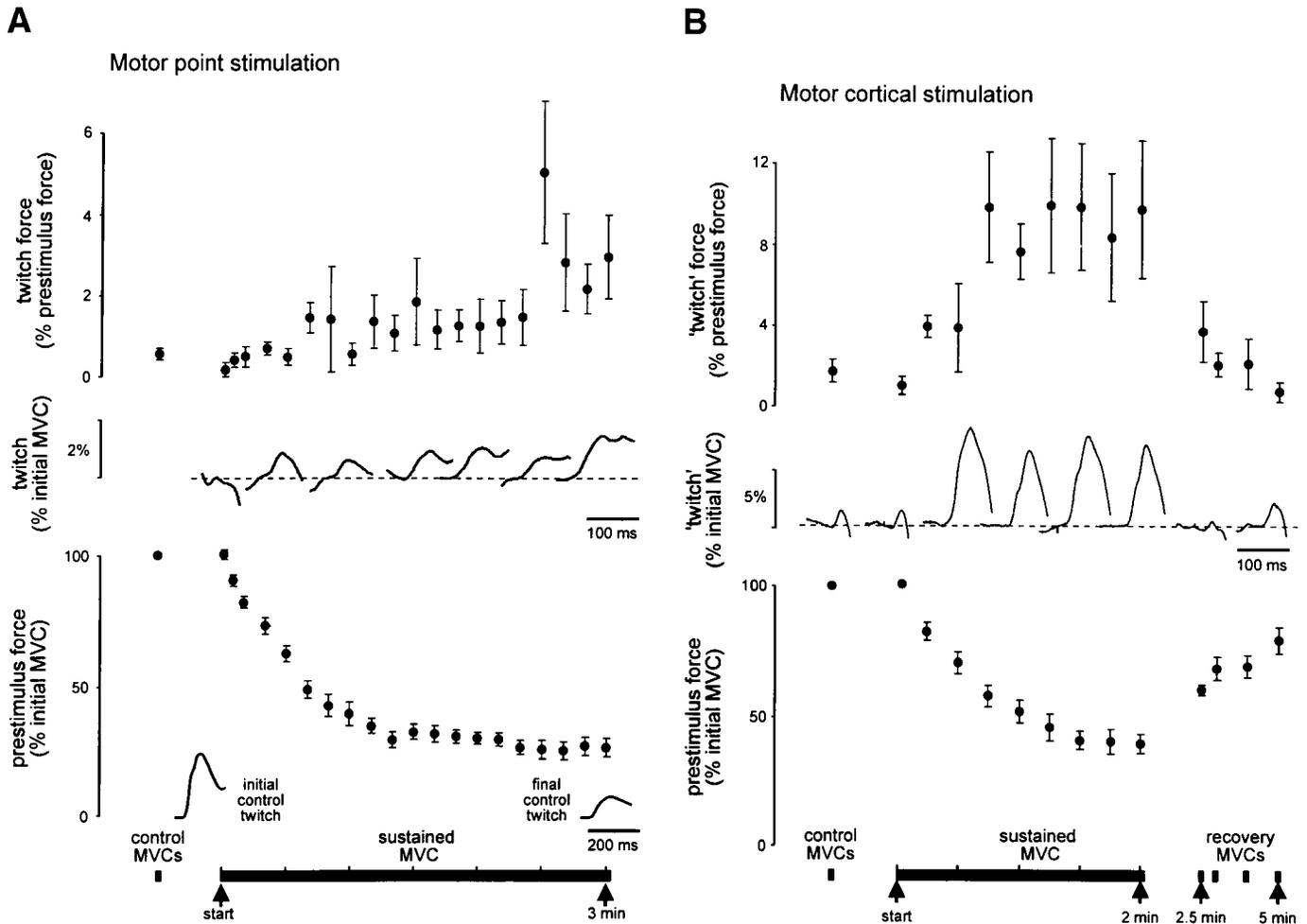
A

Motor point stimulation

B

Motor cortical stimulation

FIG. 13. Reduction in voluntary force and the increase in nerve- and cortically evoked twitches during a sustained MVC of elbow flexor muscles. *A*: *top panel* shows the increment in force generated by a twitch evoked by motor-point stimulation of biceps brachii. Twitch force is expressed as a percentage of the voluntary force measured at the time of stimulus (*bottom panel*). The twitch force superimposed on the MVC increases progressively during the contraction. Values are group means ± SE. *Middle panel* shows typical force traces from one subject. Traces show the twitch response to the stimuli delivered at the start and each 30 s through the contraction. Each trace shows 25 ms before the stimulus and has been truncated after the peak of the twitch. The horizontal dotted lines mark force at the time of stimulation. *Bottom panel* shows the decline in voluntary force, expressed as a percentage of the initial MVC. *Insets* in the *bottom panel* show typical twitches elicited from the relaxed muscle before and after the MVC to confirm development of peripheral fatigue. *B*: similar display as for *A*. Force increments produced by magnetic stimulation of the motor cortex. [From Gandevia et al. (260).]

force profile (e.g., Refs. 169, 462), and they interfere with accurate task performance. Thus their development is an ominous sign. Additional force produced by subjects when asked to perform a "super" effort is another glaring hallmark of central fatigue (Fig. 14) (e.g., Refs. 61, 69). Interestingly, in patients with myesthenia gravis in whom higher motoneuron firing rates would increase neuromuscular block and hence peripheral fatigue, there is a reserve of force available for such super efforts (662a).

B. Muscular "Wisdom": The Decline in Motor Unit Firing Rates

The muscular wisdom hypothesis proposes that motoneuron firing rates decline to match the muscle's con-

tractile speed. The hypothesis relies on a match between the observed decline in motor unit firing rate and the contractile speed of the muscle during MVC. Whether or not such a match occurs through design, by reflex action, or it arises fortuitously under some situations (such as isometric contractions), a neural dilemma occurs if a motoneuron's firing rate is not matched to the contractile behavior of its muscle fibers during fatigue. If the motoneuron rate fails to decline sufficiently to match the slowing of a motor unit's contraction, then firing rates will exceed those for fusion and thus maximize tetanic force, but large reductions in drive to the motoneuron would be needed to reduce force. If the motoneuron rate declines too much, then voluntary activation will be insufficient to obtain maximal force, and central fatigue must appear.
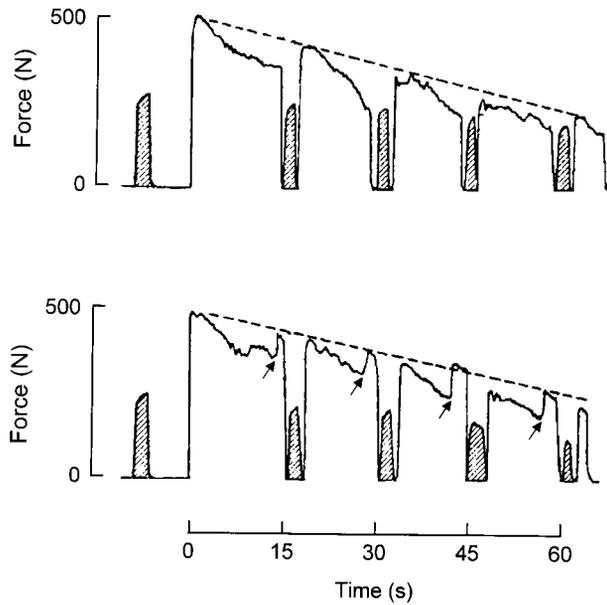
The inability of motoneurons to remain at their initially high firing rates in a sustained MVC can be explained by factors acting at spinal and supraspinal sites (Fig. 6). At a peripheral level the behavior of muscle receptors changes with fatigue as summarized in Figure 15. At a spinal level relevant factors include the intrinsic behavior of the motoneuron, recurrent inhibition, reflex inputs reaching α- and γ-motoneurons and their presynaptic modulation, as well as other neuromodulatory influences acting on motoneurons and spinal circuitry. At a supraspinal level, the output of descending (including corticospinal) paths to motoneurons and the factors that control this output are likely to be important. The contribution of these various factors will vary during the course of fatiguing exercise. For example, in the first few seconds of a strong sustained contraction, the initial propensity of motoneurons to adapt their discharge rate will drive down the firing rate, possibly aided by recurrent inhibition and muscle spindle "disfacilitation," while later, depending on the metabolic activity of the muscle fibers and the extent to which the contraction is ischemic, the reflex inputs from small-diameter muscle afferents will become more important.

While slowing of firing rates and contractile speed develop with fatigue, the two processes would be hard to regulate at a single motor unit level. Each unit would need its firing rate adjusted individually according to its contractile speed and force output. These contractile "out-

Likely changes in muscle afferent behavior during a sustained voluntary contraction
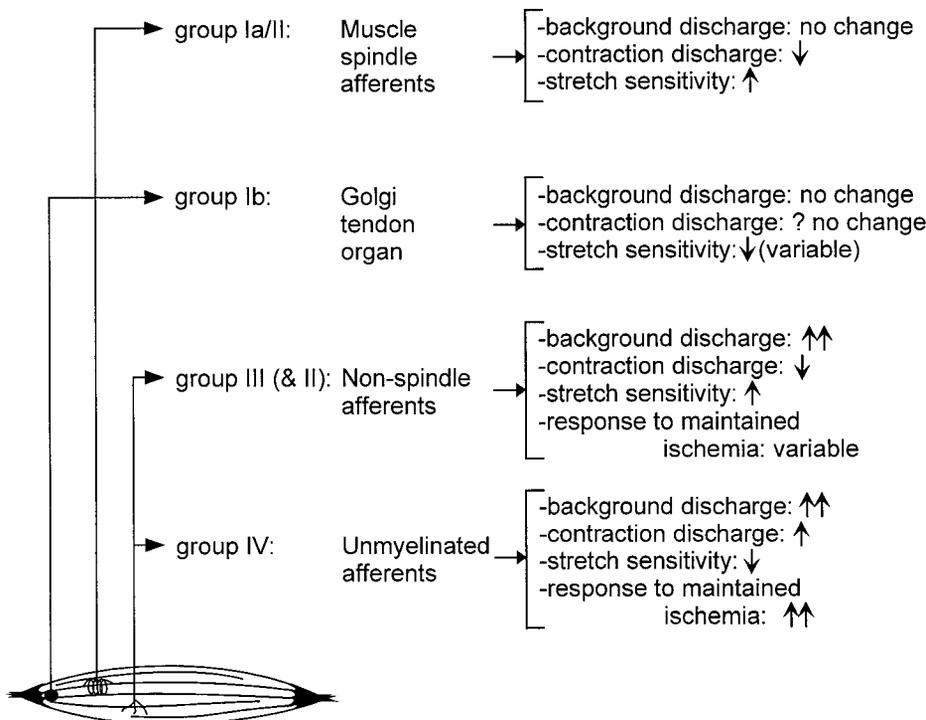
puts" are labile in time and dependent on the temperature, metabolic state, and contraction history of the muscle (with variable degrees of potentiation and fatigue). They vary with the length of the muscle, and they differ among motor units. The "hard lessons" of spinal cord physiology indicate that such an individualistic control of motoneurons is highly improbable, at least via reflex circuitry (461). However, reflex effects may be distributed across the motoneuron pool with the net effect of reducing firing rates. Alternatively, or in addition, so-called intrinsic motoneuron properties generate a declining firing pattern (Fig. 16), and they may be tailored to the motoneuron type (e.g., Refs. 403, 404, 685; cf. Ref. 651). Reliance on an intrinsic property with a short recovery time would preserve the capacity for brief bursts of strength (Fig. 16*A*) and allow frequency modulation of force, albeit in a rather automatic way. For extreme activities such as sustained or repeated maximal contractions, extrinsic sources of drive to motoneurons would become especially necessary.

Although studies in humans can document the changes in firing rate of motoneurons with fatigue, they are not necessarily able to establish unequivocally the cause for the decline. A series of independent studies by Bigland-Ritchie and co-workers (767) and subsequently by Garland et al. (276) founded the view that a spinal reflex arising in group III and IV afferents caused the decline in motoneuron firing rates that underpinned the "muscular wisdom" observed in human MVCs. The evidence for this view is considered below, and then a number of potential spinal mechanisms are considered.

Based on populations of motor unit firing rates, Bigland-Ritchie and colleagues (767) found that the mean firing rate declined during MVCs of biceps brachii and did not recover during 3 min of rest while the arm was maintained ischemic, but they did recover within 3 min after resumption of blood flow (76). A subsequent study of adductor pollicis ruled out the possibility that a loss of excitability at the neuromuscular junction or sarcolemma was responsible because M_{max} (produced by ulnar stimulation) remained fairly constant while voluntary EMG was depressed (767). Subsequently, Garland et al. (276) supported these results. They used electrical stimulation at 15 Hz to fatigue tibialis anterior under ischemia and found that voluntary EMG was then depressed, although central motor pathways had not been used to fatigue the muscle (276). In this study it was judged that voluntary activation was high, but given that common peroneal nerve stimulation was used for twitch interpolation, even large failures of voluntary activation would not have been detected because of the plantarflexion torque evoked by the peroneal muscles. Because voluntary pathways were felt to be uninvolved, they argued this left reflex inhibition of α-motoneurons as the likely cause. (The arguments are further complicated: if the proposition was that group III
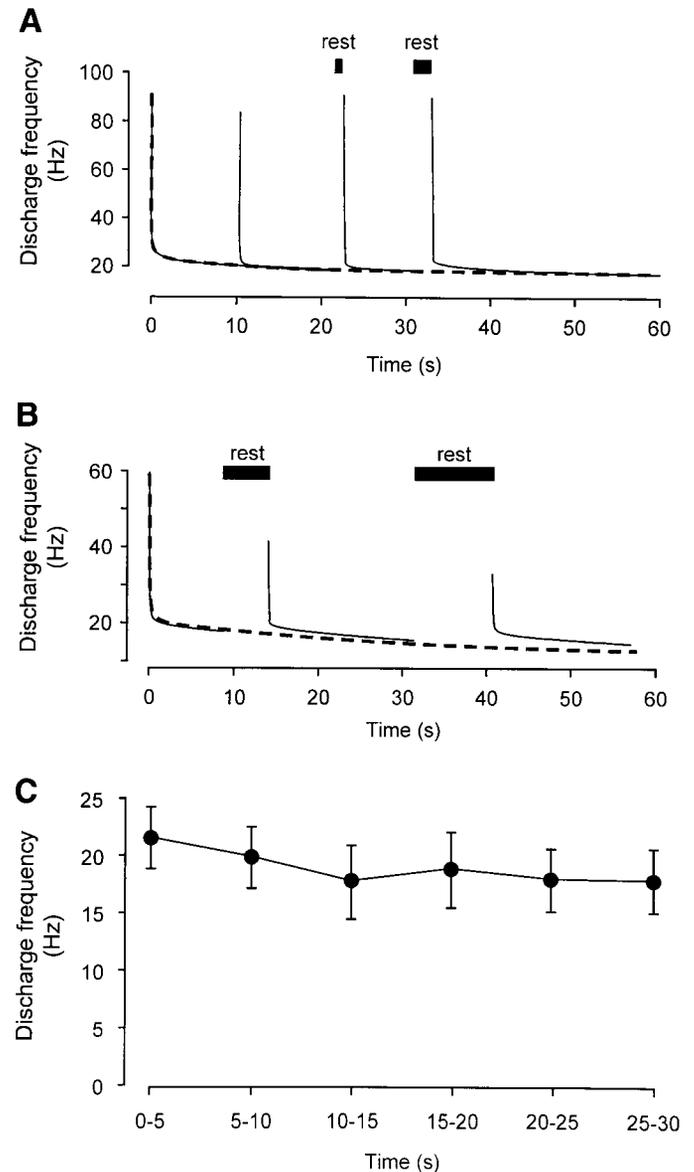
FIG. 16. Adaptation of discharge frequency of rat motoneurons during current injections and maximal sustained firing of "deafferented" human motoneurons. *A*: dashed curve shows response to current injection lasting 1 min in rat motoneuron studied in vitro. If the stimulus current was briefly interrupted ("rest," horizontal bars), the initial adaptation recovered. *B*: same as for *A*. The late adaptation in the rat motoneuron did not recover unless several seconds of "rest" elapsed. [Redrawn from Sawczuk et al. (651).] *C*: this shows the mean firing rates of 7 tibialis anterior motoneurons recorded in human subjects proximal to a complete block of peroneal nerve. Values are means ± SE, computed each 5 s. Subjects made sustained maximal attempts to contract the paralyzed muscle. The decline in firing rates was not statistically significant. The absence of overt decline may be technical (the initial firings were missed) or physiological (the decline requires afferent input). If the latter, a probable explanation is that this population of motoneurons could not be driven to high enough firing rates (due to the loss of "reflex" facilitation) for the "intrinsic" decline to be clearer. [From Macefield et al. (477).]

and IV muscle afferents inhibited motoneurons, voluntary activation should have declined.)

In two subsequent studies the ankle plantarflexors

were used in a similar protocol with electrically induced contractions under ischemia to allow evaluation of the soleus H reflex. In the first (278), the H reflex was significantly depressed after fatigue had been induced, while ischemia alone and electrical stimulation without ischemia failed to reduce the H reflex. The reflexes were not tested in the first 30 s after the fatiguing contraction because they are known to be depressed for ~10 s due to a premotoneuronal effect (226, 445, 654). In the second, compression of the sciatic nerve was used to preferentially block large fibers, as judged by the loss of the soleus H reflex (274). In subjects in whom the block remained stable (and the H reflex absent), electrically induced fatigue under ischemia was still associated with reduced voluntary EMG in a test MVC. When combined with the first study, the data were interpreted to signify that group III and IV muscle afferents inhibited motoneurons.

Interpretation of these studies needs caution. In the first, the combined effect of the arterial cuff (ischemia) and local nerve compression, along with the impulse load of tetanic stimulation, will increase the temporal dispersion of the Ia volley evoked in the maximal H reflex and hence spuriously reduce its size. Furthermore, the biophysical differences between afferent and efferent axons make it likely that there will be a change in shape of the recruitment curve for determination of the maximal H reflex (109). The maximal H reflex depends not only on spinal "excitability" but on the relative excitability of group Ia and motor axons, and hence on the composition of the afferent and antidromic volleys evoked by the stimulus. In the second, voluntary activation was said to be complete in the main subjects, but paradoxically, Ia afferent activity was blocked at the compression site. Complete loss of afferent input reduces maximal firing rates of motor units and hence voluntary activation (264, 477). The H reflex volley may have dispersed sufficiently to slow the rise time of the motoneuronal excitatory postsynaptic potentials (EPSPs) such that the H reflex appeared "blocked." On balance, it would be premature to claim on the basis of these studies that group III and IV afferents unequivocally cause spinal inhibition (and muscular wisdom) in human muscle fatigue. Further evidence from stimulation of the corticospinal tract in humans supports this view (see sect. IV*E*).

The role for reflex inhibition mediated by small-diameter muscle afferents became more firmly entrenched as a result of a combination of human and animal studies. Experiments on humans looked for a peripheral receptor that would signal the changing contractile speed of the muscle. Contractile speed was altered by temperature (72, 484) and by changing the length of the muscle (77, 730). In both situations, once peak force had been reached, motoneuron firing rates did not change as predicted by the muscular wisdom hypothesis. This rules out the possibility that inputs from spindle and tendon organ afferents were acting as "fusion" receptors and then reflexly matching the discharge rates of motor units to the muscle's changing contractile speed. For example, at a short muscle length, higher stimulus rates were needed for tetanic fusion, but in maximal static contractions, the firing rates of motor units had an identical distribution to that at the control length. This was not because firing rates in MVCs were supra-tetanic because voluntary activation was often incomplete (see also Ref. 266). An unidentified central mechanism made contractions at short length smoother than at the control length (77).

Studies in the cat revealed a potential spinal mechanism whereby the inhibitory effects of contractile fatigue in one muscle (medial gastrocnemius) reflexly affected the motor nucleus of an unfatigued synergist (soleus) (320). This inhibition relied on muscle afferent fibers stimulated only at high electrical intensities (~10 times threshold), presumably group III afferents. Sacco et al. (635) found evidence for inhibition in the human triceps surae, although both spinal and supraspinal factors could contribute to it (Fig. 17*A*).

The muscular wisdom hypothesis needs reevaluation because some studies of human isometric muscle fatigue hint at a disparity between the changes in firing rate of motor units and muscle's contraction speed. Vollestad et al. (742) studied repeated intermittent voluntary contractions of quadriceps (6-s duration, with 4-s rest intervals) performed at a range of intensities (30–60% MVC) to "exhaustion" while contractile changes were checked with submaximal electrical stimulation. Negligible changes occurred in the contraction time while the half-relaxation time decreased at 30 and 45% MVC and varied at 60% MVC depending on the stimulus frequency. Tetanic fusion was reduced across a range of stimulus frequencies. These changes differ from the whole muscle contractile slowing accompanying sustained maximal voluntary or stimulated contractions (e.g., Refs. 65, 347, 348), but similar to those during intermittent MVCs performed at a low duty cycle (i.e., the time between MVCs was relatively long) (515). In sustained submaximal contractions of elbow flexor (275) and extensor muscles (277), changes in the firing rates of motor units varied, with a decline usually observed in motor units active throughout the task. Estimated relaxation times did not change (277).

The studies above suffer from two general disadvantages: first, the portion of whole muscle being tested (i.e., stimulated) may not be identical to that being fatigued, and second, the frequencies of single motor units are being correlated with contractile properties of the whole muscle (or parts of it when submaximal stimulation is used). Microstimulation within human motor nerves provides a way to excite a motor unit (via its axon) and measure changes in the dynamics of contraction. So far, data for motor units acting on the digits of the hand have not shown the shift to the left in the force-frequency relation with mild fatigue
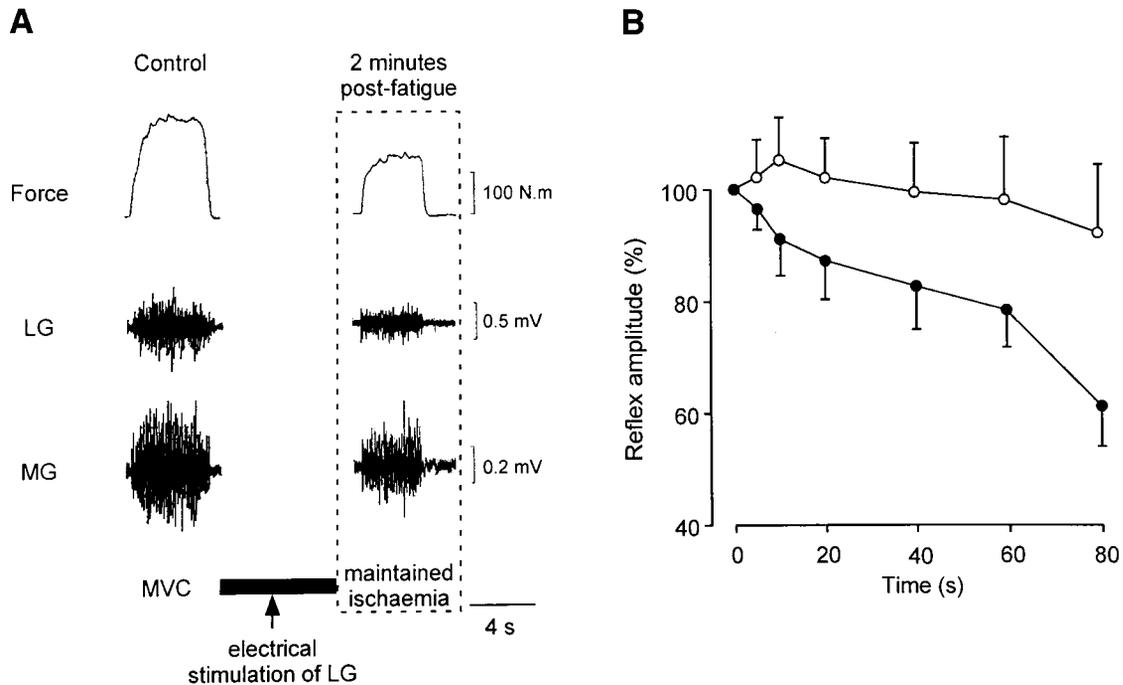
FIG. 17. Changes produced by fatigue in the voluntary and reflex responses of muscles. *A*: effects of fatigue produced by electrical stimulation of lateral gastrocnemius on the voluntarily generated electromyogram (EMG) in medial (MG) and lateral gastrocnemii (LG). Data are shown for before and after fatiguing stimulation. The reduction in voluntary EMG could not be explained by changes in the compound muscle action potential. [Redrawn from Sacco et al. (635).] *B*: short- and long-latency reflex responses in abductor pollicis brevis recorded during a weak contraction after sustained MVCs of different durations up to 80 s. Reflex responses were elicited by median nerve stimulation during a weak effort. Data for the short-latency H reflex are shown as solid symbols and for the long-latency response as open symbols. Values are group means ± SE. [Redrawn from Duchatean and Hainaut (198).]

produced by axonal stimulation (246, 708). In one study, the frequency required for production of half-maximal force increased almost 50% after "fatiguing" stimulation, despite other evidence for contractile slowing of twitch responses. Despite the apparent inconsistency, the authors concluded that "with fatigue higher activation rates must be delivered to motor units to maintain the same relative level of force" (246). Data from studies in the cat also warn against the applicability of the original muscle wisdom concept, since it is well known that the contractile properties of motor units change according to their type. With repeated contractions, the twitch contraction time of slow (type S) motor units decreases whereas that of fast (type FR and FF) units increases (e.g., Ref. 193). Hence, a uniform decline in firing rates would not optimize force production by all muscle fibers.

C. Contributions to Central Fatigue at Spinal Level

1. Muscle spindle inputs

Human muscle spindle endings are recruited though spinal fusimotor neurons and probably also skeletofusimotor neurons during voluntary isometric contractions (117, 211, 725, 752). However, their discharge in a static voluntary effort declines with a rapid then slow phase. This pattern, especially the early decline, was evident in the original microneurographic recordings (e.g., Refs. 726, 727), with the later decline being documented formally in one study (474). Superficially, the decline in spindle firing rate parallels that of motor units in a sustained MVC. As the strength of the voluntary contraction increases, mean rates of spindle discharge increase, and there is some recruitment of previously silent endings (120, 211, 727, 752). The highest discharge rates even in brief efforts are rarely sustained above ~30 Hz, so that while overall muscle spindle input rises with increasing isometric efforts (at least to ~30% MVC), the net facilitation available through conventional monosynaptic links between Ia afferents and motoneurons is lower than for voluntary tasks in the cat (598) (for review see Ref. 596). This assumes that excitation produced by individual spindle afferents in motoneurons is the same as in the cat.

It must be stressed that human (or animal) spindle behavior has not yet been recorded during natural muscle fatigue accompanying strong contractions. Firing rates declined in 72% of spindle endings during sustained voluntary contractions of human ankle dorsiflexors lasting a minute at submaximal intensities (up to 30% MVC) (474).

The EMG required to maintain the target force increased, and thus these contractions were almost certainly fatiguing. Spindle afferents with the highest initial rates showed the biggest decline (Fig. 18). The afferents could still discharge at higher rates if stretch was applied locally to their receptors so that overall spindle input should still be able to grow with increased fusimotor drive or local length changes. When force declines during fatigue there will be progressively less extrafusal unloading so that coactivated muscle spindle afferents might have then been expected to increase their firing rates. The pattern and amount of spindle input will be sensitive to the discharge rate of neighboring motor units, particularly when this declines below fusion frequencies (761).

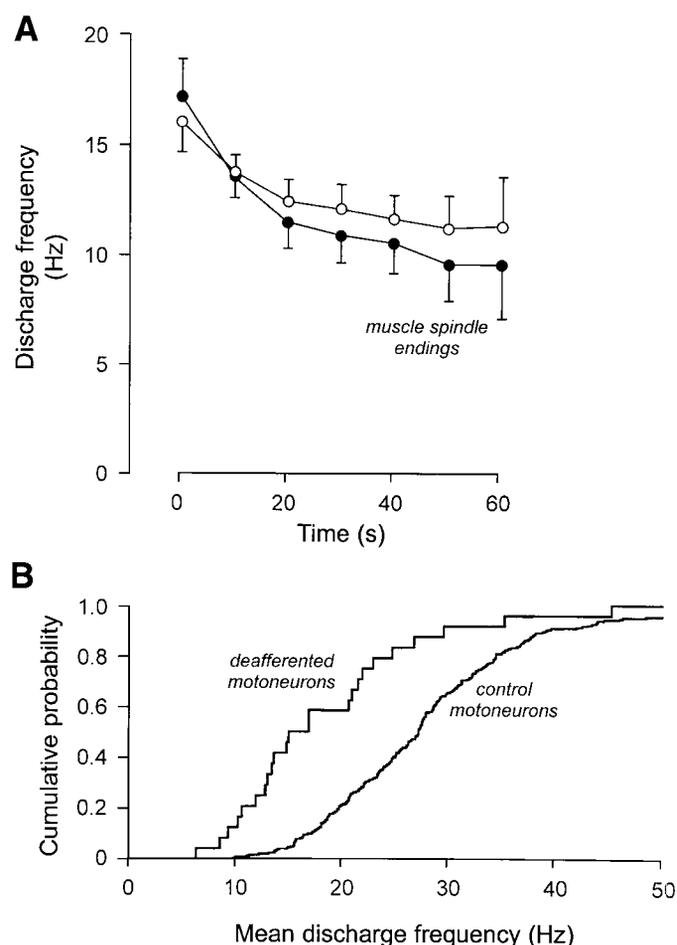In animal studies the background discharge and dy-

FIG. 18. Behavior of muscle spindle endings with fatigue, and reflex "support" to the firing of motoneurons. *A*: discharge of muscle spindle endings in ankle dorsiflexors was recorded during sustained contractions of ~20% MVC lasting 1 min. Open circles show data averaged for all units, and solid circles show data for units that declined in firing rate during the effort. Values are group means ± SE. [From Macefield et al. (474).] *B*: cumulative distribution of the firing rate of tibialis anterior motoneurons recorded proximal to a complete peroneal nerve block (deafferented motoneurons) and of normally innervated tibialis anterior motor units (control motoneurons). All recordings were made during attempted maximal contractions. [From Macefield et al. (477).]

namic (but not static) length sensitivity of passive spindle endings increases during muscle fatigue produced by electrical stimulation of ventral roots at an intensity that activates fusimotor axons (548, 680). Because these changes did not occur with stimulus intensities activating only skeletomotor axons, the effect depends critically on intrafusal muscle fibers, presumably a thixotropic effect (99, 298; for review, see Ref. 600). Populations of feline spindle endings show a reduced capacity to signal changes in muscle length following muscle fatigue (577). The unknown effects of fusimotor drive during fatigue complicate translation of these findings to human muscles recruited voluntarily. For example, the discharge of fusimotor neurons adapts to sustained supraspinal drive (395), and with very high rates of electrical stimulation of fusimotor axons there is "intrafusal fatigue" (222). In addition, in the cat, chemically induced discharges in group III and IV muscle afferents can reflexly increase fusimotor discharge (381, 456) and hence spindle discharge during muscle fatigue (455, 457). Whether these fusimotor reflex effects are present during human muscle contractions is not known, as muscle spindle discharge has probably not yet been recorded under the right conditions (e.g., high-intensity contractions of long duration).

Several arguments suggest that muscle spindle inputs can facilitate human motoneurons during strong isometric contractions and fatigue. First, the firing rate of motor units decreases and becomes more irregular during a partial block of the motor nerve with a local anesthetic that tends to block preferentially small fibers (including fusimotor axons) (307; see also Ref. 314). Second, tendon vibration that activates muscle spindle endings can increase force during an isometric MVC of ankle dorsiflexors (87; cf. Ref. 88). This result should not necessarily be used to argue that the decline in maximal motor unit firing rates during sustained MVCs is caused only by reduced muscle spindle facilitation. Instead, it shows that augmentation of muscle spindle discharge facilitates motoneuron discharge when voluntary activation has declined during fatigue. Third, the discharge rates of motor axons recorded proximal to a complete motor nerve block were ~30% lower than the maximal firing rates when the muscle was normally innervated (Fig. 18*B*) (264, 477; see also Ref. 279). This sets an upper boundary on the net contribution from muscle reflex facilitation, although it does not reveal the afferent species which generated it (see also Refs. 676, 771). Fourth, Hagbarth et al. (305) found that the size of the unloading reflex was reduced in fatigued extensors of the index finger. This was attributed to reduced spindle-mediated facilitation, although there will have been confounding effects from the antagonist cocontraction, and also the altered muscle mechanics that would slow the unloading of the agonist muscle spindle afferents. Finally, the decline in motor unit firing rate during sustained contractions may be minimized

when limb movements are superimposed to generate a "nonisometric" afferent input during the testing (299).

The arguments above fit with views of spindle-derived excitation in animals. There is increasing evidence that the traditional monosynaptic facilitation provided to α-motoneurons by muscle spindle afferents can be enhanced by disynaptic pathways (e.g., Refs. 612, 613). Furthermore, it can be switched on by particular tasks. This group I-evoked extensor enhancement is active during locomotion (19, 303). In some motor nuclei (e.g., those for peroneal but not gastrocnemius muscles), contraction-induced activation of muscle spindle afferents induces strong oligosynaptic excitation (416). Muscle spindle excitation produces much weaker facilitation of fusimotor neurons compared with α-motoneurons (244, 716).

If, as seems likely, human muscle spindle discharge declines during fatiguing isometric contraction, then this may progressively disfacilitate motoneurons. This surmise rests nonetheless on shaky assumptions about the input-output relationships for the muscle spindle-motoneuron link and presynaptic inhibition (see below). Against this, the "gain" of muscle spindle inputs during fatigue in the cat seems to increase (138), an effect that would tend to offset the effect of contractile fatigue. Despite a reduction in contractile force, spindle afferents responded to the relaxation phase of a twitch. However, instead of supporting a progressive increase in spindle reflex gain as proposed, the opposite is likely in sustained MVCs once the contraction becomes more uneven. Because muscle spindle primary endings are preferentially sensitive to small local high-frequency length changes (489, 589), they would provide more effective facilitatory feedback early in a sustained contraction when the internal length changes produced by unfused motor unit contractions are small, rather than later when there are larger slow force fluctuations accompanying central fatigue.

A seemingly attractive way to examine the role of muscle spindle endings in the declining firing rate of motoneurons with fatigue is to measure reflex changes in EMG evoked by a stimulus that activates the receptors or their afferent fibers under control and fatigued conditions. To be incisive, tests need to satisfy five key conditions.

1) The stimuli should evoke identical volleys in the same afferents.

2) Volleys should reach spinal motoneurons (and interneurons) with the same temporal spread.

3) The central neurons should be discharging at the same rate in an attempt to "clamp" their excitability. Although this condition can be met with an isolated motoneuron in a reduced or animal preparations, it is harder to achieve with in vivo studies.

4) Presynaptic inhibition should ideally be unchanged.

5) The evoked EMG should be corrected, where pos-sible, for activity-dependent changes in the maximal compound action potentials (more strictly, in the motor units under study).

These taxing conditions are extraordinarily difficult to fulfill. Despite this, studies of short- and long-latency reflexes to muscle stretch and electrical stimulation of muscle afferents hint at some changes with fatigue, but each study needs to be examined in the light of the five caveats cited above.

The long-latency EMG response of flexor pollicis longus to stretch (which did not evoke a short-latency reflex) was enhanced with muscle fatigue produced by voluntary contractions, in such a way as to compensate for the force loss (485; see also Refs. 162, 407). However, this may largely reflect an "automatic gain control" at the motoneuron pool whereby an input activates more (and larger) motoneurons as the drive to the pool increases (490). Stretch of the first dorsal interosseous muscle fatigued by a sustained MVC showed reduced short- and medium-latency responses (by ~25%) with the long-latency EMG response unchanged (34; see also Ref. 406). Similar peripheral fatigue induced by electrical stimulation over the motor point enhanced the long-latency response, but this was due to the activation of cutaneous afferents at the site of stimulation. The differential effects of voluntarily versus electrically induced fatigue on the short-latency response may depend on the supramaximality of the electrical stimulus, the involvement of "intrafusal" fatigue, plus any central effect of volition on the reflex pathway. Consistent with the view that short-latency stretch reflexes decline with voluntary fatigue, the unloading response is also attenuated (305; cf. Ref. 406). Most of the assessments above were made during voluntary contractions, but if the muscle is tested when relaxed after fatigue, tendon jerks increase (309), with spindle "sensitivity" likely to be increased due to muscle thixotropy (298, 600, 753; see also Ref. 455).

Electrical stimulation of muscle spindle afferents generates the largely but not completely monosynaptic H reflex, which differs from the stretch reflex in many ways apart from simply bypassing the receptor (110, 111, 728). For distal muscles, long-latency responses can also be evoked by stimulation of the muscle nerve (184, 721). Immediately after a voluntary contraction the H reflex is reduced, and this effect is prominent after fatiguing contractions (e.g., Refs. 198, 278). Although this effect is usually presumed to occur at the motoneuron, it will also reflect postactivation depression of the afferent Ia synapses on motoneurons where transmitter release is impaired for ~10 s (343, 766). For abductor pollicis brevis, the H reflex declined by 30%, and its duration increased by 20% while its long-latency response was unchanged when measured during weak contractions after maximal force had been reduced by half (either by volition or an electrically induced contraction) (198). Reflex latencies were

stable. Figure 17*B* shows the time course of changes in the short- and long-latency responses. Central reflex compensation for the reduced force output occurred because, when first dorsal interosseous was fatigued voluntarily, the long-latency reflex of the unfatigued adjacent abductor pollicis brevis increased in proportion to the H-reflex decline in the fatigued muscle. The H reflex may also decline in nonexercised muscles of the same limb (566).

2. Golgi tendon organ inputs

Because Golgi tendon organs sample the forces produced by muscle fibers from several motor units, their discharge should parallel the force at the tendon. This has been confirmed for isometric and isotonic contractions in the cat (e.g., Refs. 297, 337, 338, 580, 694; for review see Refs. 363, 599), and it holds for the population of tendon organs (see also Ref. 259). However, individual afferents may behave nonlinearly due to the force "steps" with recruitment and derecruitment of single motor units and to fatigue preferentially affecting some units. The small fraction of Ib afferents with their receptors located within the extramuscular tendon, rather than at myotendinous junctions (37, 95), could theoretically signal absolute force on the tendon even during fatigue.

When assessed in the cat, the sensitivity of tendon organs to passive length changes declined after a fatiguing contraction (351, 680). However, the size of the effect for a group of afferents was modest (321), and its significance is unclear. This depression could also follow prolonged firing of the Ib afferents induced by vibration (without contraction of the muscle). A desensitization at receptor level was proposed to underlie the reduced discharge rate of Ib afferents to activation by their "driving" motor units after a strong tetanic contraction (713).

On the basis of relatively few recordings from human Ib afferents (7, 20, 106, 116, 211, 726, 727, 724), their properties are similar to those of feline afferents (for review see Ref. 363). Their contraction thresholds are low, and they do not respond strongly to muscle stretch. Compared with those in the cat, their discharge frequencies during voluntary contractions (including standing) are low (rarely exceeding 50 Hz), although a higher proportion have a background discharge in humans (20). Tendon organ discharge shows an initial adaptation at the onset of contraction, but it may increment with motor unit recruitment (211, 727). As both Ib and Ia afferents may fire less frequently during a sustained MVC and exert some opposing effects on motoneurons, it would be illogical to claim either as a sole cause of the declining motoneuron firing rate.

The central actions of Ib afferents are problematic to derive because the afferents are hard to activate selectively, their effects are modulated presynaptically (e.g., Refs. 185, 205, 430, 786), and their projection includes a class of spinal interneuron receiving convergent input from Ia afferents (e.g., Refs. 159, 365; for review, see Ref. 364). Their classical actions include homonymous inhibition and widespread inhibition of synergists (202, 203, 437). This central inhibitory action occurs during a tetanic contraction but is progressively gated out in both α- and γ-motoneurons, possibly by presynaptic inhibition (430, 786). More recent data have identified potential positive feedback produced by appropriate switching of interneuronal circuits receiving Ib inputs (19, 151, 575, 594). In humans, when intramuscular ascorbate injections were used to activate group III and IV muscle afferents, the inhibitory action attributed to Ib afferents was attenuated (619, 620). Another study in humans deduced that the gain of "force-related" feedback (from both spindle and tendon organ afferents) provided important compensation for peripheral muscle fatigue. Stiffness of the elbow joint decreased much less than expected from the degree of weakness, and this was associated with an increase in reflexly evoked EMG (406, 407). How the balance of inhibitory and excitatory reflex actions onto homonymous and synergetic motoneurons changes during human muscle contractions has not been established. Attenuation of the homonymous group Ib inhibitory actions would be appropriate (which in simple terms would follow the decline in afferent discharge rate as force declined), and their widespread spinal projections would support the recruitment of muscles remote from the main ones generating the force. All such actions are likely to be modifiable through interneurons receiving corticospinal and other drives (469).

3. Small-diameter muscle afferents

Group III and IV muscle afferents innervate free nerve endings that are plentiful and distributed widely throughout muscle. These afferents are either silent or maintain low background discharge rates (<1 Hz). They respond to local mechanical, biochemical, and thermal events (Fig. 19). Many factors cause their discharge to increase during strong contractions and fatigue, particularly if the contraction intensity is sufficient to impair muscle perfusion. Biochemical factors, usually tested by close intra-arterial injection in the cat include potassium ions, lactate, histamine, arachidonic acid, and bradykinin (386, 520–522, 624, 625, 677). The discharge of these afferents in response to such stimuli, for example, a local increase in extracellular potassium produced by contraction (665), are likely to depend on the amount and level of the contraction as well as muscle perfusion. The small-diameter muscle afferents also respond to muscle stretch, palpation, and contraction (e.g., Refs. 144, 220, 321, 352, 523, 568), as well as hypoxemia and muscle ischemia (387–389, 432, 523). Group III afferents innervating tendons are plentiful and may exert presynaptic inhibition on

A

Fused tetanus   Unfused tetanus

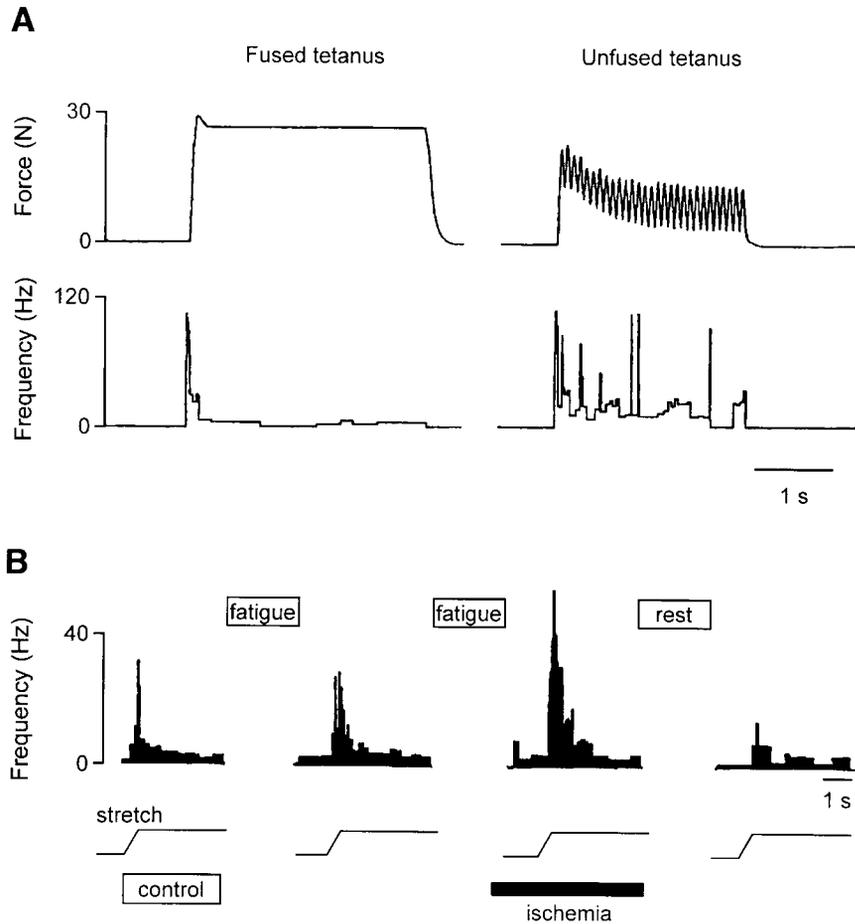Force (N)

30

0

Frequency (Hz)

120

0

1 s

FIG. 19. Behavior of small-diameter muscle afferents innervating triceps surae in the cat. *A*: response of a unit during smooth (*left*) and unfused (*right*) contractions. Note the increased output during unfused contractions. [Redrawn from Cleland et al. (144).] *B*: altered mechanical response of a group III afferent to muscle stretch before and after a prolonged fatiguing contraction, and after ischemia. [Redrawn from Hayward et al. (321).]

B

Frequency (Hz)

40

0

fatigue   fatigue   rest

stretch

control

ischemia

1 s

human group Ia fibers (595). In addition, some endings appear to "monitor" vasodilation within the muscle (315) and perhaps respond to changes in local fluid volumes, much as occurs for pulmonary C fibers (569). The corresponding afferents in the dog (429) and monkey (238) have similar response properties to those studied in the cat. In human studies, injection of hypertonic saline has been used to activate small-diameter muscle afferents (e.g., Refs. 294, 394, 778), although a number of other pain-inducing chemicals have been successfully tried.

Little is known about the discharge properties of this afferent class during natural movements. Group III and IV muscle afferents discharge during locomotion in the decerebrate cat (2, 3, 584). If this is not due to receptor sensitization produced by humoral factors released during surgery, it provides important evidence for their role during voluntary contractions because the natural recruitment order and asynchronous firing of motor units is preserved in locomotion. The majority of units discharged within 2 s of the onset of locomotion and their sensitivity to contraction increased after arterial occlusion (3). Only two studies have examined the properties of small-diameter muscle afferents in humans using microneurography, and it was not feasible to study the afferent discharge during voluntary contractions or fatigue (481, 675). Sen-

sory responses to intraneural microstimulation at 8 Hz established the ability of the discharge of a small number of these afferents (perhaps only one) to evoke focal cramplike muscle pain. Units were slowly adapting and usually silent at rest.

Hayward et al. (321) examined how the properties of small-diameter muscle afferents innervating the cat triceps surae changed after repeated fatiguing tetanic contractions (Fig. 19*B*). For both group III and IV muscle afferents the background discharge rates usually increased. However, the mechanical sensitivity of the afferents varied. For group III afferents the responsiveness to evoked muscle contraction diminished in the first 5 min and recovered slowly, whereas that to mechanical perturbations (stretch and pressure on muscle surface) increased. The temporal change in sensitivity to muscle contraction may reflect the changing "ripple" on the test contractions as fatigue develops. There were larger changes in background discharge and stretch sensitivity for group III afferents than for afferents innervating the specialized intramuscular receptors (i.e., Ia, Ib, and spindle group II afferents).

For group IV afferents, altered mechanical responsiveness during muscle contraction may depend on whether the afferent has a nociceptive rather than mech-

anoreceptive stimulus profile. In the presence of metabolic by-products or ischemia, the mechanoreceptors may be desensitized, whereas the nociceptors become more mechanically sensitive (411, 520, 523). Muscle ischemia maintained after muscle contraction sustains the discharge of many small-diameter muscle afferents (3, 321, 388, 389; cf. Ref. 568), especially of group IV afferents (388, 389, 523). It may increase stretch sensitivity (321) but reduce contraction sensitivity (523). Muscle ischemia maintained after a contraction prevents the contraction-induced elevation in blood pressure from returning to control levels. The remaining elevation is a reflex supported by the firing of small-diameter muscle afferents. Thus maintained muscle ischemia is useful in testing for somatic reflex effects of these afferents at spinal and supraspinal sites (see sects. III*B* and IV).

Given the large number of small-diameter muscle afferents, a major ensemble input must arise from them both during and immediately after strong fatiguing contractions. Full recovery may take some minutes (e.g., Refs. 321, 523).

Based on studies in the cat, the spinal reflex effects of group III and IV muscle afferents are usually considered to fall into the classical picture of the flexor reflex afferent pathway, at least in the lower limb (206; for review, see Ref. 33). The flexor and extensor effects are controlled by separate systems descending from the brain stem (336) and by opioid compounds and may be switchable according to the motor task. Interestingly, for group IV afferents, their reflex effect on cat flexor motoneurons may change from excitation to inhibition as the duration of stimulation increases (745). The descending modulation used to be considered specific for effects on nociceptive reflexes (for review, see Refs. 200, 770), but this is no longer tenable as muscle group II and low-threshold cutaneous reflex paths are also modulated (e.g., Ref. 368; for review, see Ref. 657).

A difficulty in studying this class of muscle afferent is that electrical stimulation at the high levels that recruits these slowly conducting afferents exposes their effects with a highly unphysiological volley entering the spinal cord. An alternative is to use injections of "excitants" into the muscle or its arterial supply, but the likelihood is that the concentrations at the receptor are unphysiologically high. Most approaches suggest that small-diameter afferents exert mixed oligosynaptic effects on hindlimb motoneurons with a tendency for preferential excitation of flexors and inhibition of extensor muscles (e.g., Refs. 412–414). Their net effect is to reduce the "area" of the afterhyperpolarization evoked by intracellular current injection (760, 762). Some wariness is warranted given that there are species differences in the sign of reflex effects from these afferents (443).

A recent study highlights the convergence of group III and IV afferents onto common interneurons in the flexion reflex path, with little interaction with group Ia-mediated excitation and reciprocal inhibition (658). Furthermore, an identified class of lumbar interneurons receives inputs from high-threshold mechanoreceptors in muscle and tendon and is associated with the complex pattern of muscle excitation and inhibition in the clasp-knife reflex (145). Selective activation of the tendon mechanoreceptors inhibits homonymous muscles (144). Fusimotor neurons innervating triceps surae can be excited by group III muscle afferents with low mechanical threshold through a secure oligosynaptic pathway (220). This would support an ongoing contraction provided the excitation could overcome potent autogenetic Ib inhibition on fusimotor neurons.

A predominant flexor reflex pattern from group III and IV afferents as described above, even if present in the human lower limb (304, 424, 518, 669), is unlikely to hold for the human upper limb with its role in reaching and manipulation. This is suggested, for example, by the widespread inhibition of forearm and hand muscles after noxious cutaneous stimulation in the upper limb (e.g., Refs. 21, 237, 418). In humans, although there is flexion withdrawal at the elbow, both flexors and extensors are excited (237). Flexion occurs because of the greater strength of flexors compared with extensors in the upper limb (146).

A recent physiological study in the rat raised the possibility that group III and IV muscle afferents exert their effects in fatigue by inhibiting group Ia terminals presynaptically (581). If confirmed, this would allow fatigue-induced signals from the muscle to diminish the importance of proprioceptive feedback in the control of motor unit firing during fatigue. Already there is some evidence that nociceptive cutaneous inputs act at a premotoneuronal site to inhibit the H reflex of tibialis anterior in humans (221), although the effect could be tested properly in only one subject. Further support has been obtained for human soleus (620). Experimentally induced pain produced by hypertonic saline infusions into human back muscles did not impair the local short-latency response to a muscle tap, evidence, at least for these muscles, that the stretch reflex is not altered by elevated firing of small-diameter afferents (778; cf. Ref. 682).

Figure 20 shows some possible arrangement for feedback from group III and IV muscle afferents and group Ia inputs during fatigue. In the first scheme their activation reinforces muscle contraction through activation of the fusimotor neuron-muscle spindle-motoneuron path (373). This view relies on the as yet unproven capacity of group III and IV afferents to exert significant excitatory effects on human spindle afferents. The second summarizes the view based on H-reflex testing after fatigue (see sect. III*B*). The third depicts the disfacilitation accompanying a decline in spindle input during sustained isometric contractions. The final panel shows a more complex (and more
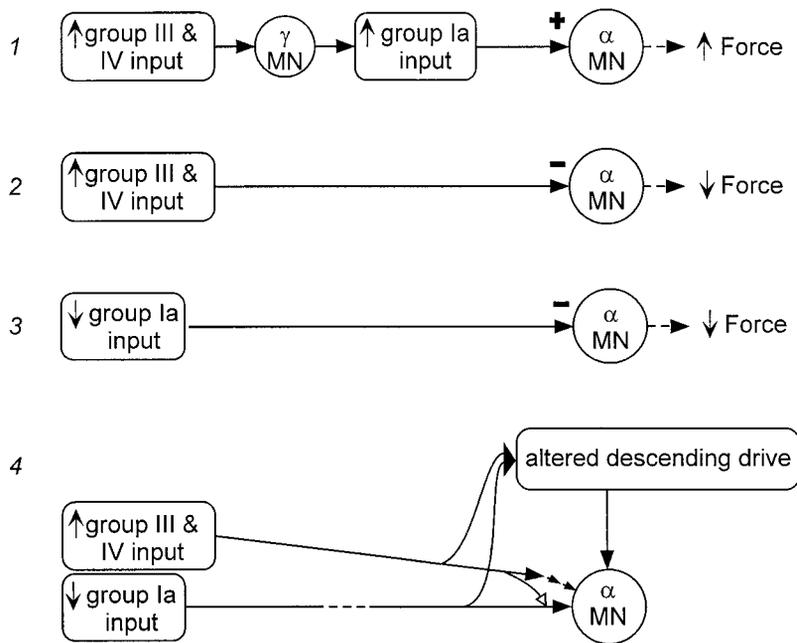
FIG. 20. Summary of possible routes for peripheral inputs to change the firing rates of motoneurons in fatigue. The effects of tendon organs are not included. Details are given in text. *Panel 1* depicts reflex facilitation of motoneurons exerted through the action of group III and IV afferents on the fusimotor-muscle spindle system. *Panel 2* depicts direct reflex inhibition of motoneurons by group III and IV afferents. *Panel 3* depicts disfacilitation of motoneurons produced by the reduction in firing of human muscle spindle endings with fatigue. *Panel 4* depicts group III and IV afferents acting via supraspinal drives and shows their complex spinal actions involving both presynaptic and polysynaptic actions.

likely) arrangement based on the presynaptic, spinal, and supraspinal action of group III and IV afferents (see also sect. IV).

4. Presynaptic modulation of afferent inputs

While the probability that presynaptic effects modulate the effectiveness of inputs to spinal and supraspinal circuits has long been recognized (204, 240), the capacity of this mechanism not only to dampen down inputs but also to filter them selectively is being emphasized (for review see Refs. 631, 751). The complexity of the neural machinery for this task has been revealed in physiological studies (e.g., Refs. 464, 630, 631), and it has been supported by an increasingly detailed picture of the ultrastructure of axo-axonic synapses on afferent terminals (e.g., Refs. 435, 495, 496, 586, 609) and perhaps interneuronal ones.

The central terminals of group Ia, Ib, and spindle group II along with specialized cutaneous afferents receive abundant presynaptic contacts capable of mediating presynaptic inhibition through release of GABA acting to inhibit neurotransmitter release by blocking or reducing the amplitude of terminal action potentials. Extracellular accumulation of potassium ions as a result of presynaptic activity is not currently favored as a contributor to presynaptic effects in the cat, although one could speculate that the unusually large afferent input accompanying maximal exercise could bring this mechanism into play (420; cf. Refs. 372). Although most terminals derived from specialized muscle afferents receive presynaptic inhibition, the effect can vary for a single afferent depending on the location of the terminal (in the ventral horn near

motoneurons or elsewhere) (747). Segmental and ascending projections of afferents can be controlled separately (366). Control of the neurons mediating presynaptic inhibition is separately organized for each afferent type such that segmental reflex potencies of Ia and Ib paths can be independently modulated (e.g., Ref. 630). This differential control on muscle spindle afferents can be exerted through descending projections from motor centers (e.g., Refs. 218, 464). An additional "presynaptic" mechanism, variably termed homosynaptic depression or postactivation depression, reduces transmitter release at previously active Ia terminals (343, 766). This mechanism can produce larger changes in postsynaptic responses than modulation by conventional presynaptic inhibition. Modeling confirms the striking potency of "nonclassical" forms of presynaptic mechanisms (including the action of neuromodulators) in modification of motoneuronal output (322).

What happens to presynaptic inhibition during human voluntary contractions? Using changes in the effectiveness of a presumed Ia monosynaptic volley, Hultborn et al. (345) found that the level of tonic presynaptic activity of muscle spindle afferents innervating the contracting muscle was reduced at the onset of contraction. However, if the contraction was maintained, the gate was rapidly reestablished even midway through ramp contractions (529). It could thus contribute to limit the initial homonymous Ia facilitation of motoneurons during the early phase of a sustained contraction. It is likely that similar presynaptic inhibition in both the upper and lower limb can be modulated by descending corticospinal inputs as well as appropriate cutaneous (6, 112) and muscle

afferent inputs (185, 207). The strength of presynaptic inhibition changes with posture. Presynaptic inhibitory effects are likely to be highly dependent on the task, with for example progressively less presynaptic inhibition of soleus spindle afferents from stance to locomotion at increasing speeds (e.g., Refs. 128, 129, 230). Presynaptic inhibition also varies with the motoneurons recruited (5), and the descending corticospinal and propriospinal inputs reaching the motoneurons (e.g., Refs. 114, 356).

5. Motoneuron properties

The temptation to ascribe the decline in motoneuron firing during a sustained MVC to an intrinsic property of the motoneuron arises because injection of current into the soma of a motoneuron through a sharp microelectrode generates an initially high firing rate that declines in at least two phases during the next 30 s (e.g., Refs. 403, 404, 651; for review, see Refs. 39, 650). Qualitatively similar behavior occurs with constant-current stimulation delivered extracellularly (e.g., Ref. 685). Here, current is a surrogate for net synaptic excitation reaching the soma (659). The association between the observed decline in firing rates in MVCs and this intrinsic behavior is attractive because *1*) virtually all neurons show some adaptation to injected current, *2*) the adaptation seems less with type S motoneurons (innervating fatigue-resistant muscle fibers) than type F motoneurons (innervating fatigue-resistant muscle fibers) (403, 404, 441, 685; cf. Ref. 651), and *3*) it is teleologically tempting to argue that "a regulatory mechanism must exist within the CNS to match the motoneuron discharge rates to the changing contractile speed of the motor units they supply" (74). The parallel between the discharge of a human motoneuron during an MVC and a rat motoneuron injected with a steady current is emphasized by comparison of Figures 4 and 16, *A* and *B*.

Binder and colleagues (651; for review, see Refs. 593, 608, 650) have dissected the motoneuronal adaptation into three phases, each of which is governed by different biophysical processes. Several features of this approach may be relevant to central fatigue. First, the initial and early adaptations recover rapidly (<1 s), whereas recovery of the late adaptation takes much longer (Fig. 16, *A* and *B*). This would ensure that high firing rates could be produced transiently during intermittent repeated contractions such as cycling or running. Second, although the firing rate increases with the net driving current, the "gain" of the motoneuron (firing frequency in Hz/nA of injected current) decreases with time (e.g., Ref. 651). So, unless the net driving current increases, motoneuron firing rate must fall in a short or long sustained effort. Third, a critical drop in net current will derecruit previously activated motoneurons, and they will be more difficult to rerecruit (660). Fourth, the late adaptation has a time course appropriate for matching motor unit firing rate

to any slowing of muscle fiber relaxation in a high-force contraction and hence could contribute to the decline in maximal voluntary firing of motor units (see sect. IIIB). Finally, during sustained current injection (delivered via an intracellular or extracellular electrode), firing frequency can eventually become more variable, and motoneurons may even stop firing altogether, a phenomenon noted in voluntary isometric contractions (e.g., Refs. 228, 579).

These basic properties of motoneurons are likely to come into play during voluntary efforts, but they will not provide the full story because motoneuron properties can be potentially modified in experimental preparations and perhaps also in humans under physiological and pathological conditions. One important instance is generated by the release of serotonin and norepinephrine in the spinal cord from fiber systems descending from the brain stem (e.g., Refs. 254, 339, 441). The relevant serotonergic cells discharge tonically in the awake state and increase their discharge with different behaviors (e.g., Refs. 739, 740; for review, see Refs. 39, 359). These and other neuromodulators can depolarize motoneurons and sometimes generate a plateau potential which, in the turtle, is mediated in part by a dihydropyridine-sensitive L-type calcium channel (340). This favors self-sustained firing or at least an accelerating discharge after recruitment, and this then slows, with a higher-than-expected firing rate when the injected current declines. During graded synaptic excitation and inhibition (in motoneurons of cat triceps surae), the threshold for the "plateau" current decreases and increases, respectively, and thus it can change markedly the gain of the motoneuron in a state- and history-dependent way (52). Susceptibility to these effects is greater in low- than high-threshold motoneurons (e.g., Ref. 441), and thus it should contribute to limit preferentially the rate of low-threshold motoneurons. Because these effects are absent with spinalization or during general anesthesia, their relevance to normal motor activities will have been underestimated.

Some features of the behavior of human motor units during isometric contractions are compatible with (but not proof of) plateau potentials modulating discharge frequency. These include the profile of initially high discharge rates of motor units at recruitment, with derecruitment at a lower force than for recruitment (e.g., Ref. 242; for discussion see Refs. 148, 405, 442). These properties would seem suited to sustain the firing of motoneurons during fatigue, particularly those of low-threshold units in proximal and midline muscles. They may also contribute to the variations in recruitment order and recruitment and derecruitment forces noted during human submaximal contractions, but they are unlikely to be the sole cause. For example, low-threshold motor units in the first dorsal interosseous showed some recruitment changes along with increased discharge variability once fatiguing contractions at 50% MVC could not be continued (228). The

average firing rates tended to diminish after the task, and the force at derecruitment usually increased. Furthermore, as exercise intensity increases, the concentrations of endogenous amines and other neuromodulators with direct actions on motoneuron properties will change (see sect. V*D*) and hence motoneuron behavior will not be fixed. The sudden involuntary contractions of muscle cramps are neurally mediated and may originate in the motoneuron soma from self-sustained firing via a plateau current (32).

Irrespective of how much classical intrinsic motoneuron properties and synaptically mediated changes to them contribute to the decline in motoneuron firing rate with fatigue, these effects do not put the motoneuron into a state in which it fails to respond to net excitatory drive. Such an "insensitive" state has been reported for cat motoneurons during fictive locomotion (101). Once central fatigue has developed, excitatory segmental Ia inputs (with muscle vibration) and descending corticospinal inputs (with motor cortical stimulation) increase the force output from the motoneuron pool when injected during a MVC (see sect. IV). That is not to deny an indirect role for motoneuron properties in central fatigue because any factors tending to decrease motoneuron gain (as in the late adaptation) will demand additional synaptic drive at a premotoneuronal level to maintain a constant firing rate. If that drive also falls, then firing rate will decline, although plateaulike behavior may also act to diminish this decline.

6. Renshaw cells and other effects

Renshaw cells provide classical autogenetic inhibition to homonymous and synergist motoneurons (736) with a weaker effect on γ-motoneurons (219, 395). Like all spinal interneurons their inputs are diverse, from descending motor systems, local interneurons, and peripheral reflex inputs. Their outputs include not only motoneurons but also Ia inhibitory interneurons, fusimotor neurons, and other Renshaw cells. They are driven more strongly by the fast-fatiguable motoneurons (344, 757).

Although Renshaw cell inhibition may limit motoneuron discharge rate in a sustained effort, particularly in high-threshold motoneurons, the effect will be complex (758, 759, 761). It will depend on the discharge pattern of Renshaw cells, the voluntary drive and muscle feedback they receive, and their influence on motoneuronal afterhyperpolarization. Experimental evidence in the cat suggests that the gain of the Renshaw effect will be high initially, decrease over the next 5–10 s, and then increase to a steady level (758, 759). Group III and IV muscle afferents activated by muscle metabolites decrease the response of Renshaw cells to a test stimulus to motor axons and hence contribute to disinhibit motoneurons (760, 762).

On the basis of an indirect H-reflex technique, Renshaw cell inhibition is reduced as the strength of a voluntary contraction increases (i.e., motoneurons are disinhibited), an effect compatible with corticofugal drive to Renshaw cells (e.g., Refs. 346, 497, 498). Limited data exist on Renshaw cell inhibition during human muscle fatigue. During a sustained submaximal contraction lasting 10 min (20% MVC), recurrent inhibition appeared to decrease (468). Paradoxically, it appeared to increase over the first 30 s of a sustained MVC of ankle plantarflexors (428). Central factors changing the after-hyperpolarization and motoneuron firing threshold, and activity-dependent changes in axonal threshold will complicate interpretation of these results (109). One plausible explanation is that Renshaw cell inhibition usually decreases (in parallel) as descending drive to motoneurons increases but that during a sustained MVC this descending inhibitory drive to Renshaw cells declines relatively more than any decline in effective descending drive to motoneurons. The possibility that recurrent inhibition is controlled differently during fatiguing submaximal and maximal efforts requires further study. The distribution of such inhibition follows the classical pattern (i.e., acting among synergists) at some human joints (e.g., elbow) but not others (e.g., wrist) (23), and this may provide a way to study further the role of Renshaw cell effects in fatigue.

Although many other classes of spinal interneurons exist, their role during fatigue has been rarely studied. Reciprocal inhibition of soleus 30 s after a fatiguing contraction of tibialis anterior decreased (717). Whether this is due to a change in the afferent volley or an intrinsic effect at the Ia inhibitory interneuron is unclear. If the latter, then the change would favor progressive cocontraction during and after sustained contractions.

D. Conclusions

Central fatigue develops during sustained or intermittent isometric MVCs. Its extent can be measured, and it will vary with the muscle group, task, and subject. A combination of results from recordings of the discharge of single motor units and the technique of twitch interpolation reveals that the average motor unit discharge usually declines too rapidly to maintain maximal evocable force. Accompanying this decline are changes in the properties of most classes of muscle receptor and thus the reflexes that they can evoke. There is likely to be a net reduction in spinal reflex facilitation and increase in inhibition during isometric MVCs, and thus motoneurons are harder to drive maximally by volition. Although their intrinsic gain probably declines within a sustained effort, they can still respond to increased supraspinal or reflex drives. The propensity for motoneurons to discharge with a declining frequency also has an intrinsic basis, and the decline can be affected by classical presynaptic and

postsynaptic effects, and by additional "nonclassical" modulatory influences. It is becoming increasingly clear that such influences are strong and may dominate changes produced in the strength of reflex paths.

The natural decline in motoneuron firing rate during isometric MVCs is partly beneficial because of the hysteresis in the force-frequency relationship and the stability of its descending limb. This discharge pattern efficiently maintains force. No evidence exists that, for each individual motor unit, this decline is driven reflexly according to the local variations in the contraction properties of its muscle fibers. As the precise pattern of motor unit firing can enhance force production and minimize fatigue, a failure of these strategies will impair voluntary activation and potentially contribute to central fatigue.

As a postscript, unless stringent criteria are met, it is difficult to assay the excitability of human motoneuron pools using classical, so-called, monosynaptic reflexes. Five criteria are proposed for assessment of reflex studies of fatigue. Furthermore, it should be emphasized that the situation is more complex during submaximal than maximal voluntary contractions when voluntary, reflex, and intrinsic effects on motoneuron firing will change with time, initial discharge frequency, and probably with motor unit type.

IV. INSIGHTS FROM STIMULATION AT SUPRASPINAL SITES

A. Background

Once it became possible to stimulate the human cerebral cortex noninvasively using high-voltage anodal stimulation delivered through the scalp (527), or a rapidly changing magnetic field evoked via a coil on the scalp (36), the techniques were used to study the behavior of the supraspinal structures, particularly the motor cortex. Both methods can evoke descending volleys in corticospinal axons by direct excitation at or near the first node of Ranvier, a finding based on studies in anesthetized animals (e.g., Refs. 208, 209, 573; for review, see Refs. 583), conscious nonhuman primates (30, 31), and anesthetized humans (e.g., Refs. 91, 118, 119, 251, 622). These initial volleys are termed D waves. They are followed by indirect volleys, termed I waves, occurring at intervals of ~1.5 ms. These have the same conduction velocity as the D wave and can last for several milliseconds based on epidural recordings in awake subjects (53, 189, 544) Two mechanisms can contribute to these I waves: synaptic bombardment of corticospinal cells by cortical interneurons excited by the stimulus (e.g., Refs. 17, 574) and an intrinsic tendency of the corticospinal cells (or those which drive them) to discharge with a burst (157, 779, 781; for review, see Ref. 582).

Transcranial magnetic or electrical stimulation over the primary motor cortex produces excitatory EMG responses in most muscles at short latency (termed motor evoked potentials, MEPs). Based on measures of central conduction time (e.g., Refs. 171, 271) and stimulus-evoked responses in single- and multi-unit EMG (e.g., Refs. 98, 170, 570) and H reflexes (154), these responses include a contribution from monosynaptic corticomotoneuronal connections. The input delivered to the motoneurons is not purely monosynaptic and will include inputs mediated by disynaptic inhibition at a spinal level [via the Ia inhibitory interneuron (367, 385) and by propriospinal (113, 293) (for review see Ref. 587), and other paths (780)]. The strength of presumed propriospinal pathways in the primate is controversial (16, 478). A late facilitation has been reported for proximal muscles, perhaps transmitted via projections from the brain stem (147, 570). The direct role of the many corticospinal cell groups that reside outside the primary motor cortex has not been examined with transcranial stimulation.

The size of the compound MEP in a muscle will depend on several factors. The first factor is the "excitability" of the underlying motor cortex. This is particularly clear for magnetic cortical stimulation but is less so for anodal electrical stimulation near threshold (for review, see Ref. 623). Voluntary contraction increases the number and size of I waves (189; cf. Ref. 383), and it reduces apparent intracortical inhibition (426, 614, 691). The final output will depend on intrinsic excitability of the output cells, the inputs to them, together with relevant biophysical properties.

The second factor is the "strength" of the mono- and oligosynaptic corticofugal connections with motoneurons. Some muscles such as triceps brachii and soleus receive an initial inhibition, thought to be mediated by disynaptic inhibition at a spinal level (97, 154, 558, 570).

The third factor is the "excitability" of the motoneurons.

The fourth factor is the properties of the muscle fiber action potential. There are activity- and fatigue-induced changes in the muscle fiber action potential (e.g., Refs. 158, 425, 508, 647), with a prominent slowing of fiber conduction velocity with fatiguing contractions (e.g., Refs. 401, 452). This slowing worsens with higher intramuscular forces as the muscle becomes more ischemic (785).

When MEPs are elicited during a voluntary contraction, all of the above factors come into play. Artifactual changes in EMG may also occur because of electrode movement. Thus, to estimate cortical responsiveness during fatigue, the size of the MEP can only be used when effects "downstream" of the motor cortex have been controlled (i.e., the third and fourth factors above).

The increase in MEP amplitude with voluntary contraction depends on the muscle: for distal muscles, the

MEP growth saturates at weak contraction levels, but for proximal muscles the growth continues to strong contraction levels (>70% MVC) (408, 701). This pattern is consistent with the dominance of frequency modulation of motor units over recruitment in the most distal muscles with the reverse pattern in proximal muscles (e.g., Refs. 173, 427).

Transcranial magnetic stimulation also generates separate inhibitory effects at a cortical level, with near silence in the EMG after an MEP has been evoked during a voluntary effort (e.g., Refs. 54, 127, 250, 335, 526, 618, 715, 755). With strong stimuli the duration of the silence outlasts the period of reduced responsiveness of spinal motoneurons by up to 100 ms (137, 250). This phenomenon has been well documented in animal studies (e.g., Refs. 421, 422) and is likely to involve intracortical inhibition acting via GABA$_B$ receptors (384). The area of cortex from which a silent period can be induced encompasses and surrounds the area from which the MEP can be evoked (755). Stimuli at levels below those that evoke the MEP can also reduce ongoing EMG (163), suggesting the likely involvement of inhibitory cortical circuitry. As the stimulus intensity increases, the silent period lengthens in both proximal and distal muscles (701). Standardized instructions requiring subjects to contract as fast as possible after the stimulus-evoked silencing of voluntary activation are needed to obtain the most reliable values (487), although it will underestimate the magnitude of changes occurring at a cortical level and make the duration of the EMG silence largely independent of the level of voluntary contraction (357, 618, 701; cf. Ref. 754), particularly at high stimulus intensities (701). This may make the silent period less sensitive to changes occurring at a cortical level.

The force increments evoked by cortical stimulation depend on the size of the MEP evoked in the contracting muscle, but also on the prevailing level of muscle force (as occurs with twitch interpolation using peripheral nerve stimulation). Because magnetic and electrical stimulation of the cortex excite cells with divergent projections to more than one muscle or muscle group, recruitment of synergists and also antagonists should be taken into account.

B. Voluntary Activation and Changes With Fatigue

Although the size and effect of any corticofugal output on motoneurons is not simple to predict when transcranial magnetic stimulation is delivered during strong contractions, some inference about voluntary activation is possible. First, the stimuli evoke small but easily detectable increments in force for truncal (269) and limb muscles (260, 329, 707). The size of the increments cannot be used to generate the conventional measure of voluntary activation because the same stimulus does not produce a maximal control twitch in the relaxed muscles. Neither is it ideal to normalize the increment to the ongoing force (703). For adductor pollicis, the force increments produced by cortical stimulation during MVCs are smaller than expected (based on ulnar nerve stimulation) because the cortical stimulus activates many muscles including antagonists.[1] Second, motor cortical stimulation can test activation of muscle groups not readily accessible to nerve stimulation such as the intercostal and abdominal muscles. For some complex tasks requiring two or more muscle groups (such as maximal inspiratory or expulsive tasks), cortical stimuli can also increase voluntary forces. Thus, during such efforts, inspiratory and expulsive pressures can show only minimal increments with interpolated phrenic nerve stimulation, but larger increments with motor cortex stimulation (269). This suggests that synergist muscles (apart from the diaphragm) are usually not maximally activated in the tasks. In general, with cortical stimulation, the presence of evoked force increments to cortical stimulation signifies suboptimal voluntary activation, but their absence does not exclude it.

When assessed with transcranial cortical stimulation, the force increment, produced in elbow flexors, is small but increases progressively during sustained or repeated isometric MVCs. This is quantitatively similar to the increase observed with twitch interpolation using nerve stimulation if allowance is made for contraction of all possible elbow flexor muscles with cortical stimulation (Fig. 13) (260). Our interpretation is that during fatigue when the motor cortical stimulus can increase the force output from the muscle, there is a limiting process effectively upstream of the site of motor cortical stimulation, and this is contributing to the central fatigue. If correct, this interpretation moves one component of central fatigue well above the motoneuron.

An obvious objection is that many other factors also reduce the net driving current for motoneurons, including altered reflex and descending inputs (see sect. III). Nonetheless, as fatigue develops, the cortical stimulus generates effective and progressively greater corticospinal output that the subject ought to be able to harness (see sect. IV*C*). Circumspection is necessary because, in twitch interpolation with peripheral nerve stimulation, all but refractory motor axons innervating the muscle can be stimulated, while with cortical stimulation it is impossible to know what fraction of relevant corticospinal axons have been excited. Furthermore, even if it were possible to

---

[1] Recent work suggests that voluntary activation of elbow flexors can be measured accurately with transcranial magnetic stimulation (above 50% MVC) provided that the stimulus produces minimal activity in tonceps brachii (Russell, Taylor, Petersen, and Gandevia, unpublished observations).

measure absolute maximal cortical output directly, the relation between it and motoneuronal output is unlikely to be linear. Transcranial stimulation cannot reveal whether the ongoing level of voluntary corticospinal output has been increased or decreased during contractions. However, a progressive increase in size of the absolute force increment produced by cortical stimulation directly indicates a central supraspinal component to any fatigue.

C. Changes in Electrophysiological Behavior of Motor Cortex With Fatigue

Different exercise protocols and measurements of cortical behavior have revealed surprising lability in the motor cortical response to exercise. Not only does drive to corticospinal cells become suboptimal, but the apparent "excitability" of cortical circuits changes (Fig. 21). Changes occur in the initial excitatory response to transcranial cortical stimulation and in the silent period in the EMG following this response (for review, see Ref. 705).

During a sustained MVC, the size of the MEP to magnetic cortical stimulation grows (in amplitude and area), even when this growth has been corrected for any increase in the muscle action potential. Growth of the MEP levels out after ~15 s (535, 703, 704). The MEP can increase to such an extent that it is bigger than M_{max}, an indication that the descending corticospinal volleys recruit some motoneurons to discharge twice at short intervals. Events at a motor cortical level contribute to this growth because the response to stimulation of descending tracts including corticospinal axons at cervicomedullary level does not increase during a sustained contraction (126, 703). Results with intracortical microstimulation in the conscious monkey are consistent with this view (29). The growth in the MEP during fatiguing contractions makes it unlikely that a significant proportion of the motoneuron pool becomes inaccessible to descending drives, a possibility proposed to explain the reduced voluntary EMG during maintained postexercise ischemia (276). While the MEP grows during a sustained MVC, its onset latency increases significantly. An increased delay at motoneuronal level may be involved, although some of the delay will be purely axonal (704).

Sustained submaximal contractions increase the MEP in elbow flexors (635, 703), while in adductor pollicis the MEP seemed to decrease before increasing once the contraction required near-maximal effort (458). The cortical events underlying the growth of the MEP will most likely be a greater number of activated corticofugal cells, each of which may discharge more I waves. This may be combined with a reduced output from corticospinal cells producing (disynaptic) inhibition of motoneurons.

The silent period in the EMG after cortical stimulation increases during a sustained MVC of an intrinsic
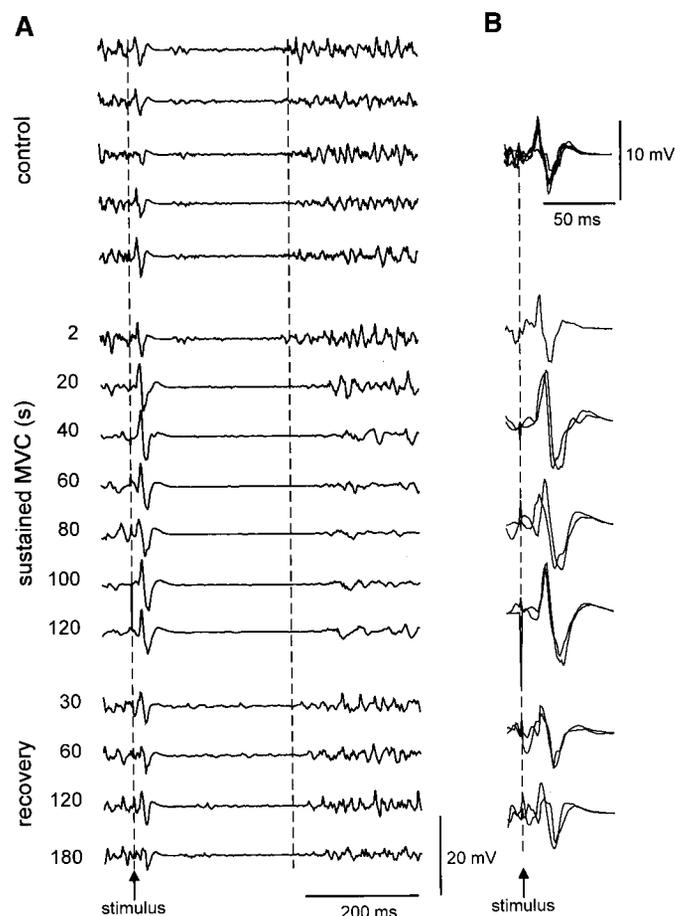

FIG. 21. EMG after magnetic cortical stimulation during MVCs. *A*: recordings of biceps brachii EMG from one experiment. Top five traces show the EMG responses evoked by magnetic cortical stimulation during brief control MVCs. Middle seven traces show the responses during a sustained 2-min MVC, and bottom four traces show the responses during recovery. Left dashed line shows time of stimulation. Right dashed line shows mean latency for return of continuous EMG in control trials and thus marks the end of the "cortical" silent period. This lengthens during the sustained MVC and recovers quickly. EMG silence is not absolute during the so-called "silent period" in control trials, and the activity (from ~65 ms poststimulus) disappears during the sustained MVC and reappears during recovery. The motor evoked potential (MEP) (just to *right* of *left* dashed line) varies but increases during the sustained MVC and recovers within 30 s. *B*: the five control MEPs are superimposed, as are sequential pairs during the sustained MVC and recovery. [From Taylor et al. (703).]

muscle (535) and of the elbow flexors (Fig. 21) (703). This occurs even when the subject is requested to pull "hard and fast" after the stimulus, and the change is restricted to the "exercised" region of cortex (e.g., Ref. 703). If the stimulus intensity is high, voluntary EMG does not resume for ~200 ms. Because this time exceeds the silent period following stimulation of the motor nerve or descending tracts, its end is determined by the resumption of corticofugal activity (e.g., Refs. 250, 335, 357, 703, 720). As weak levels of cortical stimulation produce a brief silent period less than ~100 ms, interpretation of such resting values and changes during exercise is problematic

because purely subcortical factors are likely to be involved. Prolongation of the silent period presumably reflects a balance at the corticofugal cell between local intracortical inhibition and excitation evoked by the stimulus and excitation derived from volition (744) and thus could be caused by a net increase in intracortical inhibition associated with the stimulus and/or reduced voluntary drive to the cortical output cell. The prolongation is not due to inadequate volitional drive to the motor cortex because the silent period prolongation recovers more quickly than central fatigue (260) and can also be dissociated from central fatigue during intermittent contractions (see sect. IVD). Further support is that the silent period may not lengthen during fatigue when a subject has low voluntary activation during the attempted maximal effort. Together, the data indicate that lengthening of the silent period produced by strong cortical stimulation is due to focal changes within the activated motor cortex.

The (peripheral) silent period produced by motor nerve stimulation also increases systematically during a sustained MVC of elbow flexor muscles (from ~45 to ~80 ms), with the magnitude of the increase being small compared with the increase to cortical stimulation (from ~240 to 335 ms). The size of the former increase would be consistent with the decreases in motor unit firing rate during sustained MVCs (704). More complex changes can occur during and after sustained submaximal contractions (155).

During a sustained submaximal contraction of elbow flexors, the cortical silent period lengthens once the initially submaximal force approaches maximal voluntary force (635, 703). For an intrinsic hand muscle, the silent period initially shortened during a prolonged contraction at 60% MVC, lengthening only when maximal effort was required. During such exercise it is likely that corticofugal drive to the active motoneuron pools increases in part to compensate for the loss in peripheral force-generating capacity (62, 467, 488). In summary, the threshold for cortical excitation and inhibition seems reduced when the motor cortex has been engaged in prolonged near-maximal contractions. Because the recruitment, usage, and cortical control of muscles differ, the exercise-induced changes in motor cortical behavior may vary for different muscles.

To determine whether such changes occur in response to cortical stimulation during more natural contractions, Taylor et al. (702) measured changes in MEP, "cortical" silent period and central fatigue during maximal intermittent isometric exercise in which the timing of contraction and rest periods varied. The increase in the cortical silent period was ~40 ms with 10–15 s of maximal effort, and it doubled over 4 min when the rest intervals were only 5 s. When the rests were 10 s, the silent period recovered between contractions but lengthened progressively within each subsequent 15-s MVC (Fig.

22B). The cortical changes mediating the lengthening accumulated if <15 s was allowed for recovery. The MEP also increased and reached a steady level after 5–10 s, but as it recovered slightly more slowly than the silent period, the MEP reached a plateau while the silent period was still lengthening (Fig. 22A). Of course, changes at the muscle fiber membrane will also affect the MEP.

Brasil-Neto and colleagues (92, 93) showed that the MEP is strikingly depressed for as much as half an hour after fatiguing exercise when the exercised muscles are tested at rest (see also Refs. 447, 642–644, 777). Immediately exercise stops, however, the MEP to magnetic cortical stimulation, also tested at rest, exceeds that before contraction, a phenomenon termed postcontraction facilitation (93, 447, 644, 646). This facilitation signifies prior cortical excitation, but is not directly related to peripheral
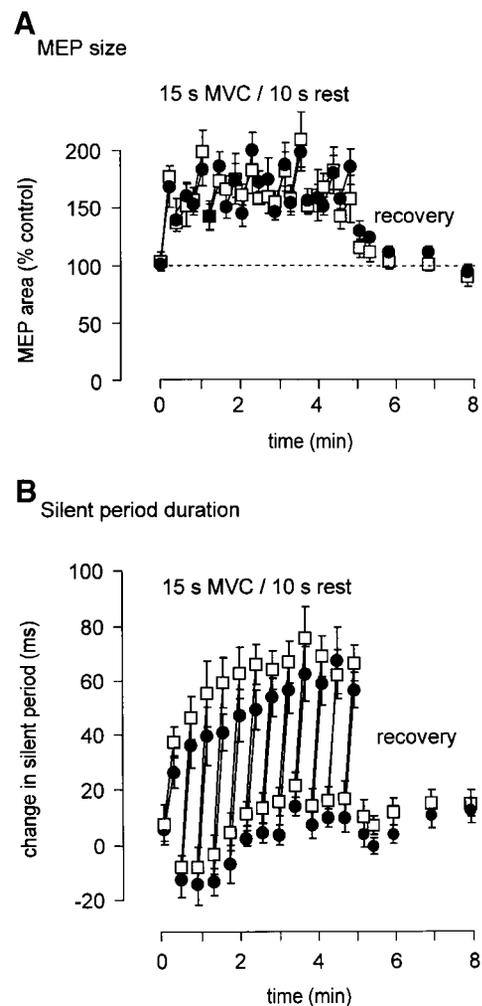
FIG. 22. Changes in size of MEP (A) and duration of silent period (B) produced by transcranial magnetic stimulation of the motor cortex during intermittent MVCs of elbow flexor muscles. Data are joined by lines derived from early and late in the same 15-s MVC. Open squares are data from biceps brachii, and solid circles are data from brachioradialis. Note that the silent period almost recovers fully in each 10-s rest. [From Taylor et al. (702).]

fatigue because it occurs with short or long contractions even at low effort (e.g., 20% MVC for 10 s) (645, 646). An example is shown in Figure 23 (*bottom traces*). This postcontraction facilitation is shortened to ~30 s with fatiguing contractions. The long-lasting depression deepens with fatigue and is associated with an smaller "map" for the exercised muscles, although the threshold for a response is unaltered (777). Repetitive transcranial magnetic stimulation of the motor cortex can produce prolonged changes in presumed intracortical inhibition and excitation (769).

Both the initial postcontraction facilitation and long-lasting inhibition during rest after fatigue cannot be explained by events at motoneuron level. This conclusion is supported by comparison of responses to magnetic and electrical cortical stimulation, and measurement of H reflexes and F waves (92, 270, 447, 777). However, McKay et al. (509) found a prolonged depression in response in tibialis anterior to transcranial electrical stimulation lasting 5 min. As high stimulus strengths were used, responses would have been (unintentionally) affected by cortical excitability. When measured during brief "test" MVCs after fatiguing contractions, the MEP and silent period returned to control preexercise levels within ~15 s (126, 702–704). Given the profundity of the motor cortical depression to magnetic stimulation after fatiguing exercise, it is remarkable that the phenomenon is absent during brief "test" voluntary efforts. Voluntary drive "upstream" of cortical output can reverse a residual hypoexcitability of previously active motor cortex.

D. Relationship Between Changes in Motor Cortical Behavior and Central Fatigue

Do the changes in motor cortical behavior described above directly cause central fatigue? Probably not. Three arguments indicate that progressive failure of voluntary activation does not require altered motor cortical excitability. First, when the elbow flexors are held ischemic after a prolonged MVC, voluntary activation and motor unit firing rates remain reduced (76, 260, 767) while the responses to magnetic cortical stimulation (MEP and silent period) return to control values within ~15 s (when tested during a brief MVC) (260, 702, 704, 705). Data for voluntary activation, force, the MEP, and silent period are shown in Figure 24. Second, after sustained or intermittent MVCs, the recovery from central fatigue takes ~1 min, while the cortical silent period and MEP recover in ~15 s, irrespective of maintained muscle ischemia (260, 702). More weight must be put on changes in the cortical silent period because the MEP changes are likely to be variably affected by changes at the spinal cord and muscle fiber. Third, the relationship between the magnitude of central fatigue and prolongation of the cortical silent period is not fixed. The same degree of central fatigue occurs when intermittent MVCs with a duty cycle of 50% (5-s contractions) increase the silent period by 20 ms, while MVCs at a higher duty cycle (86%, 30-s contractions) increase it by more than 40–60 ms over the same duration of exercise or duration of contraction (702). Thus the motor cortical cells with corticospinal projections are not the prime site of generation of central fatigue. However, such cells are involved in many processes associated with it. Those cells immediately "upstream" of the output cells are particularly important. Thus one report suggests that the baseline level of presumed intracortical inhibition (measured with paired magnetic pulses) may correlate with amount of exercise that can be performed voluntarily (706).

Studies of conscious subhuman primates have provided little information about the motor cortex during fatigue. During intermittent self-paced isometric contrac-
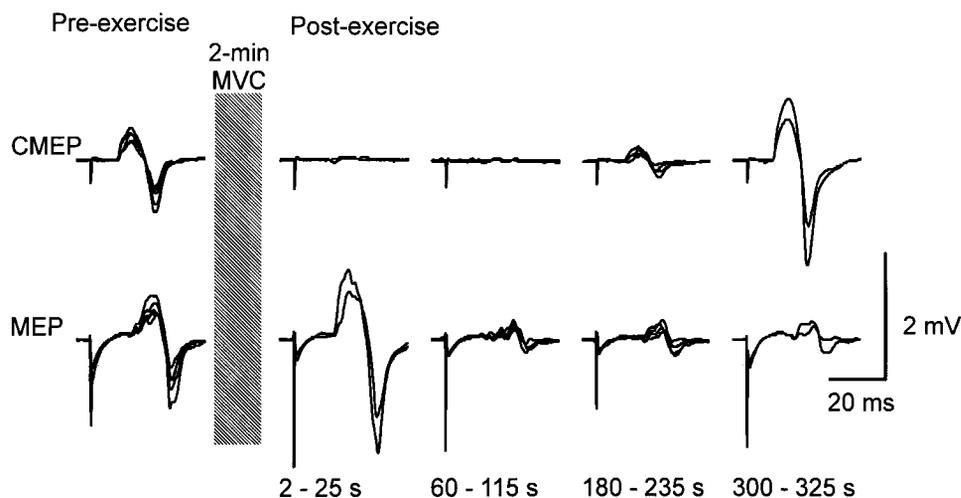
FIG. 23. EMG responses in biceps brachii with transmastoid (*top traces*) and motor cortical stimulation (*bottom traces*) before and after fatigue. The intensity of the transmastoid stimulus was adjusted so that the size of the initial CMEP (produced by cervicomedullary stimulation of descending tracts) approximated that of the MEP (produced by motor cortical stimulation) (~5–10% of the maximal M-wave). The transmastoid stimulation was shown to activate corticospinal output. Responses are superimposed for sets of stimuli before and at various times after a sustained MVC of 2-min duration. Immediately after the MVC, the CMEPs were reduced, while the MEPs were initially enhanced (postcontraction facilitation), and then declined. The largest MEPs occurred immediately after the MVC, when the CMEPs were almost abolished. [From Gandevia et al. (270).]
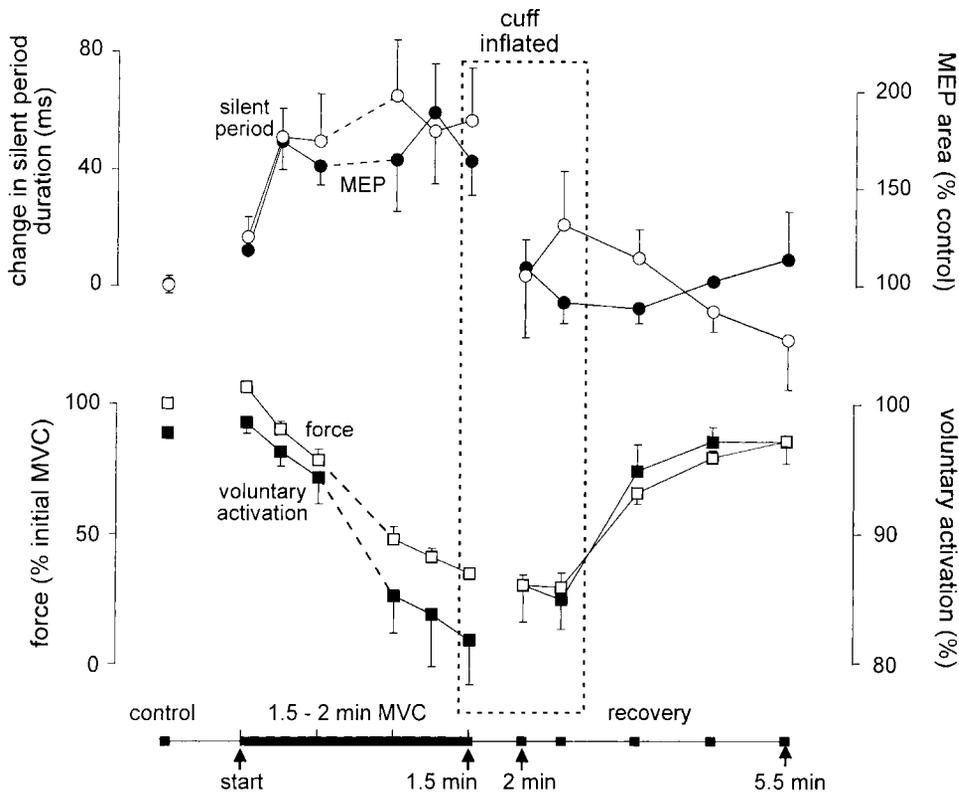
FIG. 24. Effect of maintained ischemia after fatigue on recovery of silent period duration, MEP area, voluntary activation, and voluntary force. *Top panel* shows the EMG responses to cortical stimulation. *Left axis* shows the change in silent period duration (open circles) and the *right axis* the MEP area (solid circles). *Bottom panel* shows the MVC (*left axis*, open squares) and voluntary activation (*right axis*, solid squares). Voluntary activation is derived indirectly from the increment in force produced by cortical stimuli relative to the ongoing force (a value that will slightly underestimate the true level of voluntary activation). Enclosed boxed area indicates when blood flow was occluded. During the sustained MVC, silent period duration and MEP area grow, whereas voluntary force and voluntary activation fall. After the sustained MVC, ischemia prevents recovery of force production by the muscle. However, silent period duration and MEP area recover quickly to control levels. Voluntary activation does not recover until blood flow resumes. Voluntary activation and force are scaled to emphasize their parallel changes. [From Gandevia et al. (260).]

tions of the elbow flexors in monkeys, the discharge of motor cortical cells producing postspike facilitation in motoneurons usually increased at the higher of two force levels (239).[2] Firing rates remained regular (at 20–45 Hz), with few short interspike intervals. The postspike facilitation usually affected both elbow flexors from which EMG was recorded. In a subsequent report, 13 of 26 motor cortical cells showed an increase, 9 a decrease, and 5 no change with repeated contractions when EMG evidence of fatigue was present (47). Some sense emerges from these data because the change in a cell's discharge rate with fatigue correlated positively with its change in rate with a higher flexor force. Cofacilitation by single cortical cells of both flexors and extensors at the elbow became more common with fatigue and would cause cocontraction (257, 601).

E. Stimulation of Descending Motor Tracts

As indicated in section IV, the MEP in limb muscles can increase in size during near-maximal efforts and return quickly to control levels when evoked during brief MVCs, but it becomes depressed for up to half an hour when evoked in relaxed muscles. The correlation of

changes in the MEP with motor cortical excitability is complicated by the ability of a transcranial stimulus to evoke different numbers of I waves from corticospinal axons and the capacity of spinal circuits to modify the motoneuron pool output (see sect. IV*A*). Stimulation of the descending motor tracts offers a simplification because single stimuli can be given to a population of rapidly conducting axons far from the cell body with the evoked response, indicating the responsiveness of spinal motoneurons.

Ugawa et al. (718) stimulated descending motor paths to intrinsic hand muscles using high-voltage electrical stimuli delivered to the skull base near the cervicomedullary junction. Because the response to transcranial electrical (718) and magnetic stimulation of the motor cortex (270) can be largely occluded by an appropriately timed transmastoid stimulus, the responses evoked at the two sites share axons, presumably corticospinal ones. Magnetic stimulation through a double-cone coil centered close to the inion can also activate descending tract axons (126, 700, 719). Although a less painful stimulus, it is less effective at evoking a large descending volley, at least with the present stimulators and coils. The activation site is likely to be the same with both forms of stimulation, probably where the corticospinal axons curve in the caudal part of the pyramidal decussation, although this has not been confirmed directly. Because both forms of cervicomedullary stimulation can also excite motor roots

---

[2] Postspike facilitation is indicative of mono- or oligosynaptic connection with motoneurons.

innervating arm muscles, it is essential to ensure that the latency of muscle responses is consistent with trans-synaptic activation of motoneurons. Observation of a large increase in size of the responses evoked by cervicomedullary stimulation (CMEP) during a weak voluntary contraction provides an additional but not sufficient check. Stimulation of the corticospinal tracts offers a comparatively direct method to access human motoneurons because corticospinal terminals in both animals and humans do not receive afferent presynaptic inhibition (557). However, this type of stimulation would not be useful for measurement of voluntary activation unless the activation of antagonist muscles was avoided.

Only two studies have mapped the change in the CMEP during a sustained MVC (126, 703), and in one the size of the CMEP was not corrected for changes in the maximal M wave (703). The uncorrected CMEP did not grow, whereas the MEP did during a sustained MVC of elbow flexor muscles. However, when related to M_{max}, the CMEP declined progressively during a long 2-min MVC (126). In contrast, when tested 15–30 s into the recovery period during a brief 2-s MVC, the CMEP had returned to preexercise levels (126). At this time, maximal voluntary activation and motor unit firing rates are depressed, but the CMEP, which should be a sensitive indicator of motoneuronal inhibition, can fully recover. This rapid recovery occurred even if the working muscles were held ischemic after the fatiguing contraction (126). Given that postcontraction ischemia prevented the elevated blood pressure from returning to normal levels (705), there can be no doubt that ischemically sensitive group III and IV muscle afferents were firing and able to exert central reflex effects. Hence, the rapid recovery of the CMEP suggests that group III and IV muscle afferents do not directly inhibit motoneurons. The ability of a brief MVC to restore the contraction-induced depression of the response to corticospinal tract stimulation indicates that the depression cannot be caused by a focal reduction in excitability of the axons themselves; if present, this should have worsened (and not recovered) in a second MVC.

What causes the CMEP elicited during a sustained MVC to decline? Activity-dependent changes at several sites could be involved. First, at a premotoneuronal level, the descending tract volley could decline due to elevations in axonal threshold (479, 655), but the rapid recovery when tested during a brief effort makes this unlikely. Because conventional presynaptic inhibition is not believed to act on corticospinal terminals, this premotoneuronal mechanism is excluded. Second, the pattern and distribution of descending tract firing in voluntary efforts and the firing rate of motoneurons will be important. If the net excitation from descending and spinal inputs is reduced, then a test input produced by transmastoid stimulation may be less effective in discharging motoneurons.

Against this, when motoneuron firing rates decline (as in a sustained MVC), the motoneuron may spend a longer fraction of its interspike interval near firing threshold (377, 491). The relevance of these factors is not easily gauged due to uncertainty about the trajectory of the motoneuron afterhyperpolarization, changes in firing threshold, and changes in the amplitude and frequency content of synaptic noise. Third, the corticomotoneuronal synapse may show some depression, at least when tested with single stimuli. This has recently been postulated to occur after a sustained MVC (270, see below). However, studies in nonhuman primates have emphasized the efficacy of high-frequency corticospinal volleys in producing facilitation of composite EPSPs in motoneurons (444, 541, 583, 590). Fourth, the "gain" of the motoneuron may diminish due to intrinsic properties of its cell membrane, such that a higher net current is required to increment the ongoing discharge (see sect. III). This concept has been confirmed based on current injection into motoneurons, during fictive locomotion in the cat (101; cf. Ref. 100). However, this experimental preparation hardly mimics conditions during voluntary effort. Fifth, the decline in CMEP amplitude may depend on intercalated interneurons activated by the transmastoid stimulation, although the initial component of the CMEP will contain a corticomotoneuronal component (for most muscles, see sect. IVA). Finally, altered afferent inputs changing the net drive to motoneurons might be involved, but there is evidence that group III and IV afferents are not directly responsible (126, 705).

If the elbow flexors are tested when relaxed after an MVC, the CMEP is profoundly depressed. This takes 2–3 min to recover and may even overshoot its control size (Fig. 25). The time course is unaffected by maintained muscle ischemia. This is not directly related to muscle fatigue as maximal voluntary force declines little in a 5-s effort, but the depression is similar for MVCs lasting from 5 to 120 s. Because the depression does not occur after maximal tetanic nerve stimulation which activates motoneurons synaptically and antidromically, it is unlikely to be due to a motoneuronal property (270). An elevated threshold in the descending tract axons resulting from their activity in the voluntary effort may develop, but it cannot fully explain the depression because it is abolished when tested during a brief MVC, a situation which should augment rather than abolish any increase in axonal thresholds (126). If axonal factors at the cervicomedullary stimulus site and postsynaptic factors within the motoneuron can be eliminated, the data favor an activity-dependent process in the corticospinal and other synapses on motoneurons as the cause for the postcontraction depression of the CMEP in the relaxed muscle. Depressed synaptic release has been well documented for central synapsis with in vitro studies (191a, 747a).

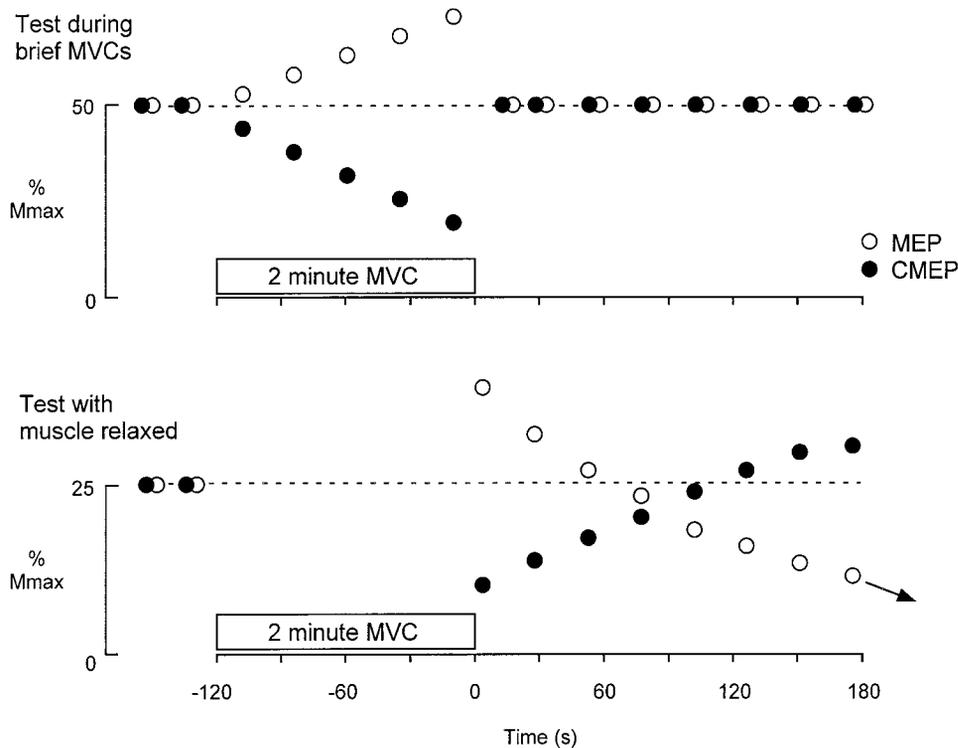When tested with motoneurons quiescent after an

FIG. 25. Summary of typical changes in EMG responses to motor cortical stimulation (MEP, open circles) and stimulation of descending motor paths including the corticospinal tracts (CMEP, solid circles) before, during, and after fatigue in a sustained MVC. The same changes occur in the MEP and CMEP after the sustained MVC whether or not the muscle is held ischemic (not shown, see text). *Top panel* shows the responses observed with all stimuli delivered during MVCs, whereas the *bottom panel* shows responses obtained with the muscles relaxed. The MEP increases during the sustained MVC, is not depressed when tested during brief MVCs in the recovery period (*top panel*), and is increased with a late prolonged depression when the muscle does not contract after the sustained MVC (arrow, *bottom panel*). In contrast, the response to a single corticospinal tract stimulus decreases during the sustained MVC and is depressed when tested during relaxation immediately after the contraction. The depression of the CMEP is removed by a brief "recovery" MVC. Fatigue-induced changes are clearly documented at the motor cortical and motoneuronal level. Further details are given in text.

MVC, there is also a late facilitation of the CMEP ~5 min after the contraction. This may be a hallmark of fatigue and prior motoneuronal activity as it is more prominent after longer voluntary contractions and occurs after tetanic stimulation. This late facilitation at a spinal level occurs concurrently with the long-lasting depression at motor cortical level.

Figure 25 summarizes changes in the MEP and CMEP during a sustained MVC when tests are performed during brief test MVCs in the recovery period (*top panel*), and changes in the MEP and CMEP when tests are performed during relaxation in the recovery period (*bottom panel*). Data have been normalized to accommodate changes in M_{max}. The figure highlights the divergent behavior of the MEP and CMEP during and after the fatiguing contraction, the rapid recovery of both responses when tested during voluntary effort, and the long-duration depression in the MEP (and perhaps increase in the CMEP) when the motor cortex and motoneurons are not involved in a voluntary effort. Note that there is a similar time course for all these postexercise changes when some group III and IV afferents are maintained active by ischemia.

F. Conclusions

Central fatigue during isometric MVCs contains a supraspinal component because transcranial stimulation of the motor cortex can add progressively more force to that generated voluntarily. This component can be differ-

entiated from changes occurring locally at the motor cortex during (and after) fatiguing voluntary contractions. Feedback of the force-generating capacity of the muscle and its biochemical status may ultimately impair the drive to the motor cortex, via effectively "supra" motor cortical sites. The time course differs for changes in voluntary activation and motor cortical "excitability," and the relationship between these changes and the intensity of exercise is complex. Stimulation of descending motor tracts (including corticospinal axons) has revealed time-dependent changes produced by voluntary activity in the apparent effectiveness of connections with motoneurons.

V. OTHER SUPRASPINAL FACTORS AND CENTRAL FATIGUE

A. Task Failure and Central Fatigue

The extent to which the muscles could have performed better when a task can no longer be performed voluntarily or when exercise ceases (as the target time has elapsed or the target event is completed) is critical to understanding the importance of central fatigue. Two examples of "open-loop" task failure were presented initially (Fig. 5, see sect. I). One involved failure to lift a weight voluntarily when electrical stimulation could do so, and the other involved failure to maintain a target force, which was subsequently maintained with tetanic stimula-

tion. Although these results were obtained under seemingly fair conditions, one unavoidable worry remains: the subjects knew that they would receive electrical stimulation whenever the task could no longer be continued voluntarily. On ethical grounds, such a position cannot be avoided. These results fit with the evidence that intermittent submaximal contractions are terminated with EMG levels often well below those predicted from control measures before the exercise (e.g., Refs. 248, 449).

Exercise that is completed after a specific time, distance, or number of contractions (i.e., "closed" loop) removes one subjective component from the point of termination, but it still means that performance can be limited by central factors. Indeed, studies described in section III document the progressive decline in voluntary activation in sustained or intermittent MVCs made under isometric conditions with limb muscles. Further studies are needed to apply electrophysiological techniques to fatiguing anisometric exercise involving one or many muscle groups.

On the evidence obtained with isometric contractions made by a variety of muscles, central fatigue is quite likely to limit performance under other conditions in which many muscles move loads. Conceptually, performance may deteriorate due to *1*) central fatigue developing at those muscles working closest to "maximal" levels, *2*) a different "motor" limit in which the capacity to coordinate the required contractions deteriorates (see sect. vC), or *3*) a "sensory" or tolerance limit because the consequences of continuing the task become sufficiently unattractive. Alternatively, there may be some local circulatory, respiratory, or metabolic event that produces task failure. No single factor has yet been identified in exercise of normal human volunteers as the cardinal "exercise stopper." A number have been proposed including muscle acidification, muscle potassium efflux, glycogen depletion, capacity to use extramuscular fat stores, fatigue of respiratory muscles, and reflex inhibition due to rises in pulmonary capillary pressure. Study of them has given more insight into basic physiological processes rather than the neural mechanisms responsible for the termination of exercise or the failure of the neuromuscular system to perform better.

B. Altered Central Fatigue in Different Tasks

To this point the focus has been on mechanisms that operate during strong contractions of limb muscles. Existence of such mechanisms does not necessarily mean that they operate similarly for all muscles under all circumstances. Indeed, they do not. Examples below will highlight the effect of the task on voluntary activation, central fatigue, and task failure (for further discussion of the task dependence of muscle fatigue, see Refs. 71, 229,

673). However, some homeostatic factors will act across tasks. An important one is perfusion of the exercising muscle. Thus force output from a stimulated muscle increases with perfusion pressure across the physiological range (236, 333, 768). Reflex inputs from the muscle signaling the adequacy of its perfusion act in a feedback loop to control perfusion and enhance peripheral performance (768). As a consequence, the neural input from the muscle, which can impair voluntary activation, is itself influenced by central factors involved in maintenance of perfusion. A failure of mechanisms to maintain or increase perfusion will directly impair peripheral performance and thus impair voluntary activation.

1. Dynamic exercise and temperature

Rhythmic exercise at moderate-high intensity as in running or cycling is eventually terminated when the target speed cannot be maintained. No single metabolic factor is tightly coupled with the decline in skeletal muscle power during this type of work (e.g., Refs. 35, 382). Either a varied combination of such factors operates in individual subjects or there is the possibility that neural control factors are also important. Indeed, there are usually competing "optima." For example, in cycling, the pedaling frequency that minimizes oxygen consumption, presumed muscle fatigue and subjective effort, and breathlessness differs by up to 40 revolutions/min (e.g., Refs. 137a, 698). Neural drive, measured indirectly from the surface EMG, declined in high-intensity bursts during cycling for 100 km (282a). The point of termination or task failure has a temperature optimum for exercise involving one (213) or many muscle groups (256).

The traditional view is that diminution of substrate supply, particularly of carbohydrates, is responsible for cessation of exercise. After the original work by Christensen and Hansen (139), influential studies establishing this view showed that endurance time lengthened with dietary manipulations that increased muscle glycogen stores at the start of exercise (e.g., Refs. 56, 295). However, this cannot be the full explanation because when task failure was delayed after a carbohydrate-rich diet, exercise not only began but ended with higher muscle glycogen levels. In addition, endurance deteriorated when the environmental temperature was high, and this could not be explained by substrate supply to, or use by, the muscles (555, 556, 588). A plausible explanation is that task failure occurs, not when there is an accumulation of "fatigue" substances, but when core temperature reaches a threshold (~40°C). High muscle temperatures (~40°C) are probably just beyond the optimum for tetanic force production by human muscle (604). At this environmental extreme, competing needs must be met: maintenance of arterial blood pressure and hence muscle perfusion versus the need to increase cutaneous blood flow and hence

sweating and evaporative cooling (for review, see Ref. 628). If a hypothalamic "off" switch is involved in exercise termination when core temperature approaches a critical value, serotonin (5-HT) may be involved. Serotonergic neurons project to, and within, the hypothalamus (see sect. vD), while supplements which decrease the ratio of free tryptophan to branched-chain amino acids significantly prolong endurance times but only by ~10% (538). The operation of such a central mechanism is unlikely to be the only one limiting performance in this temperature extreme.

2. Task dependence and respiratory muscle performance

Human respiratory muscles perform a crucial ventilatory role, but they can also contract in quasi-static efforts at constant lung volumes (e.g., Valsalva and Mueller maneuvers). Depending on the task performed, the diaphragm can develop either a large degree or no central fatigue. Twitch interpolation using phrenic nerve stimulation reveals that voluntary activation of the unfatigued diaphragm can be almost complete in maximal voluntary inspiratory tasks and maximal expulsive maneuvers (48, 267). However, diaphragmatic endurance was different under the two conditions: the final sustainable force was relatively lower for expulsive than inspiratory efforts (268). This was attributed to impaired diaphragmatic perfusion during the expulsive task in which high pressures develop within the abdomen. With intermittent submaximal expulsive efforts, much of the decline in voluntary expulsive force during fatigue reflected impaired voluntary drive to the diaphragm (49). Hence, repeated expulsive efforts not only produced substantial peripheral fatigue (presumably through blood flow limitation), but also increased central fatigue. During submaximal expulsive efforts which eventually required maximal effort, central fatigue developed (final voluntary activation ~60%). Fortunately, when the task was changed, there was no central fatigue for maximal inspiratory efforts that were performed after the expulsive efforts (voluntary activation ~95%) (514). Premotoneuronal events must underlie this differential central fatigue. The central mechanisms behind the susceptibility of the diaphragm to central fatigue during expulsive efforts are unexplored. It is as if the system acts to preserve blood flow to the exercising muscle, perhaps via a reflex circuit (333, 768; cf. Ref. 448). Somatic or visceral afferents from the thorax and abdomen may be responsible because voluntary activation of the unfatigued diaphragm in inspiratory tasks is well suboptimal at lung volumes below functional residual capacity and increases with lung volume (512).

An extension of the task dependence shown by the respiratory muscles is the observation that with a similar fatigue protocol involving intermittent maximal efforts of inspiratory or limb muscles in the same subjects, central fatigue developed with limb muscles but not the diaphragm (514). Indeed, when performing inspiratory tasks, the inspiratory muscles show considerable resistance to fatigue at both a peripheral and central level (e.g., Refs. 201, 514). This comparison has been made at the same time during equivalent limb and inspiratory exercise, rather than when the limb and inspiratory muscles show an equal degree of peripheral fatigue (514). This does not undermine evidence that fatigue of inspiratory muscles may develop during maximal whole body exercise (e.g., Refs. 26, 374) or under some clinical conditions (for review, see Refs. 176, 513). Fatigue and task failure occur when breathing through an added external inspiratory resistive (and other) loads. It used to be claimed that subjects stopped the task due to peripheral fatigue of the diaphragm (e.g., Refs. 50, 626, 627). However, studies with twitch interpolation during such loading indicate that as end-tidal CO_2 levels rise, voluntary activation of the diaphragm remains constant or increases, while twitch force of the diaphragm declines only slightly (292, 511; cf. Ref. 431). Task failure occurs when there is minimal peripheral fatigue in the diaphragm but intolerable levels of respiratory discomfort (or dyspnea) produced by a combination of the intense respiratory contractions and sensations attributed directly to an elevated arterial CO_2 level (see also Ref. 292; cf. Ref. 431).

Studies of respiratory muscle performance, although technically difficult, have provided insight into some extremes: a situation in which voluntary activation is almost halved (in maximal expulsive efforts), and one in which task failure occurs with no prior decrease (or even an increase) in voluntary activation. Although the inspiratory muscles are an essential ventilatory pump "overbuilt" for most activities including exercise, ultimately their performance depends on the competing ventilatory and postural demands placed on them, along with limits imposed by the cardiovascular system and the working milieu of the muscle. Their capacity is doubly ensured by peripheral fatigue resistance (including a marked ability to increase their blood flow) (480) and an apparent resistance to central fatigue. However, the blood flow requirement of the exercising limb muscles and the metabolic milieu created by their contractions may ultimately impair peripheral diaphragm performance (24, 25).

3. Exercise and altitude

The challenge to cellular respiration provided by hypoxia at altitude has suggested interesting task-dependent possibilities for fatigue. Exercise at low barometric pressures stops with less biochemical evidence for peripheral fatigue, including less lactate production (e.g., Refs, 296, 696, 748). Although H reflexes and M_{max} may be preserved (392), voluntary activation tested with twitch interpola-

tion can be impaired (281). At this extreme, central fatigue may develop more rapidly with exercise of large limb muscles than small ones (393; see also Ref. 673). The proposal that such an interaction and the paradoxically reduced lactate production during heavy exercise at altitude reflect a centrally mediated limit imposed by hypoxia remains tenable (73). However, such a limit is probably not imposed, as originally thought (see Ref. 212), by diaphragm fatigue (649).

4. Pulmonary C fibers and exercise

An influential hypothesis based on studies in animals is that a reflex arising in the lungs inhibits motoneurons (18, 286, 569). This could occur when pulmonary C fibers are activated by the rises in pulmonary capillary pressure accompanying exercise. While this potent viscerosomatic inhibition has been documented in a variety of conditions in animals (e.g., Refs. 180, 585), and while intravenous lobeline can be used to excite the pulmonary C fibers in animals (603) and to cause noxious pulmonary sensations in humans (262, 603), the somatic component of the reflex evoked by stimulation of pulmonary C fibers is absent in awake humans (262). Thus, despite the sustained noxious respiratory sensations evoked by high doses of lobeline, awake human subjects showed no evidence of direct or indirect inhibition of motoneurons. Production of voluntary force with limb muscles and locomotion were unimpaired. The exercise-stopping capacity of the pulmonary C fibers in animals appears to be overridden in human subjects. This would favor cognitive evaluation of the situation causing the excitation of the afferents and would leave the muscles under supraspinal command rather than under control by spinal reflex inhibition.

5. Maintenance of maximal voluntary activation by use

Exercise-related factors impair voluntary activation during exercise, but a lack of exercise also impairs voluntary activation. A muscle's size, maximal force and EMG levels, twitch and tetanic force, and contraction and relaxation times are believed to diminish with disuse (for review, see Refs. 89, 641; cf. Refs. 196, 197, 337a, 560). After immobilization of the hand for 6 wk, the tetanic force of adductor pollicis decreased by 33%, whereas maximal voluntary force declined by 55% (165, 196, 249; cf. Ref. 245). The disproportionate loss of voluntary force suggests that maximal voluntary activation declines with reduced use. Any deficit in net drive to motoneurons may be overestimated if contractile speed increases with hypoactivity (cf. Ref. 774) so that lower motor unit firing rates would generate maximal evocable force. In previously immobilized muscles, maximal firing rates of motor units decreased by more than 25%, and short interruptions occurred in their discharge (197). It is not known which

comes first, the changes in muscle properties or the changes in motor unit firing rates. In addition, immobilization reduced the modulation of muscle spindle and tendon organ discharge by motor unit contraction (560) so that the afferent input during voluntary contractions may change. A measure of "reflex potentiation" also declined after immobilization (560, 640).

There are several corollaries. First, there may be a critical level of motoneuronal activity below which maximal voluntary activation deteriorates. Activation may be low in muscles with low peak or sustained motor unit firing rates. Second, training may improve voluntary activation in muscles with low initial maximal voluntary drive (see sect. IIA). Hence, a training effect on maximal performance may depend on the baseline level of voluntary activity in the motoneuron pool as well as the dynamics of the muscle fibers. Eccentric contractions may be especially important (337a). Third, the increasingly evident plasticity of motoneurons and supraspinal sites involved in movement control, including the human sensorimotor cortex, may be functionally linked to the maintenance of appropriate levels of voluntary drive to motoneuron pools (e.g., Refs. 105, 243, 410, 542, 563, 572, 687, 764). However, use is not the sole enhancer of maximal voluntary drive as this can decline with excessive training (417).

C. Other Central Changes Accompanying Muscle Fatigue

Exercise is not only accompanied by central fatigue but by a sense of increased effort, greater unsteadiness and tremor, along with progressive recruitment of other muscles during the task.

1. Changes in proprioception

An increasing sense of effort develops during muscle fatigue. The mechanisms responsible have long been debated, but inputs from specialized muscle, joint, and cutaneous receptors, signals related to the magnitude of outgoing motor "commands," plus central-peripheral interactions are all involved (for review, see Refs. 259, 379, 500). As indicated in section III, the properties of all groups of muscle receptors change during fatigue. This must affect their direct contribution to proprioception through supraspinal projections, and their indirect contribution through changes in reflex "support" to contractions. When the latter changes, the size of the required central motor commands changes to compensate (e.g., Refs. 21, 502). The progressive increase in effort as fatigue supervenes derives from the increased central command needed to recruit more motoneurons, to increase their rate in initially submaximal tasks, and to attempt to maintain their output in maximal ones. Motoneuronal properties demand that if a motoneuron is transiently dere-

cruited during a fatiguing effort, a relatively larger input will be required to rerecruit it than would have been necessary to maintain its output.

Inputs from Golgi tendon organs and small-diameter afferents seem especially useful to signal the altered muscle behavior in fatigue. Along with peripheral signals, motor command signals can be sensed independently as an index of the timing of efforts (446, 501), the destination of commands (272), and their magnitude (e.g., Ref. 265). Under artificial conditions, subjects can distinguish the two types of signal (e.g., Refs. 107, 501, 502), although this distinction becomes difficult during muscle fatigue (e.g., Refs. 378, 380). The generator for this effort signal requires input to the motor cortex and may involve a fatigue-related ascending signal from the basal ganglia (182, 183, 258; see also Refs. 135, 617).

Knowledge of joint angle forms another component sensation within kinesthesia, and muscle receptors, particularly muscle spindle endings, are involved (e.g., Ref. 290; for review, see Ref. 500). There is increasing evidence that input from joint and cutaneous receptors is "integrated" into judgements (e.g., Refs. 149, 210, 234, 473, 606). While motor performance may deteriorate acutely during fatigue, measured in terms of limb or postural steadiness (546, 666, 683) and accuracy or speed of performance, simple tests of joint "position" sense show either no systematic change (671, 679, 689) or a mild deterioration (130, 370, 440, 578, 652, 679). Eccentric exercise may systematically distort senses of static position and force for more than a day after exercise (96). Here, damage to muscle fibers and receptors may be involved.

2. Tremor and synchronization

Particularly after severe exercise, tremor increases across a wide frequency range (e.g., Refs. 102, 453), and the tendency persists for many hours (255, 434, 652). The properties of the tremor in a low (4–8 Hz) and the physiological frequency range (8–12 Hz) depend on whether it is generated under isometric or isotonic conditions (124, 285). Mechanisms for the altered tremor include changes in muscle contraction dynamics, proprioceptive reflexes, muscle receptor properties, and purely central factors. Given that low-frequency tremor fails to result from fatigue induced by electrical stimulation (454), fatigue-induced tremor is reduced when the afferent input from muscle spindle afferents is reduced (156), and overt tremor is not evident in the neurogram measured proximal to a nerve block during sustained maximal efforts (265; cf. Ref. 255), central factors involving short- and long-latency reflex loops must play an important part.

A small but statistically detectable synchronization exists between the firing probability of motor units within a muscle during voluntary contractions, suggesting some common excitatory (or inhibitory) presynaptic drive (e.g.,

Refs. 102, 174, 187, 662, 717a). This occurs within all motoneuron pools and may even involve synergists with a common mechanical action (688). During voluntary contractions, the degree of synchronization varies with the task (94, 656) and the subject's level of skill (536; cf. Ref. 667). The relationship between synchronization and fatigue-induced tremor remains unclear (102, 561, 668), although the association is widely accepted (61). Some force fluctuations in fatigue arise simply because motor units tend to fire at similar rates (15), a situation enhanced by the firing rate "compression" occurring during isometric contractions. Based on detailed analysis of motoneuronal and muscle spindle contributions to the stretch reflex, Matthews (492) points out that once firing rates of motor units become unduly low in relation to the speed of muscle contraction (as argued in sect. III), then the stabilizing effect of the stretch reflex will decline and tremor will develop. Failure of the matching, which would occur with the decline in voluntary activation, will promote tremor across a broad low-frequency band.

3. Synkinesis and muscle rotation

During a strong isometric contraction of a limb muscle, as fatigue develops there is an obvious progressive contraction of other muscles. This "synkinesis" has long been known to occur in other situations in which effort increases such as with central lesions producing weakness (e.g., stroke). In healthy subjects it may even involve contraction of homologous muscles on the contralateral side (190, 191, 781a). This "irradiation" of effort to other muscles can recruit antagonists (e.g., Refs. 305, 601, 621), but this may be less obvious during repetitive nonisometric tasks (253). The effect of synkinesis increases sequentially, because additional muscles must then be recruited to balance the torques generated by the initial contractions. When fatigue occurs for forces generated at a particular finger joint, complex patterns of force production occur at joints of the other fingers (160). Eventually muscles can be recruited with no biomechanical utility for the task such as facial and trunk muscles during a fatiguing contraction with a limb (699).

This "irradiation" does not require peripheral feedback, being evident when muscles are paralyzed as a result of a stroke or when muscles are completely paralyzed in normal subjects (265). It is likely to involve excitation spreading "laterally" within the motor cortex, a site where excitability increases during fatigue (see sect. IV), with this change being driven by increased volitional and peripheral input to the motor cortex. This is shown diagrammatically in Figure 26. Many spinal mechanisms will come into play secondarily, particularly through changes in reciprocal inhibition and the many reflex effects evoked by the increasingly widespread contractions.

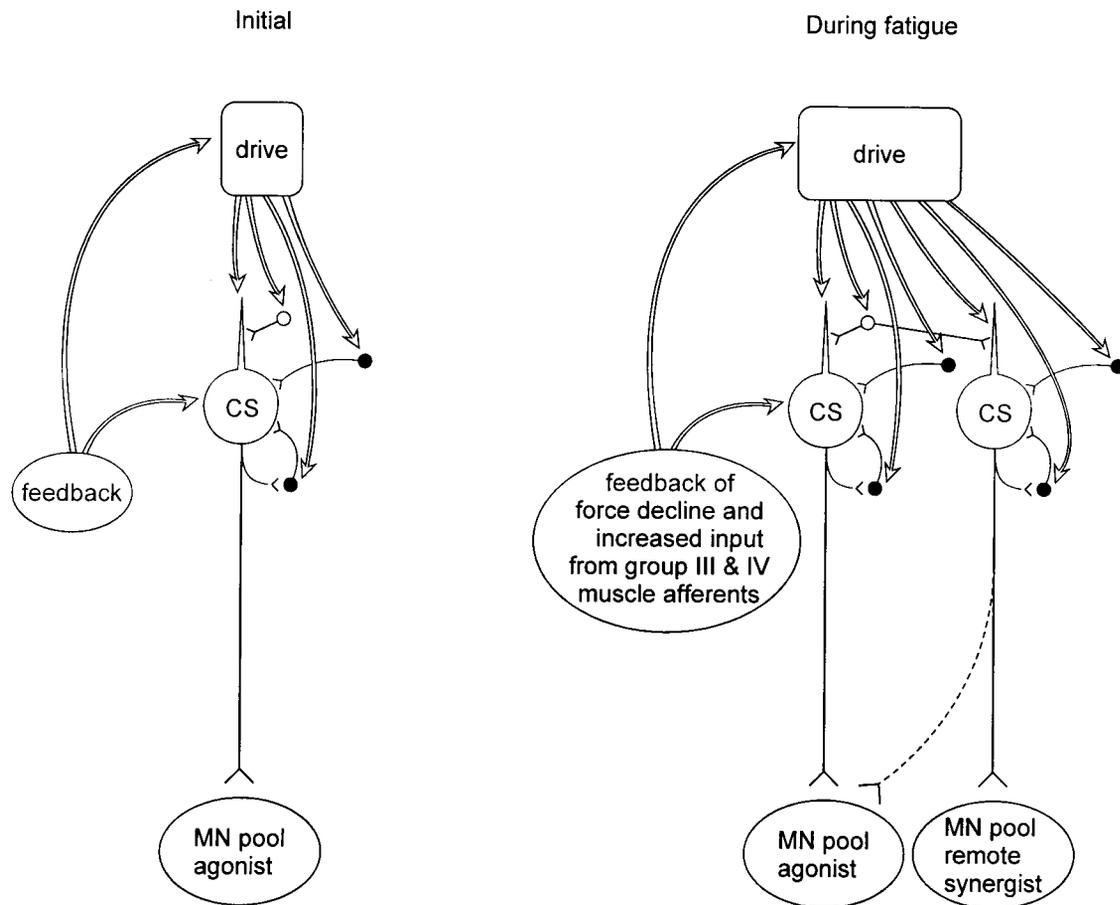During fatiguing tasks, EMG may appear to rotate

FIG. 26. Diagram of possible changes at a motor cortical level with muscle fatigue. Simplified schema for reflex input and "supra" motor cortical input to a corticospinal cell (CS) under control conditions (*left*) and during fatigue (*right*). Solid cells are inhibitory, and open ones are excitatory. Although shown diagrammatically, the types and locations of connections depicted occur in the motor cortex. During fatigue there is increased drive to corticospinal cells and more are "recruited." With this scheme local excitation and inhibition would be increased when tested with transcranial magnetic stimulation.

within and between muscles. The latter effect presumably reflects an attempt to use a different mechanical or muscle strategy to perform the same task (e.g., Ref. 142; cf. Ref. 323). During submaximal plantarflexion of the ankle which is sustained to the point of task failure, there are periods of coactivation among the synergist muscles and some instances of trade-offs between them, with considerable variation between subjects (678). The possibility of intramuscular "rotation" among motor units is more controversial. Zijdewind et al. (782) explored this phenomenon with surface electrodes over intrinsic hand muscles after finding some reduction in EMG during a sustained submaximal endurance task. The extent to which the effects reflected genuine rotation, activity in remote muscles, or focal changes in sarcolemmal function is unresolved (784). With strong contractions there was little evidence for rotation among single units whose activity was followed in the supraspinatus muscle during fatiguing contractions (371; cf. Ref. 749a).

D. CNS Biochemical Changes and Central Fatigue

Given that intense exercise challenges the cardiovascular, respiratory, endocrine, and peripheral and central motor systems, changes in many CNS transmitter systems would be expected to accompany exercise and task failure. Widespread central actions of many of these systems make it unlikely that any one is uniquely responsible for central fatigue. For example, there are serotonergic projections from brain stem raphe nuclei to the cortex, hippocampus, hypothalamus, medulla, and spinal cord (for review, see Ref. 714) and the noradrenergic projections from the locus subcoeruleus. Arousal, motivation, attention, tolerance to discomfort, and sensitivity to stress can each alter voluntary drive, at least subjectively, suggesting that many neural systems can modify central fatigue. For example, the concept that heavy exercise acts as a "stressor" to the immune system via a cocktail of factors including cortisol, cytokines, and other acute-phase reac-

tants is well established (for review, see Refs. 334, 559, 576). It is emerging that some cytokines such as interleukin-6 can be produced at high rates by the exercising muscle (567, 686).

A popular theory underlying "central" components to fatigue is that they reflect a central disturbance of amino acid metabolism involving the serotonergic system. This system is attractive because disturbances to it mediate changes in sleep-wakefulness, the hypothalamic-pituitary axis, and some motor functions (for review, see Refs. 39, 358, 359), and it is well developed in primates (714). During exercise, the entry of tryptophan into the CNS via the blood-brain barrier is competitively favored by increased muscle use of branched-chain amino acids and elevated plasma fatty acids as this elevates the ratio of unbound tryptophan to branched-chain amino acids. Its entry leads to elevated 5-HT levels in the hypothalamus, brain stem, and cerebrospinal fluid in rats running on a treadmill (86, 133, 134). Put simply, changes in muscle metabolism and the supply of substrates may feed back via humoral mechanisms to alter key CNS transmitter systems. Evidence for a serotonergic role in human central fatigue remains indirect; nonetheless, the potential for a contribution is clear based on many neurochemical and neuropharmacological studies in animals (for review, see Refs. 131, 132). For example, exercise increases 5-HT turnover in the striatum, midbrain, and hippocampus (27, 134). "Run time" to exhaustion improves with 5-HT antagonists and declines with 5-HT agonists. It is unlikely to reflect altered substrates for muscle contraction, temperature regulation, changes in sympathetic nerve output, or hypothalamic-pituitary effects (167).

Pharmacological interventions in humans suggest that blocking the reuptake of neurally released 5-HT before cycling or running (27, 167, 693, 756) increases perceived effort and decreases endurance time. Nutritional interventions designed to reduce the free tryptophan/branched-chain amino acid ratio have given equivocal results. Improved exercise performance occurred in some studies (85, 538), but not all double-blind crossover studies have confirmed this benefit (693, 735, 738), although perceived exertion and perceived mental function were slightly improved (84, 318).

Dopamine also plays a crucial role in motor control, as evidenced, for example, by the bradykinesia and tremor in Parkinson's disease. During various motor activities, including exercise, central dopamine levels increase (e.g., Refs. 27, 83, 133, 241, 319, 517). Amphetamine enhancement of dopaminergic activity has long been thought to improve human endurance (354, 439). In the rat, levels of dopamine and its metabolite increased within 1 h of exercise but returned toward rest levels at the point of task failure, whereas 5-HT levels continued to increase until task failure occurred (27). One suggestion is that dopaminergic activity, by inhibiting 5-HT synthesis,

may delay task failure (168). Perhaps when dopaminergic activity and motor drive diminish in the last part of treadmill running the rising levels of 5-HT act at some supraspinal site to terminate the exercise. Although this speculation may fit some observations, it begs the question of the neural mechanisms initiating "central" fatigue (as defined in sect. IB). It fails to account for the accepted view that descending 5-HT projections to the spinal cord attenuate nociception (e.g., Refs. 143, 287, 531) but facilitate motoneurons and locomotion (232, 339; for review, see Refs. 358, 359). Hence, other important factors are likely to be involved.

There are several other transmitters and their subtypes that will need to be examined for their role in central fatigue. Already it is known that brain GABA levels diminish with exercise in the rat (133, 134). Baclofen acting at GABA$_B$ receptors can delay task failure in rats running on a treadmill with the rear of the cage electrified (1), an effect which may be exerted independently of an action via brain stem 5-HT pathways (763). Both GABA$_A$ and GABA$_B$ agonists injected into the median raphe nucleus rapidly evoke locomotion in rats (763).

Other potential humoral signals derived from muscle activity include glutamine (diminished after exercise) and ammonia (increased). Cytokines may also be involved in prolonged or repeated bouts of physical activity. It is reasonable to consider that muscle biochemistry, neurohumoral factors, and CNS chemistry are linked during fatiguing exercise, but our knowledge of the critical links is still rudimentary.

VI. SUMMARY AND CONCLUSIONS

The CNS is given a homeostatic challenge when required to balance actively the cardiovascular and respiratory demands of exercise with the need to optimize the voluntary force output of one or many muscle groups. Factors limiting exercise will depend on its type and intensity, the muscle groups involved, and the physical environment in which it is performed. Even when studied under conditions designed to maximize supraspinal drive, voluntary activation of muscle is commonly not maximal in measurements of isometric strength. This deficiency varies with the subject, task, and the muscle group. It can be measured with refinements to the original technique of twitch interpolation. With fatiguing tasks requiring maximal effort from limb muscles, there will undoubtedly be significant peripheral fatigue, but central fatigue may add substantially to the decline in performance, even under optimal experimental conditions. Some of this reflects a failure of supraspinal drive to motoneurons, so-called "supraspinal" fatigue. It will act to "protect" the muscle from further peripheral fatigue, but at the expense of truly

maximal performance. Central fatigue may impinge to such an extent that exercise stops when the muscle has not fatigued sufficiently at a peripheral level to limit performance of the task. An extreme example occurs with exercise of the inspiratory muscles in which task failure can occur with minimal peripheral fatigue.

Because central fatigue appears so commonly in human performance, one might expect that its development confers some evolutionary advantage. Perhaps drive is limited because continued drive to the muscle would put the neuromuscular junction or more likely the intracellular events accompanying excitation-contraction coupling and actin-myosin interactions into a catastrophic state, one from which recovery was delayed or impossible. In addition, central fatigue may impair performance when its continuation would compromise another vital homeostatic mechanism such as maintenance of temperature, blood pressure, and ventilation. Alternatively and nihilistically, one may propose that at the supraspinal level maximal human muscle performance is "as good as it gets" and, provided the CNS controls when exercise stops, there are plenty of "downstream" sites in the muscle for evolutionary adaptation. Unlike some mammals, conscious humans do not allow phylogenetically primitive reflexes (for example, the J reflex) to stop exercise.

The peripheral and central components of muscle fatigue can now be measured for a range of exercise regimens, but the exact techniques used must be critically selected. Accompanying the changes in voluntary activation and motor unit firing in fatigue are focal changes in the "excitability" and "inhibitability" of the motor cortex, as revealed by studies using transcranial cortical stimulation. There may even be activity-induced changes in the effectiveness of corticospinal action on motoneurons. The latter changes have been measured by stimulation of the corticospinal tract after voluntary contractions. Not all such central changes lead to reduced muscle force. Further work is needed to extract those supraspinal changes that cause the changes in voluntary activation and cause the changes in motor cortex excitability, and to correlate these central changes with indices of performance in different subject groups and experimental tasks.

During fatiguing maximal contractions, the muscle fibers of each motor unit alter their force-frequency properties depending on muscle length, local biochemical changes, temperature, and contraction history. However, it is highly improbable that the discharge of each unit is regulated individually by reflex action to tailor firing rate with the frequency required for twitch fusion. Instead, during isometric contractions, the CNS routinely uses a strategy whereby the firing rates of units decline with an early and late phase in a way that takes advantage of hysteresis in the force-frequency relationship and that provides some indispensable but inadequate compensa-

tion for the slowing in relaxation rate that occurs under some, but not all, fatiguing conditions.

During fatigue, feedback of the declining peripheral performance and the muscle's milieu is available via the full array of intramuscular receptors. At a spinal level this produces competing excitatory and inhibitory influences on the motoneuron pool, many of which could contribute to the decline in motor unit firing rate observed during maximal isometric contractions. The potency or gain of these effects may be small compared with the changes in firing induced by intrinsic, activity-dependent properties of the motoneuron membrane. Such activity-dependent changes will be occurring elsewhere, including at corticospinal cells. At a supraspinal level, the feedback drives appropriate changes in the output to motoneuron pools of agonist, synergist, and ultimately remote muscles. Input from small-diameter muscle afferents, particularly the group IV muscle afferents transmitting nociceptive input, reduces voluntary drive through a supraspinal action and not via direct postsynaptic inhibition of motoneurons. The actions of group III and IV muscle afferents are complex and not exerted at one point in the pathways responsible for force production. Because the properties of proprioceptive afferents and the central motor output vary with fatigue, there are consequent changes in proprioceptive sensations that rely on peripheral input, knowledge of central motor commands and their combination, along with other changes in motor performance.

REFERENCES

1. ABDELMALKI A, MERINO D, BONNEAU D, BIGARD AX, AND GUEZENNEC CY. Administration of a GABA$_B$ agonist baclofen before running to exhaustion in the rat: effects on performance and on some indicators of fatigue. *Int J Sports Med* 18: 75–78, 1997.
2. ADREANI CM, HILL JM, AND KAUFMAN MP. Responses of group III and IV muscle afferents to dynamic exercise. *J Appl Physiol* 82: 1811–1817, 1997.
3. ADREANI CM AND KAUFMAN MP. Effect of arterial occlusion on responses of group III and IV afferents to dynamic exercise. *J Appl Physiol* 84: 1827–1833, 1998.
4. ADRIAN ED AND BRONK DW. The discharge of impulses in motor nerve fibres. Part II: The frequency of discharge in reflex and voluntary contractions. *J Physiol (Lond)* 67: 119–151, 1929.
5. AIMONETTI JM, VEDEL JP, SCHMIED A, AND PAGNI S. Distribution of presynaptic inhibition on type-identified motoneurones in the ex-

tensor carpi radialis pool in man. *J Physiol (Lond)* 522: 125–135, 2000.

6. AIMONETTI JM, VEDEL JP, SCHMIED A, AND PAGNI S. Mechanical cutaneous stimulation alters Ia presynaptic inhibition in human wrist extensor muscles: a single motor unit study. *J Physiol (Lond)* 522: 137–145, 2000.

7. AL-FALAHE NA, NAGAOKA M, AND VALLBO AB. Response profiles of human muscle afferents during active finger movements. *Brain* 113: 325–346, 1990.

8. ALLEN DG, LANNERGREN J, AND WESTERBLAD H. Muscle cell function during prolonged activity: cellular mechanisms of fatigue. *Exp Physiol* 80: 497–527, 1995.

9. ALLEN GM, GANDEVIA SC, AND MCKENZIE DK. Reliability of measurements of muscle strength and voluntary activation using twitch interpolation. *Muscle Nerve* 18: 593–600, 1995.

10. ALLEN GM, GANDEVIA SC, AND MIDDLETON J. Quantitative assessments of elbow flexor muscle performance using twitch interpolation in post-polio patients: no evidence for deterioration. *Brain* 120: 663–672, 1997.

11. ALLEN GM, GANDEVIA SC, NEERING IR, HICKIE I, JONES R, AND MIDDLETON J. Muscle performance, voluntary activation and perceived effort in normal subjects and patients with prior poliomyelitis. *Brain* 117: 661–670, 1994.

12. ALLEN GM, HICKIE I, GANDEVIA SC, AND MCKENZIE DK. Impaired voluntary drive to breathe: a possible link between depression and unexplained ventilatory failure in asthmatic patients. *Thorax* 49: 881–884, 1994.

13. ALLEN GM, MCKENZIE DK, AND GANDEVIA SC. Twitch interpolation of the elbow flexor muscles at high forces. *Muscle Nerve* 21: 318–328, 1998.

14. ALLEN GM, MCKENZIE DK, GANDEVIA SC, AND BASS S. Reduced voluntary drive to breathe in asthmatic subjects. *Respir Physiol* 93: 29–40, 1993.

15. ALLUM JH, DIETZ V, AND FREUND HJ. Neuronal mechanisms underlying physiological tremor. *J Neurophysiol* 41: 557–571, 1978.

16. ALSTERMARK B, ISA T, OHKI Y, AND SAITO Y. Disynaptic pyramidal excitation in forelimb motoneurons mediated via C-3-C-4 propriospinal neurons in the *Macaca fuscata*. *J Neurophysiol* 82: 3580–3585, 1999.

17. AMASSIAN VE, STEWART N, QUIRK BJ, AND ROSENTHAL JL. Physiological basis of motor effects of a transient stimulus to cerebral cortex. *Neurosurgery* 20: 74–93, 1987.

18. ANAND A AND PAINTAL AS. Reflex effects following selective stimulation of J receptors in the cat. *J Physiol (Lond)* 299: 553–572, 1980.

19. ANGEL MJ, GUERTIN P, JIMÉNEZ I, AND MCCREA DA. Group I extensor afferents evoke disynaptic EPSPs in cat hindlimb extensor motoneurones during fictive locomotion. *J Physiol (Lond)* 494: 851–861, 1996.

20. ANISS AM, DIENER HC, HORE J, GANDEVIA SC, AND BURKE D. Behavior of human muscle receptors when reliant on proprioceptive feedback during standing. *J Neurophysiol* 64: 661–670, 1990.

21. ANISS AM, GANDEVIA SC, AND MILNE RJ. Changes in perceived heaviness and motor commands produced by cutaneous reflexes in man. *J Physiol (Lond)* 397: 113–126, 1988.

22. AWISZUS F, WAHL B, AND MEINECKE I. Influence of stimulus cross talk on results of the twitch-interpolation technique at the biceps brachii muscle. *Muscle Nerve* 20: 1187–1190, 1997.

23. AYMARD C, DECCHI B, KATZ R, LAFITTE C, PENICAUD A, RAOUL S, AND ROSSI A. Recurrent inhibition between motor nuclei innervating opposing wrist muscles in the human upper limb. *J Physiol (Lond)* 499: 267–282, 1997.

24. BABCOCK MA, JOHNSON BD, PEGELOW DF, SUMAN OE, GRIFFIN D, AND DEMPSEY JA. Hypoxic effects on exercise-induced diaphragmatic fatigue in normal healthy humans. *J Appl Physiol* 78: 82–92, 1995.

25. BABCOCK MA, PEGELOW DF, MCCLARAN SR, SUMAN OE, AND DEMPSEY JA. Contribution of diaphragmatic power output to exercise-induced diaphragm fatigue. *J Appl Physiol* 78: 1710–1719, 1995.

26. BABCOCK. MA, PEGELOW DF, TAHA BH, AND DEMPSEY JA. High frequency diaphragmatic fatigue detected with paired stimuli in humans. *Med Sci Sports Exercise* 30: 506–511, 1998.

27. BAILEY SP, DAVID JM, AND AHLBORN EN. Neuroendocrine and substrate responses to altered brain 5-HT activity during prolonged exercise to fatigue. *J Appl Physiol* 74: 3006–3012, 1993.

28. BAKELS R AND KERNELL D. Threshold-spacing in motoneuron pools of rat and cat: possible relevance for manner of force gradation. *Exp Brain Res* 102: 69–74, 1994.

29. BAKER SN, OLIVIER E, AND LEMON RN. An investigation of the intrinsic circuitry of the motor cortex of the monkey using intra-cortical microstimulation. *Exp Brain Res* 123: 397–411, 1998.

30. BAKER SN, OLIVIER E, AND LEMON RN. Recording an identified pyramidal volley evoked by transcranial magnetic stimulation in a conscious macaque monkey. *Exp Brain Res* 99: 529–532, 1994.

31. BAKER SN, OLIVIER E, AND LEMON RN. Task-related variation in corticospinal output evoked by transcranial magnetic stimulation in the macaque monkey. *J Physiol (Lond)* 488: 795–801, 1995.

32. BALDISSERA F, CAVALLARI P, AND DWORZAK F. Motor neuron "bistability." A pathogenetic mechanism for cramps and myokymia. *Brain* 117: 929–939, 1994.

33. BALDISSERA F, HOLTBORN H, AND ILLERT M. Integration of spinal neuronal systems. In: *Handbook of Physiology. The Nervous System. Motor Control.* Bethesda, MD: Am Physiol Soc, 1981, sect. 1, vol. II, pt. 1, chapt. 12, p. 509–595.

34. BALESTRA C, DUCHATEAU J, AND HAINAUT K. Effects of fatigue on the stretch reflex in a human muscle. *Electroencephalogr Clin Neurophysiol* 85: 46–52, 1992.

35. BANGSBO J, GRAHAM TE, KIENS B, AND SALTIN B. Elevated muscle glycogen and anaerobic energy production during exhaustive exercise in man. *J Physiol (Lond)* 451: 205–227, 1992.

36. BARKER AT, JALINOUS R, AND FREESTON IL. Non-invasive stimulation of human motor cortex. *Lancet* 1: 1106–1107, 1985.

37. BARKER D. The morphology of muscle receptors. In: *Handbook of Sensory Physiology. Muscle Receptors*, edited by Hunt CC. New York: Springer, 1974, p. 1–190.

38. BAWA PCB. Repetitive doublets in human flexor carpi radialis muscle. *J Physiol (Lond)* 339: 123–132, 1983.

39. BAYLISS DA, VIANA F, TALLEY EM, AND BERGER AJ. Neuromodulation of hypoglossal motoneurons: cellular and developmental mechanisms. *Respir Physiol* 110: 139–150, 1997.

40. BEELEN A, NOLLET F, AND SARGEANT AJ. Maximal voluntary activation of quadriceps muscle in prior polio patients. *J Physiol (Lond)* 491: 127P, 1996.

41. BEELEN A, SARGEANT AJ, JONES DA, AND DE RUITER CJ. Fatigue and recovery of voluntary and electrically elicited dynamic force in humans. *J Physiol (Lond)* 484: 227–235, 1995.

42. BEHM DG AND SALE DG. Velocity specificity of resistance training. *Sports Med* 15: 374–388, 1993.

43. BEHM DG, ST-PIERRE DM, AND PEREZ D. Muscle inactivation: assessment of interpolated twitch technique. *J Appl Physiol* 81: 2267–2273, 1996.

44. BELANGER AY AND MCCOMAS AJ. A comparison of contractile properties in human arm and leg muscles. *Eur J Appl Physiol* 54: 326–330, 1985.

45. BELANGER AY AND MCCOMAS AJ. Extent of motor unit activation during effort. *J Appl Physiol* 51: 1131–1135, 1981.

46. BELANGER AY, MCCOMAS AJ, AND ELDER GB. Physiological properties of two antagonist human muscle groups. *Eur J Appl Physiol* 51: 381–393, 1983.

47. BELHAJ-SAIF A, FOURMENT A, AND MATON B. Adaptation of the precentral cortical command to elbow muscle fatigue. *Exp Brain Res* 111: 405–416, 1996.

48. BELLEMARE F AND BIGLAND-RITCHIE B. Assessment of human diaphragm strength and activation using phrenic nerve stimulation. *Respir Physiol* 58: 263–277, 1984.

49. BELLEMARE F AND BIGLAND-RITCHIE B. Central components of diaphragmatic fatigue assessed by phrenic nerve stimulation. *J Appl Physiol* 62: 1307–1316, 1987.

50. BELLEMARE F AND GRASSINO A. Effect of pressure and timing of contraction on human diaphragm fatigue. *J Appl Physiol* 53: 1190–1195, 1982.

51. BELLEMARE F, WOODS JJ, JOHANSSON R, AND BIGLAND-RITCHIE B. Motor-unit discharge rates in maximal voluntary contractions of three human muscles. *J Neurophysiol* 50: 1380–1392, 1983.

52. BENNETT DJ, HULTBORN H, FEDIRCHUK B, AND GORASSINI M. Synaptic activation of plateaus in hindlimb motoneurons of decerebrate cats. *J Neurophysiol* 80: 2023–2037, 1998.

53. BERARDELLI A, INGHILLERI M, CRUCCU G, AND MANFREDI M. Descending

volley after electrical and magnetic transcranial stimulation in man. *Neurosci Lett* 112: 54–58, 1990.

54. BERARDELLI A, INGHILLERI M, GILIO F, ROMEO S, PEDACE F, CURRA A, AND MANFREDI M. Effects of repetitive cortical stimulation on the silent period evoked by magnetic stimulation. *Exp Brain Res* 125: 82–86, 1999.

55. BERGMANS J. *The Physiology of Single Human Nerve Fibres.* Vander: University of Louvain, 1970.

56. BERGSTROM J, HERMANSEN L, HULTMAN E, AND SALTIN B. Diet, muscle glycogen and physical performance. *Acta Physiol Scand* 71: 140–150, 1967.

57. BEVAN L, LAOURIS Y, REINKING RM, AND STUART DG. The effect of the stimulation pattern on the fatigue of single motor units in adult cats. *J Physiol (Lond)* 449: 85–108, 1992.

58. BICKERS MJ. Does verbal encouragement work? The effect of verbal encouragement on a muscular endurance task. *Clin Rehabil* 7: 196–200, 1993.

59. BIGLAND B AND LIPPOLD OCJ. Motor unit activity in the voluntary contraction of human muscle. *J Physiol (Lond)* 125: 322–335, 1954.

60. BIGLAND B AND LIPPOLD OCJ. Motor unit activity in the voluntary contraction of human muscles. *J Physiol (Lond)* 125: 322–335, 1954.

61. BIGLAND-RITCHIE B. EMG and fatigue of human voluntary and stimulated contractions. *Ciba Found Symp* 82: 130–156, 1981.

62. BIGLAND-RITCHIE B, CAFARELLI E, AND VOLLESTAD NK. Fatigue of submaximal static contractions. *Acta Physiol Scand Suppl* 556: 137–148, 1986.

63. BIGLAND-RITCHIE B, FURBUSH F, AND WOODS JJ. Fatigue of intermittent submaximal voluntary contractions: central and peripheral factors. *J Appl Physiol* 61: 421–429, 1986.

64. BIGLAND-RITCHIE B, JOHANSSON R, LIPPOLD OC, SMITH S, AND WOODS JJ. Changes in motoneurone firing rates during sustained maximal voluntary contractions. *J Physiol (Lond)* 340: 335–346, 1983.

65. BIGLAND-RITCHIE B, JOHANSSON R, LIPPOLD OC, AND WOODS JJ. Contractile speed and EMG changes during fatigue of sustained maximal voluntary contractions. *J Neurophysiol* 50: 313–324, 1983.

66. BIGLAND-RITCHIE B, JOHANSSON R, LIPPOLD OCJ, SMITH S, AND WOODS JJ. Changes in motoneurone firing rates during sustained maximal voluntary contractions. *J Physiol (Lond)* 340: 335–346, 1983.

67. BIGLAND-RITCHIE B, JONES DA, HOSKING GP, AND EDWARDS RH. Central and peripheral fatigue in sustained maximum voluntary contractions of human quadriceps muscle. *Clin Sci Mol Med* 54: 609–614, 1978.

68. BIGLAND-RITCHIE B, JONES DA, HOSKING GP, AND EDWARDS RHT. Central and peripheral fatigue in sustained maximum voluntary contractions of human quadriceps muscle. *Clin Sci Mol Med* 54: 609–614, 1978.

69. BIGLAND-RITCHIE B, JONES DA, AND WOODS JJ. Excitation frequency and muscle fatigue: electrical responses during human voluntary and stimulated contractions. *Eur J Neurol* 64: 414–427, 1979.

70. BIGLAND-RITCHIE B, KUKULKA CG, LIPPOLD OCJ, AND WOODS JJ. The absence of neuromuscular transmission failure in sustained maximal voluntary contractions. *J Physiol (Lond)* 330: 265–278, 1982.

71. BIGLAND-RITCHIE B, RICE CL, GARLAND SJ, AND WALSH ML. Task-dependent factors in fatigue of human voluntary contractions. *Adv Exp Med Biol* 384: 361–380, 1995.

72. BIGLAND-RITCHIE B, THOMAS CK, RICE CL, HOWARTH JV, AND WOODS JJ. Muscle temperature, contractile speed, and motoneuron firing rates during human voluntary contractions. *J Appl Physiol* 73: 2457–2461, 1992.

73. BIGLAND-RITCHIE B AND VOLLESTAD NK. Fatigue and hypoxia: how are they related? In: *Hypoxia: The Tolerable Limits*, edited by Sutton JR, Houston CS, and Costes G. Indianapolis, IN: Benchmark, 1984, p. 337–352.

74. BIGLAND-RITCHIE B AND WOODS JJ. Changes in muscle contractile properties and neural control during human muscular fatigue. *Muscle Nerve* 7: 691–699, 1984.

75. BIGLAND-RITCHIE B, ZIJDEWIND I, AND THOMAS CK. Muscle fatigue induced by stimulation with and without doublets. *Muscle Nerve* 23: 1348–1355, 2000.

76. BIGLAND-RITCHIE BR, DAWSON NJ, JOHANSSON RS, AND LIPPOLD OCJ. Reflex origin for the slowing of motoneurone firing rates in fatigue

of human voluntary contractions. *J Physiol (Lond)* 379: 451–459, 1986.

77. BIGLAND-RITCHIE BR, FURBUSH FH, GANDEVIA SC, AND THOMAS CK. Voluntary discharge frequencies of human motoneurons at different muscle lengths. *Muscle Nerve* 15: 130–137, 1992.

78. BINDER MD, HECKMAN CJ, AND POWERS RK. The physiological control of motoneuron activity. In: *Handbook of Physiology. Exercise: Regulation and Integration of Multiple Systems.* Bethesda, MD: Am Physiol Soc, 1996, sect. 12, chapt. 2, p. 3–53.

79. BINDER MD, ROBINSON FR, AND POWERS RK. Distribution of effective synaptic currents in cat triceps surae motoneurons. VI. Contralateral pyramidal tract. *J Neurophysiol* 80: 241–248, 1998.

80. BINDER-MACLEOD SA AND BARKER CB. Use of a catchlike property of human skeletal muscle to reduce fatigue. *Muscle Nerve* 14: 850–857, 1991.

81. BINDER-MACLEOD SA AND CLAMANN HP. Force output of cat motor units stimulated with trains of linearly varying frequency. *J Neurophysiol* 61: 208–217, 1989.

82. BLIMKIE CJ, SALE DG, AND BAR-OR O. Voluntary strength, evoked twitch contractile properties and motor unit activation of knee extensors in obese and non-obese adolescent males. *Eur J Appl Physiol* 61: 313–318, 1990.

83. BLISS EL AND AILION J. Relationship of stress and activity on brain dopamine and homovanillic acid. *Life Sci* 10: 1161–1169, 1971.

84. BLOMSTRAND E, HASSMÉN P, EK S, EKBLOM B, AND NEWSHOLME EA. Influence of ingesting a solution of branched-chain amino acids on perceived exertion during exercise. *Acta Physiol Scand* 159: 41–49, 1997.

85. BLOMSTRAND E, HASSMEN P, EKBLOM E, AND NEWSHOLME EA. Administration of branched-chain amino acids during sustained exercise: effects on performance and on plasma concentration of some amino acids. *Eur J Appl Physiol* 63: 83–88, 1991.

86. BLOMSTRAND E, PERRETT D, PARRY-BILLINGS M, AND NEWSHOLME EA. Effect of sustained exercise on plasma amino acid concentrations and on 5-hydroxytryptamine metabolism in six different brain regions in the rat. *Acta Physiol Scand* 136: 473–481, 1989.

87. BONGIOVANNI LG AND HAGBARTH KE. Tonic vibration reflexes elicited during fatigue from maximal voluntary contractions in man. *J Physiol (Lond)* 423: 1–14, 1990.

88. BONGIOVANNI LG, HAGBARTH KE, AND STJERNBERG L. Prolonged muscle vibration reducing motor output in maximal voluntary contractions in man. *J Physiol (Lond)* 423: 15–26, 1990.

89. BOOTH FW. Effect of limb immobilization on skeletal muscle. *J Appl Physiol* 52: 1113–1118, 1982.

90. BOOTH FW AND THOMASON DB. Molecular and cellular adaptation of muscle in response to exercise: perspectives of various models. *Physiol Rev* 71: 541–585, 1991.

91. BOYD SG, ROTHWELL JC, COWAN JM, WEBB PJ, MORLEY T, ASSELMAN P, AND MARSDEN CD. A method of monitoring function in corticospinal pathways during scoliosis surgery with a note on motor conduction velocities. *J Neurol Neurosurg Psychiat* 49: 251–257, 1986.

92. BRASIL-NETO JP, COHEN LG, AND HALLETT M. Central fatigue as revealed by postexercise decrement of motor evoked potentials. *Muscle Nerve* 17: 713–719, 1994.

93. BRASIL-NETO JP, PASCUAL-LEONE A, VALLS-SOLÉ J, CAMMAROTA A, COHEN LG, AND HALLETT M. Postexercise depression of motor evoked potentials: a measure of central nervous system fatigue. *Exp Brain Res* 93: 181–184, 1993.

94. BREMNER FD, BAKER JR, AND STEPHENS JA. Effect of task on the degree of synchronization of intrinsic hand muscle motor units in man. *J Neurophysiol* 66: 2072–2083, 1991.

95. BRIDGMAN CF. Comparisons in structure of tendon organs in the rat, cat and man. *J Comp Neurol* 138: 369–372, 1970.

96. BROCKETT C, WARREN N, GREGORY JE, MORGAN DL, AND PROSKE U. A comparison of the effects of concentric versus eccentric exercise on force and position sense at the human elbow joint. *Brain Res* 771: 251–258, 1997.

97. BROUWER B AND ASHBY P. Corticospinal projections to lower limb motoneurons in man. *Exp Brain Res* 89: 649–654, 1992.

98. BROUWER B AND ASHBY P. Corticospinal projections to upper and lower limb spinal motoneurons in man. *Electroencephalogr Clin Neurophysiol* 76: 509–519, 1990.

99. BROWN MC, GOODWIN GM, AND MATTHEWS PBC. After-effects of

fusimotor stimulation on the response of muscle spindle primary afferent endings. *J Physiol (Lond)* 205: 677–694, 1969.

100. BROWNSTONE RM, GOSSARD JP, AND HULTBORN H. Voltage-dependent excitation of motoneurones from spinal locomotor centres in the cat. *Exp Brain Res* 102: 34–44, 1994.

101. BROWNSTONE RM, JORDAN LM, KRIELLAARS DJ, NOGA BR, AND SHEFCHYK SJ. On the regulation of repetitive firing in lumbar motoneurones during fictive locomotion in the cat. *Exp Brain Res* 90: 441–455, 1992.

102. BUCHTHAL F AND MADSEN A. Synchronous activity in normal and atrophic muscle. *Electroencephalogr Clin Neurophysiol* 2: 425–444, 1950.

103. BULOW PM, NORREGAARD J, DANNESKIOLD-SAMSOE B, AND MEHLSEN J. Twitch interpolation technique in testing of maximal muscle strength: influence of potentiation, force level, stimulus intensity and preload. *Eur J Appl Physiol* 67: 462–466, 1993.

104. BULOW PM, NORREGAARD J, MEHLSEN J, AND DANNESKIOLD-SAMSOE B. The twitch interpolation technique for study of fatigue of human quadriceps muscle. *J Neurosci Methods* 62: 103–109, 1995.

105. BUONOMANO DVM. Cortical plasticity: from synapses to maps. *Annu Rev Neurosci* 21: 149–186, 1998.

106. BURG D, SZUMSKI AJ, STRUPPLER A, AND VELHO F. Afferent and efferent activation of human muscle receptors involved in reflex and voluntary contraction. *Eur J Neurol* 41: 754–768, 1973.

107. BURGESS PR AND JONES LF. Perceptions of effort and heaviness during fatigue and during the size-weight illusion. *Somatosens Motor Res* 14: 189–202, 1997.

108. BURKE D AND GANDEVIA SC. Influence of stimulus cross talk on results of the twitch-interpolation technique at the biceps brachii muscle. *Muscle Nerve* 21: 970–971, 1998.

109. BURKE D AND GANDEVIA SC. Properties of human peripheral nerves: implications for studies of human motor control. In: *Peripheral and Spinal Mechanisms in the Neural Control of Movement*, edited by Binder MD. Amsterdam: Elsevier, 1999, p. 427–435.

110. BURKE D, GANDEVIA SC, AND MCKEON B. The afferent volleys responsible for spinal proprioceptive reflexes in man. *J Physiol (Lond)* 339: 535–552, 1983.

111. BURKE D, GANDEVIA SC, AND MCKEON B. Monosynaptic and oligosynaptic contributions to human ankle jerk and H-reflex. *J Neurophysiol* 52: 435–448, 1984.

112. BURKE D, GRACIES JM, MAZEVET D, MEUNIER S, AND PIERROT-DESEILLIGNY E. Convergence of descending and various peripheral inputs onto common propriospinal-like neurones in man. *J Physiol (Lond)* 449: 655–671, 1992.

113. BURKE D, GRACIES JM, MAZEVET D, MEUNIER S, AND PIERROT-DESEILLIGNY E. Non-monosynaptic transmission of the cortical command for voluntary movement in man. *J Physiol (Lond)* 480: 191–202, 1994.

114. BURKE D, GRACIES JM, MEUNIER S, AND PIERROT-DESEILLIGNY E. Changes in presynaptic inhibition of afferents to propriospinal-like neurones in man during voluntary contractions. *J Physiol (Lond)* 449: 673–687, 1992.

115. BURKE D, HAGBARTH KE, AND LOFSTEDT L. Muscle spindle activity in man during shortening and lengthening contractions. *J Physiol (Lond)* 277: 131–142, 1978.

116. BURKE D, HAGBARTH KE, LOFSTEDT L, AND WALLIN BG. The responses of human muscle spindle endings to vibration of non-contracting muscles. *J Physiol (Lond)* 261: 673–693, 1976.

117. BURKE D, HAGBARTH KE, AND SKUSE NF. Voluntary activation of spindle endings in human muscles temporarily paralysed by nerve pressure. *J Physiol (Lond)* 287: 329–336, 1979.

118. BURKE D, HICKS R, GANDEVIA SC, WOODFORTH I, AND CRAWFORD M. Direct comparison of corticospinal volleys in human subjects to transcranial magnetic and electrical stimulation. *J Physiol (Lond)* 470: 383–393, 1993.

119. BURKE D, HICKS RG, AND STEPHEN JP. Corticospinal volleys evoked by anodal and cathodal stimulation of the human motor cortex. *J Physiol (Lond)* 425: 283–299, 1990.

120. BURKE D, MCKEON B, AND WR A. Induced changes in the thresholds for voluntary activation of human spindle endings. *J Physiol (Lond)* 302: 171–181, 1980.

121. BURKE D AND SCHILLER HH. Discharge pattern of single motor units

122. BURKE RE. Motor units: anatomy, physiology, and functional organization. In: *Handbook of Physiology. The Nervous System. Motor Control.* Bethesda, MD: Am Physiol Soc, 1981, sect. 1, vol. II. pt. 1, chapt. 10, p. 345–421.

123. BURKE RE, RUDOMIN P, AND ZAJAC FE. Catch property in single mammalian motor units. *Science* 168: 122–124, 1970.

124. BURNE JA, LIPPOLD OCJ, AND PRYOR M. Proprioceptors and normal tremor. *J Physiol (Lond)* 348: 559–572, 1984.

125. BUTLER JE, MCKENZIE DK, AND GANDEVIA SC. Discharge properties and recruitment of human diaphragmatic motor units during voluntary inspiratory tasks. *J Physiol (Lond)* 518: 907–920, 1999.

126. BUTLER JE, TAYLOR JL, AND GANDEVIA SC. Responses to stimulation of corticospinal axons are reduced during sustained maximal voluntary contractions in humans. *Soc Neurosci Abstr* 25: 113, 1999.

127. CANTELLO R, GIANELLI M, CIVARDI C, AND MUTANI R. Magnetic brain stimulation: the silent period after the motor evoked potential. *Neurology* 42: 1951–1959, 1992.

128. CAPADAY C AND STEIN RB. Amplitude modulation of the soleus H-reflex in the human during walking and standing. *J Neurosci* 6: 1308–1313, 1986.

129. CAPADAY C AND STEIN RB. Difference in the amplitude of the human soleus H reflex during walking and running. *J Physiol (Lond)* 392: 513–522, 1987.

130. CARPENTER JE, BLASIER RB, AND PELLIZZON GG. The effects of muscle fatigue on shoulder joint position sense. *Am J Sports Med* 26: 262–265, 1998.

131. CHAOULOFF F. Effects of acute physical exercise on central serotonergic systems. *Med Sci Sports Exercise* 29: 58–62, 1997.

132. CHAOULOFF F. Physical exercise and brain monoamines: a review. *Acta Physiol Scand* 137: 1–13, 1989.

133. CHAOULOFF F, KENNETT GA, SERRURRIER B, MERINO D, AND CURZON G. Amino acid analysis demonstrates that increased plasma free tryptophan causes the increase of brain tryptophan during exercise in the rat. *J Neurochem* 46: 1647–1650, 1986.

134. CHAOULOFF F, LAUDE D, GUEZENNEC Y, AND ELGHOZI JL. Motor activity increases tryptophan, 5-hydroxyindoleacetic acid, and homovanillic acid in ventricular cerebrospinal fluid of the conscious rat. *J Neurochem* 46: 1313–1316, 1986.

135. CHAUDHURI A AND BEHAN PO. Fatigue and basal ganglia. *J Neurol Sci* 179: 34–42, 2000.

136. CHEN R, LOZANO AM, AND ASHBY P. Mechanism of the silent period following transcranial magnetic stimulation. Evidence from epidural recordings. *Exp Brain Res* 128: 539–542, 1999.

137. CHEN R, TAM A, BUTEFISCH C, CORWELL B, ZIEMANN U, ROTHWELL JC, AND COHEN LG. Intracortical inhibition and facilitation in different representations of the human motor cortex. *J Neurophysiol* 80: 2870–2881, 1998.

137a.CHIN BY, JONES NL, AND KILLIAN KJ. Is there a conflict between maintaining minimizing effort and energy expenditure with increasing velocities of muscle contraction in humans? *J Physiol (Lond)* 518: 933–940, 1999.

138. CHRISTAKOS CN AND WINDHORST U. Spindle gain increase during muscle unit fatigue. *Brain Res* 365: 388–392, 1986.

139. CHRISTENSEN EH AND HANSEN O. Arbeitsfahigkeit und ernahrung. *Scand Arch Physiol* 81: 160–171, 1939.

140. CIBA. *Ciba Foundation Symposium Human Muscle Fatigue: Physiological Mechanisms.* London: Pitman, 1981.

141. CLAMANN HP AND SCHELHORN TB. Nonlinear force addition of newly recruited motor units in the cat hindlimb. *Muscle Nerve* 11: 1079–1089, 1988.

142. CLARK GT AND CARTER MC. Electromyographic study of human jaw-closing muscle endurance, fatigue and recovery at various isometric force levels. *Arch Oral Biol* 30: 563–569, 1985.

143. CLARKE RW, HARRIS J, AND HOUGHTON AK. Spinal 5-HT-receptors and tonic modulation of transmission through a withdrawal reflex pathway in the decerebrated rabbit. *Br J Pharmacol* 119: 1167–1176, 1996.

144. CLELAND CL, HAYWARD L, AND RYMER WZ. Neural mechanisms underlying the clasp-knife reflex in the cat. II. Stretch-sensitive muscular-free nerve endings. *J Neurophysiol* 64: 1319–1330, 1990.

145. CLELAND CL AND RYMER WZ. Functional properties of spinal inter-

neurons activated by muscular free nerve endings and their potential contributions to the clasp-knife reflex. *J Neurophysiol* 69: 1181–1191, 1993.

146. COLEBATCH JG AND GANDEVIA SC. The distribution of muscular weakness in upper motor neuron lesions affecting the arm. *Brain* 112: 749–763, 1989.

147. COLEBATCH JG, ROTHWELL JC, DAY BL, THOMPSON PD, AND MARSDEN CD. Cortical outflow to proximal arm muscles in man. *Brain* 113: 1843–1856, 1990.

148. COLLINS DF, BURKE D, AND GANDEVIA SC. Large involuntary forces consistent with plateau-like behavior of human motoneurons. *J Neurosci* 21: 4059–4065, 2001.

149. COLLINS DF AND PROCHAZKA A. Movement illusions evoked by ensemble cutaneous input from the dorsum of the human hand. *J Physiol (Lond)* 496: 857–871, 1996.

150. CONNELLY DM, RICE CL, ROOS MR, AND VANDERVOORT AA. Motor unit firing rates and contractile properties in tibialis anterior of young and old men. *J Appl Physiol* 87: 843–852, 1999.

151. CONWAY BA, HULTBORN H, AND KIEHN O. Proprioceptive input resets central locomotor rhythm in the spinal cat. *Exp Brain Res* 68: 643–656, 1987.

152. COOPER RG, EDWARDS RH, GIBSON H, AND STOKES MJ. Human muscle fatigue: frequency dependence of excitation and force generation. *J Physiol (Lond)* 397: 585–599, 1988.

153. COPE TC AND SOKOLOFF AJ. Orderly recruitment tested across muscle boundaries. *Prog Brain Res* 123: 177–190, 1999.

154. COWAN JM, DAY BL, MARSDEN CD, AND ROTHWELL JC. The effect of percutaneous motor cortex stimulation on H reflexes in muscles of the arm and leg in intact man. *J Physiol (Lond)* 377: 333–347, 1986.

155. COX DM AND CAFARELLI E. The mixed nerve silent period is prolonged during a submaximal contraction sustained to failure. *Muscle Nerve* 22: 320–328, 1999.

156. CRESSWELL AG AND LOSCHER WN. Significance of peripheral afferent input to the alpha-motoneurone pool for enhancement of tremor during an isometric fatiguing contraction. *Eur J Appl Physiol* 82: 129, 2000.

157. CREUTZFELDT OD, LUX HD, AND NACIMIENTO AC. Intracelluläre reizung corticaler nervenzellen. *Pflügers Arch* 281: 129–151, 1964.

158. CUPIDO CM, GALEA V, AND MCCOMAS AJ. Potentiation and depression of the M wave in human biceps brachii. *J Physiol (Lond)* 491: 541–550, 1996.

159. CZARKOWSKA J, JANKOWSKA E, AND SYBIRSKA E. Common interneurones in reflex pathways from group 1a and 1b afferents of knee flexors and extensors in the cat. *J Physiol (Lond)* 310: 367–380, 1981.

160. DANION F, LATASH ML, LI ZM, AND ZATSIORSKY VV. The effect of fatigue on multifinger co-ordination in force production tasks in humans. *J Physiol (Lond)* 523: 523–532, 2000.

161. DARCUS HD AND SALTER N. The effect of repeated muscular exertion on muscle strength. *J Physiol (Lond)* 129: 325–336, 1955.

162. DARLING WG AND HAYES KC. Human servo responses to load disturbances in fatigued muscle. *Brain Res* 267: 345–351, 1983.

163. DAVEY NJ, ROMAIGUERE P, MASKILL DW, AND ELLAWAY PH. Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man. *J Physiol (Lond)* 477: 223–235, 1994.

164. DAVIES CT, DOOLEY P, MCDONAGH MJ, AND WHITE MJ. Adaptation of mechanical properties of muscle to high force training in man. *J Physiol (Lond)* 365: 277–284, 1985.

165. DAVIES CT, RUTHERFORD IC, AND THOMAS DO. Electrically evoked contractions of the triceps surae during and following 21 days of voluntary leg immobilization. *Eur J Appl Physiol* 56: 306–312, 1987.

166. DAVIES J, PARKER DF, RUTHERFORD OM, AND JONES DA. Changes in strength and cross sectional area of the elbow flexors as a result of isometric strength training. *Eur J Appl Physiol* 57: 667–670, 1988.

167. DAVIS JM. Carbohydrates, branched-chain amino acids, and endurance: the central fatigue hypothesis. *Int J Sports Nutr* 5: S29–S38, 1995.

168. DAVIS JM AND BAILEY SP. Possible mechanisms of central nervous system fatigue during exercise. *Med Sci Sports Exercise* 29: 45–57, 1997.

169. DAWSON MJ, GADIAN DG, AND WILKIE DR. Muscular fatigue investigated by phosphorus nuclear magnetic resonance. *Nature* 274: 861–866, 1978.

170. DAY BL, DRESSLER D, MAERTENS DE NOORDHOUT A, MARSDEN CD, NAKASHIMA K, ROTHWELL JC, AND THOMPSON PD. Electrical and magnetic stimulation of human motor cortex; surface EMG and single motor unit responses. *J Physiol (Lond)* 412: 449–473, 1989.

171. DAY BL, ROTHWELL JC, THOMPSON PD, DICK JP, COWAN JM, BERARDELLI A, AND MARSDEN CD. Motor cortex stimulation in intact man. 2. Multiple descending volleys. *Brain* 110: 1191–1209, 1987.

172. DEANDRADE GRANT C JR AND DIXON ASJ. Joint distension and reflex muscle inhibiiton in the knee. *J Bone Joint Surg* 47: 313–322, 1965.

173. DE LUCA CJ, LEFEVER RS, MCCUE MP, AND XENAKIS AP. Behaviour of human motor units in different muscles during linearly varying contractions. *J Physiol (Lond)* 329: 113–128, 1982.

174. DE LUCA CJ, ROY AM, AND ERIM Z. Synchronization of motor-unit firings in several human muscles. *J Neurophysiol* 70: 2010–2023, 1993.

175. DEMIÉVILLE HN AND PARTRIDGE LD. Probability of peripheral interaction between motor units and implications for motor control. *Am J Physiol Regulatory Integrative Comp Physiol* 238: R119–R137, 1980.

176. DEMPSEY JA AND BABCOCK MA. An integrative view of limitations to muscular performance. *Adv Exp Med Biol* 384: 393–399, 1995.

177. DENNY-BROWN D. On inhibition as a reflex accompaniment of the tendon jerk and of other forms of active muscular response. *Proc R Soc Lond B Biol Sci* 103: 321–336, 1928.

178. DENSLOW JS. Double discharges in human motor units. *J Neurophysiol* 107: 209–215, 1948.

179. DE SERRES SJ AND ENOKA RM. Older adults can maximally activate the biceps brachii muscle by voluntary command. *J Appl Physiol* 84: 284–291, 1998.

180. DESHPANDE SS AND DEVANANDAN MS. Reflex inhibition of monosynaptic reflexes by stimulation of type J pulmonary endings. *J Physiol (Lond)* 206: 345–357, 1970.

181. DESMEDT JE AND GODAUX E. Ballistic contractions in man: characteristic recruitment pattern of single motor units of the tibialis anterior muscle. *J Physiol (Lond)* 264: 673–693, 1977.

182. DETTMERS C, LEMON RN, STEPHAN KM, FINK GR, AND FRACKOWIAK RS. Cerebral activation during the exertion of sustained static force in man. *Neuroreport* 7: 2103–2110, 1996.

183. DETTMERS C, RIDDING MC, STEPHAN KM, LEMON RN, ROTHWELL JC, AND FRACKOWIAK RS. Comparison of regional cerebral blood flow with transcranial magnetic stimulation at different forces. *J Appl Physiol* 81: 596–603, 1996.

184. DEUSCHL G, SCHENCK E, AND LUCKING CH. Long-latency responses in human thenar muscles mediated by fast conducting muscle and cutaneous afferents. *Neurosci Lett* 55: 361–366, 1985.

185. DEVANANDAN MS, ECCLES RM, AND STENHOUSE D. Presynaptic inhibition evoked by muscle contraction. *J Physiol (Lond)* 185: 471–485, 1966.

186. DICK TE AND KELSEN SG. Relationship between diaphragmatic activation and twitch tension to superimposed electrical stimulation in the cat. *Respir Physiol* 76: 337–345, 1989.

187. DIETZ V, BISCHOFBERGER E, WITA C, AND FREUND HJ. Correlation between the discharges of two simultaneously recorded motor units and physiological tremor. *Electroencephalogr Clin Neurophysiol* 40: 97–105, 1976.

188. DI LAZZARO V, OLIVIERO A, PROFICE P, INSOLA A, MAZZONE P, TONALI P, AND ROTHWELL JC. Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. *Exp Brain Res* 124: 520–524, 1999.

189. DI LAZZARO V, RESTUCCIA D, OLIVIERO A, PROFICE P, FERARA L, INSOLA A, MAZZONE P, TONALI P, AND ROTHWELL JC. Effects of voluntary contraction on descending volleys evoked by transcranial stimulation in conscious humans. *J Physiol (Lond)* 508: 625–633, 1998.

190. DIMITRIJEVIC MR, KOFLER M, MCKAY WB, SHERWOOD AM, VAN DER LINDEN C, AND LISSENS MA. Early and late lower limb motor evoked potentials elicited by transcranial magnetic motor cortex stimulation. *Electroencephalogr Clin Neurophysiol* 85: 365–373, 1992.

191. DIMITRIJEVIC MR, MCKAY WB, SARJANOVIC I, SHERWOOD AM, SVIRTLIH L, AND VRBOVA G. Co-activation of ipsi- and contralateral muscle groups during contraction of ankle dorsiflexors. *J Neurol Sci* 109: 49–55, 1992.

191a. DITTMAN JS AND REGEHR WG. Calcium dependence and recovery kinetics of presynaptic depression at the climbing fiber to Purkinje cell synapses. *J Neurosci* 18: 6147–6162, 1998.

192. DOWLING JJ, KONERT E, LJUCOVIC P, AND ANDREWS DM. Are humans able to voluntarily elicit maximum muscle force? *Neurosci Lett* 179: 25–28, 1994.

193. DUBOSE L, SCHELHORN TB, AND CLAMANN HP. Changes in contractile speed of cat motor units during activity. *Muscle Nerve* 10: 744–752, 1987.

194. DUCHATEAU J AND HAINAUT K. Isometric or dynamic training: differential effects on mechanical properties of a human muscle. *J Appl Physiol* 56: 296–301, 1984.

195. DUCHATEAU J AND HAINAUT K. Nonlinear summation of contractions in striated muscle. I. Twitch potentiation in human muscle. *J Muscle Res Cell Motil* 7: 11–17, 1986.

196. DUCHATEAU J AND HAINAUT K. Electrical and mechanical changes in immobilized human muscle. *J Appl Physiol* 62: 2168–2173, 1987.

197. DUCHATEAU J AND HAINAUT K. Effects of immobilization on contractile properties, recruitment and firing rates of human motor units. *J Physiol (Lond)* 422: 55–65, 1990.

198. DUCHATEAU J AND HAINAUT K. Behaviour of short and long latency reflexes in fatigued human muscles. *J Physiol (Lond)* 471: 787–799, 1993.

199. DUDLEY GA, HARRIS RT, DUVOISIN MR, HATHER BM, AND BUCHANAN P. Effect of voluntary vs. artificial activation on the relationship of muscle torque to speed. *J Appl Physiol* 69: 2215–2221, 1990.

200. DUGGAN AW AND NORTH RA. Electrophysiology of opioids. *Pharmacol Rev* 35: 219–281, 1984.

201. EASTWOOD PR, HILLMAN DR, AND FINUCANE KE. Ventilatory responses to inspiratory threshold loading and role of muscle fatigue in task failure. *J Appl Physiol* 76: 185–195, 1994.

202. ECCLES JC, ECCLES RM, AND LUNDBERG A. The convergence of monosynaptic excitatory afferents on to many different species of alpha motoneurones. *J Physiol (Lond)* 137: 22–50, 1957.

203. ECCLES JC, ECCLES RM, AND LUNDBERG A. Synaptic actions of motoneurones caused by impulses in Golgi tendon organs. *J Physiol (Lond)* 138: 227–252, 1957.

204. ECCLES JC, ECCLES RM, AND MAGNI F. Central inhibitory action attributable to presynaptic depolarization produced by muscle afferent volleys. *J Physiol (Lond)* 159: 147–166, 1961.

205. ECCLES JC, SCHMIDT RF, AND WILLIS WD. Depolarization of central terminals of group Ib afferent fibers of muscle. *J Neurophysiol* 26: 1–27, 1963.

206. ECCLES RM AND LUNDBERG A. Synaptic actions in motoneurones by afferents which may evoke the flexion reflex. *Arch Ital Biol* 97: 199–221, 1959.

207. EDAMURA M, YANG JF, AND STEIN RB. Factors that determine the magnitude and time course of human H-reflexes in locomotion. *J Neurosci* 11: 420–427, 1991.

208. EDGLEY SA, EYRE JA, LEMON RN, AND MILLER S. Comparison of activation of corticospinal neurons and spinal motor neurons by magnetic and electrical transcranial stimulation in the lumbosacral cord of the anaesthetized monkey. *Brain* 120: 839–853, 1997.

209. EDGLEY SA, EYRE JA, LEMON RN, AND MILLER S. Excitation of the corticospinal tract by electromagnetic and electrical stimulation of the scalp in the macaque monkey. *J Physiol (Lond)* 425: 301–320, 1990.

210. EDIN BB AND JOHANSSON N. Skin strain patterns provide kinaesthetic information to the human central nervous system. *J Physiol (Lond)* 487: 243–251, 1995.

211. EDIN BB AND VALLBO AB. Muscle afferent responses to isometric contractions and relaxations in humans. *J Neurophysiol* 63: 1307–1313, 1990.

212. EDWARDS HT. Lactic acid in rest and work at high altitude. *Am J Physiol* 116: 367–375, 1936.

213. EDWARDS RH, HARRIS RC, HULTMAN E, KAIJSER L, KOH D, AND NORDESJO LO. Effect of temperature on muscle energy metabolism and endurance during successive isometric contractions, sustained to fatigue, of the quadriceps muscle in man. *J Physiol (Lond)* 220: 335–352, 1972.

214. EDWARDS RH, HILL DK, AND JONES DA. Effect of fatigue on the time course of relaxation from isometric contractions of skeletal muscle in man. *J Physiol (Lond)* 227: 26P–27P, 1972.

215. EDWARDS RH, HILL DK, JONES DA, AND MERTON PA. Fatigue of long duration in human skeletal muscle after exercise. *J Physiol (Lond)* 272: 769–778, 1977.

216. EDWARDS RH, TOESCU V, AND GIBSON H. Historical perspective: a framework for interpreting pathobiological ideas on human muscle fatigue. *Adv Exp Med Biol* 384: 481–494, 1995.

217. EDWARDS RHT. Human muscle function and fatigue. *Ciba Found Symp* 82: 1–18, 1981.

218. EGUIBAR QUEVEDO J JR, JIMÉNEZ I, AND RUDOMIN P. Selective cortical control of information flow through different intraspinal collaterals of the same muscle afferent fiber. *Brain Res* 643: 328–333, 1994.

219. ELLAWAY PH. Recurrent inhibition of fusimotor neurones exhibiting background discharges in the decerebrate and the spinal cat. *J Physiol (Lond)* 216: 419–439, 1971.

220. ELLAWAY PH, MURPHY PR, AND TRIPATHI A. Closely coupled excitation of gamma-motoneurones by group III muscle afferents with low mechanical threshold in the cat. *J Physiol (Lond)* 331: 481–498, 1982.

221. ELLRICH J, ANDERSEN OK, TREEDE RD, AND ARENDT-NIELSEN L. Convergence of nociceptive and non-nociceptive input onto the medullary dorsal horn in man. *Neuroreport* 9: 3213–3217, 1998.

222. EMONET-DENAND F AND LAPORTE Y. Selective neuromuscular block in extrafusal junctions of skeleto-fusimotor axons produced by high frequency repetitive stimulation. *C R Hebd Seances Acad Sci D Sci Nat* 279: 2083–2085, 1974.

223. ENOKA RM. Neural adaptations with chronic physical activity. *J Biomech* 30: 447–455, 1997.

224. ENOKA RM AND FUGLEVAND AJ. *Neuromuscular Basis of the Maximal Voluntary Force Capacity of Muscle*. Champaign, IL: Human Kinetics, 1993.

225. ENOKA RM AND FUGLEVAND AJ. Neuromuscular basis of the maximum voluntary force capacity of muscle. In: *General Issues in Biomechanics*, edited by Grabiner MD. Champaign, IL: Human Kinetics, 1993, p. 215–235.

226. ENOKA RM, HUTTON RS, AND ELDRED E. Changes in excitability of tendon tap and Hoffmann reflexes following voluntary contractions. *Electroencephalogr Clin Neurophysiol* 48: 664–672, 1980.

227. ENOKA RM, ROBINSON GA, AND KOSSEV AR. A stable, selective electrode for recording single motor-unit potentials in humans. *Eur J Neurol* 99: 761–764, 1988.

228. ENOKA RM, ROBINSON GA, AND KOSSEV AR. Task and fatigue effects on low-threshold motor units in human hand muscle. *J Neurophysiol* 62: 1344–1359, 1989.

229. ENOKA RM AND STUART DG. Neurobiology of muscle fatigue. *J Appl Physiol* 72: 1631–1648, 1992.

230. FAIST M, DIETZ V, AND PIERROT-DESEILLIGNY E. Modulation, probably presynaptic in origin, of monosynaptic Ia excitaiton during human gait. *Exp Brain Res* 109: 441–449, 1996.

231. FAVERO TG. Sarcoplasmic reticulum Ca^{2+} release and muscle fatigue. *J Appl Physiol* 87: 471–483, 1999.

232. FEDIRCHUK B, NIELSEN J, PETERSEN N, AND HULTBORN H. Pharmacologically evoked fictive motor patterns in the acutely spinalized marmoset monkey (*Callithrix jacchus*). *Exp Brain Res* 122: 351–361, 1998.

233. FERGUSON GT. Use of twitch pressures to assess diaphragmatic function and central drive. *J Appl Physiol* 77: 1705–1715, 1994.

234. FERRELL WR, GANDEVIA SC, AND MCCLOSKEY DI. The role of joint receptors in human kinaesthesia when intramuscular receptors cannot contribute. *J Physiol (Lond)* 386: 63–71, 1987.

235. FITTS RH. Cellular mechanisms of muscle fatigue. *Physiol Rev* 74: 49–94, 1994.

236. FITZPATRICK R, TAYLOR JL, AND MCCLOSKEY DI. Effects of arterial perfusion pressure on force production in working human hand muscles. *J Physiol (Lond)* 495: 885–891, 1996.

237. FLOETER MK, GERLOFF C, KOURI J, AND HALLETT M. Cutaneous withdrawal reflexes of the upper extremity. *Muscle Nerve* 21: 591–598, 1998.

238. FOREMAN RD, SCHMIDT RF, AND WILLIS WD. Effects of mechanical and chemical stimulation of fine muscle afferents upon primate spinothalamic tract cells. *J Physiol (Lond)* 286: 215–231, 1979.

239. FOURMENT A, BELHAJ-SAÏF A, AND MATON B. Functional linkages between motor cortical cells and elbow flexor muscles. Evidence

for and characteristics of postspike facilitation. *J Neurophysiol* 74: 130–141, 1995.

240. FRANK K AND FUORTES MGF. Presynaptic and postsynaptic inhibition of monosynaptic reflexes. *Federation Proc* 16: 39–40, 1957.

241. FREED CR AND YAMAMOTO BK. Regional brain dopamine metabolism: a marker for speed, direction, and posture of moving animals. *Science* 229: 62–65, 1985.

242. FREUND HJ, BUDINGEN HJ, AND DIETZ V. Activity of single motor units from human forearm muscles during voluntary isometric contractions. *J Neurophysiol* 38: 933–946, 1975.

243. FROC DJ, CHAPMAN CA, TREPEL C, AND RACINE RJ. Long-term depression and depotentiation in the sensorimotor cortex of the freely moving rat. *J Neurosci* 20: 438–445, 2000.

244. FROMM C, HAASE J, AND WOLF E. Depression of the recurrent inhibition of extensor motoneurons by the action of group II afferents. *Brain Res* 120: 459–468, 1977.

245. FUGLEVAND AJ, BILODEAU M, AND ENOKA RM. Short-term immobilization has a minimal effect on the strength and fatigability of a human hand muscle. *J Appl Physiol* 78: 847–855, 1995.

246. FUGLEVAND AJ, MACEFIELD VG, AND BIGLAND-RITCHIE B. Force-frequency and fatigue properties of motor units in muscles that control digits of the human hand. *J Neurophysiol* 81: 1718–1729, 1999.

247. FUGLEVAND AJ, WINTER DA, AND PATLA AE. Models of recruitment and rate coding organization in motor-unit pools. *J Neurophysiol* 70: 2470–2488, 1993.

248. FUGLEVAND AJ, ZACKOWSKI KM, HUEY KA, AND ENOKA RM. Impairment of neuromuscular propagation during human fatiguing contractions at submaximal forces. *J Physiol (Lond)* 460: 549–572, 1993.

249. FUGLSANG-FREDERIKSEN A AND SCHEEL U. Transient decrease in number of motor units after immobilisation in man. *J Neurol Neurosurg Psychiat* 41: 924–929, 1978.

250. FUHR P, AGOSTINO R, AND HALLETT M. Spinal motor neuron excitability during the silent period after cortical stimulation. *Electroencephalogr Clin Neurophysiol* 181: 257–262, 1991.

251. FUJIKI M, ISONO M, HORI S, AND UENO S. Corticospinal direct response to transcranial magnetic stimulation in humans. *Electroencephalogr Clin Neurophysiol* 101: 48–57, 1996.

252. FUKUNAGA T, ROY RR, SHELLOCK FG, HODGSON JA, DAY MK, LEE PL, KWONG-FU H, AND EDGERTON VR. Physiological cross-sectional area of human leg muscles based on magnetic resonance imaging. *J Orthop Res* 10: 928–934, 1992.

253. FULCO CS, LEWIS SF, FRYKMAN PN, BOUSHEL R, SMITH S, HARMAN EA, CYMERMAN A, AND PANDOLF KB. Quantitation of progressive muscle fatigue during dynamic leg exercise in humans. *J Appl Physiol* 79: 2154–2162, 1995.

254. FUNG SJ, MANZONI D, CHAN JY, POMPEIANO O, AND BARNES CD. Locus coeruleus control of spinal motor output. *Prog Brain Res* 88: 395–409, 1991.

255. FURNESS P, JESSOP J, AND LIPPOLD OCM. Long-lasting increases in the tremor of human hand muscles following brief, strong effort. *J Physiol (Lond)* 265: 821–831, 1977.

256. GALLOWAY SDR, SHIRREFFS SM, LEIPER JB, AND MAUGHAN RJ. Exercise in the heat: factors limiting exercise capacity and methods for improving heat tolerance. *Sports Exercise Inj* 3: 19–24, 1997.

257. GAMET D AND MATON B. The fatigability of two agonistic muscles in human isometric voluntary submaximal contraction: an EMG study. I. Assessment of muscular fatigue by means of surface EMG. *Eur J Appl Physiol* 58: 361–368, 1989.

258. GANDEVIA SC. The perception of motor commands or effort during muscular paralysis. *Brain* 105: 151–159, 1982.

259. GANDEVIA SC. Kinesthesia: roles for afferent signals and motor commands. In: *Handbook of Physiology. Exercise: Regulation and Integration of Multiple Systems.* Bethesda, MD: Am Physiol Soc, 1996, sect. 12, p. 128–172.

260. GANDEVIA SC, ALLEN GM, BUTLER JE, AND TAYLOR JL. Supraspinal factors in human muscle fatigue: evidence for suboptimal output from the motor cortex. *J Physiol (Lond)* 490: 529–536, 1996.

261. GANDEVIA SC, ALLEN GM, AND MCKENZIE DK. Central fatigue. Critical issues, quantification and practical implications. *Adv Exp Med Biol* 384: 281–294, 1995.

262. GANDEVIA SC, BUTLER JE, TAYLOR JL, AND CRAWFORD MR. Absence of viscerosomatic inhibition with injections of lobeline designed to activate human pulmonary C fibres. *J Physiol (Lond)* 511: 289–300, 1998.

263. GANDEVIA SC, HERBERT RD, AND LEEPER JB. Voluntary activation of human elbow flexor muscles during maximal concentric contractions. *J Physiol (Lond)* 512: 595–602, 1998.

264. GANDEVIA SC, MACEFIELD G, BURKE D, AND MCKENZIE DK. Voluntary activation of human motor axons in the absence of muscle afferent feedback. The control of the deafferented hand. *Brain* 113: 1563–1581, 1990.

265. GANDEVIA SC, MACEFIELD VG, BIGLAND-RITCHIE B, GORMAN RB, AND BURKE D. Motoneuronal output and gradation of effort in attempts to contract acutely paralysed leg muscles in man. *J Physiol (Lond)* 471: 411–427, 1993.

266. GANDEVIA SC AND MCKENZIE DK. Activation of human muscles at short muscle lengths during maximal static efforts. *J Physiol (Lond)* 407: 599–613, 1988.

267. GANDEVIA SC AND MCKENZIE DK. Activation of the human diaphragm during maximal static efforts. *J Physiol (Lond)* 367: 45–56, 1985.

268. GANDEVIA SC AND MCKENZIE DK. Human diaphragmatic endurance during different maximal respiratory efforts. *J Physiol (Lond)* 395: 625–638, 1988.

269. GANDEVIA SC, MCKENZIE DK, AND PLASSMAN BL. Activation of human respiratory muscles during different voluntary manoeuvres. *J Physiol (Lond)* 428: 387–403, 1990.

270. GANDEVIA SC, PETERSEN N, BUTLER JE, AND TAYLOR JL. Impaired response of human motoneurones to corticospinal stimulation after voluntary exercise. *J Physiol (Lond)* 521: 749–759, 1999.

271. GANDEVIA SC AND PLASSMAN BL. Responses in human intercostal and truncal muscles to motor cortical and spinal stimulation. *Respir Physiol* 73: 325–337, 1988.

272. GANDEVIA SC AND ROTHWELL JC. Knowledge of motor commands and the recruitment of human motoneurons. *Brain* 110: 1117–1130, 1987.

273. GARDNER GW. Specificity of strength changes of the exercised and nonexercised limb following isometric training. *Res Q* 34: 98–101, 1963.

274. GARLAND SJ. Role of small diameter afferents in reflex inhibition during human muscle fatigue. *J Physiol (Lond)* 435: 547–558, 1991.

275. GARLAND SJ, ENOKA RM, SERRANO LP, AND ROBINSON GA. Behavior of motor units in human biceps brachii during a submaximal fatiguing contraction. *J Appl Physiol* 76: 2411–2419, 1994.

276. GARLAND SJ, GARNER SH, AND MCCOMAS AJ. Reduced voluntary electromyographic activity after fatiguing stimulation of human muscle. *J Physiol (Lond)* 401: 547–556, 1988.

277. GARLAND SJ, GRIFFIN L, AND IVANOVA T. Motor unit discharge rate is not associated with muscle relaxation time in sustained submaximal contractions in humans. *Neurosci Lett* 239: 25–28, 1997.

278. GARLAND SJ AND MCCOMAS AJ. Reflex inhibition of human soleus muscle during fatigue. *J Physiol (Lond)* 429: 17–27, 1990.

279. GARLAND SJ AND MILES TS. Control of motor units in human flexor digitorum profundus under different proprioceptive conditions. *J Physiol (Lond)* 502: 693–701, 1997.

280. GARNER SH, HA L, AND MA J. Prolongation of twitch potentiating mechanism throughout muscle fatigue and recovery. *Eur J Neurol* 103: 277–281, 1989.

281. GARNER SH, SUTTON BURSE RL, MCCOMAS AJ, CYMERMAN A JR, AND HOUSTON CS. Operation Everest II: neuromuscular performance under conditions of extreme simulated altitude. *J Appl Physiol* 68: 1167–1172, 1990.

282. GERLOFF C, COHEN LG, FLOETER MK, CHEN R, CORWELL B, AND HALLETT M. Inhibitory influence of the ipsilateral motor cortex on responses to stimulation of the human cortex and pyramidal tract. *J Physiol (Lond)* 510: 249–259, 1998.

282a.GIBSON AS, SCHABORT EJ, AND NOAKES TD. Reduced neuromuscular activity and force generation during prolonged cycling. *Am J Physiol Regulatory Interactive Comp Physiol* 281: R187–R196, 2001.

283. GIBSON H, CARROLL N, CLAGUE JE, AND EDWARDS RH. Exercise performance and fatiguability in patients with chronic fatigue syndrome. *J Neurol Neurosurg Psychiat* 56: 993–998, 1993.

284. GIBSON H, COOPER RG, STOKES MJ, AND EDWARDS RH. Mechanisms resisting fatigue in isometrically contracting human skeletal muscle. *Q J Exp Physiol* 73: 903–914, 1988.

285. GILLIES JD. Measurement of physiological and essential tremor. In: *Science and Practice in Clinical Neurology*, edited by Gandevia SC, Burke D, and Anthony M. Cambridge, UK: Cambridge Univ. Press, 1993, p. 191–201.

286. GINZEL KH AND ELDRED E. A possible physiological role for the depression of somatic motor function by reflexes from the cardiopulmonary region. *Proc West Pharmacol Soc* 13: 188–191, 1970.

287. GLAUM SR, PROUDFIT HK, AND ANDERSON EG. Reversal of the antinociecptive effects of intrathecally administered serotonin in the rat by a selective $5HT_3$ receptor antagonist. *Neurosci Lett* 95: 313–317, 1988.

288. GOLLNICK PD, KORGE P, KARPAKKA J, AND SALTIN B. Elongation of skeletal muscle relaxation during exercise is linked to reduced calcium uptake by the sarcoplasmic reticulum in man. *Acta Physiol Scand* 142: 135–136, 1991.

289. GOOCH JL, NEWTON BY, AND PETAJAN JH. Motor unit spike counts before and after maximal voluntary contraction. *Muscle Nerve* 13: 1146–1151, 1990.

290. GOODWIN GM, MCCLOSKEY DI, AND MATTHEWS PB. The contribution of muscle afferents to kinaesthesia shown by vibration induced illusions of movement and by the effects of paralysing joint afferents. *Brain* 95: 705–748, 1972.

291. GORASSINI MA, BENNETT DJ, AND YANG JF. Self-sustained firing of human motor units. *Neurosci Lett* 247: 13–16, 1998.

292. GORMAN RB, MCKENZIE DK, AND GANDEVIA SC. Task failure, breathing discomfort and CO_2 accumulation without fatigue during inspiratory resistive loading in humans. *Respir Physiol* 115: 273–286, 1999.

293. GRACIES JM, MEUNIER S, AND PIERROT-DESEILLIGNY E. Evidence for corticospinal excitation of presumed propriospinal neurones in man. *J Physiol (Lond)* 475: 509–518, 1994.

294. GRAVEN-NIELSEN T, MCARDLE A, PHOENIX J, ARENDT-NIELSEN L, JENSEN TS, JACKSON MJ, AND EDWARDS RH. In vivo model of muscle pain: quantification of intramuscular chemical, electrical, and pressure changes associated with saline-induced muscle pain in humans. *Pain* 69: 137–143, 1997.

295. GREEN HJ, BALL-BURNETT M, SYMON S, GRANT S, AND JAMIESON G. Short-term training, muscle glycogen, and cycle endurance. *Can J Appl Physiol* 20: 315–324, 1995.

296. GREEN HJ, SUTTON J, YOUNG P, CYMERMAN A, AND HOUSTON CS. Operation Everest II: muscle energetics during maximal exhaustive exercise. *J Appl Physiol* 66: 142–150, 1989.

297. GREGORY JE AND PROSKE U. The responses of Golgi tendon organs to stimulation of different combinations of motor units. *J Physiol (Lond)* 295: 251–262, 1979.

298. GREGORY JE, WISE AK, WOOD SA, PROCHAZKA A, AND PROSKE U. Muscle history, fusimotor activity and the human stretch reflex. *J Physiol (Lond)* 513: 927–934, 1998.

299. GRIFFIN L, IVANOVA T, AND GARLAND SJ. Role of limb movement in the modulation of motor unit discharge rate during fatiguing contractions. *Exp Brain Res* 130: 392–400, 2000.

300. GRIMBY L, HANNERZ J, BORG J, AND HEDMAN B. Firing properties of single human motor units on maintained maximal voluntary effort. *Ciba Found Symp* 82: 157–177, 1981.

301. GRIMBY L, HANNERZ J, AND HEDMAN B. The fatigue and voluntary discharge properties of single motor units in man. *J Physiol (Lond)* 316: 545–554, 1981.

302. GRIMBY LHJ. Firing rate and recruitment order of toe extensor motor units in different modes of voluntary conraction. *J Physiol (Lond)* 264: 865–879, 1977.

303. GUERTIN P, ANGEL MJ, PERREAUL C, AND MCCREA DA. Ankle extensor group I afferents excite extensors throughout the hindlimb during MLR-evoked fictive locomotion in the cat. *J Physiol (Lond)* 487: 197–209, 1995.

304. HAGBARTH KE. Spinal withdrawal reflexes in the human lower limbs. *J Neurol Neurosurg Psychiat* 23: 222–227, 1960.

305. HAGBARTH KE, BONGIOVANNI LG, AND NORDIN M. Reduced servo-control of fatigued human finger extensor and flexor muscles. *J Physiol (Lond)* 485: 865–872, 1995.

307. HAGBARTH KE, KUNESCH EJ, NORDIN M, SCHMIDT R, AND WALLIN EU. Gamma loop contributing to maximal voluntary contractions in man. *J Physiol (Lond)* 380: 575–591, 1986.

308. HAKKINEN K, AND KOMI PV. Changes in neuromuscular performance in voluntary and reflex contraction during strength training in man. *Int J Sports Med* 4: 282–288, 1983.

309. HAKKINEN K AND KOMI PV. Electromyographic and mechanical characteristics of human skeletal muscle during fatigue under voluntary and reflex conditions. *Electroencephalogr Clin Neurophysiol* 55: 436–444, 1983.

310. HAKKINEN K AND KOMI PV. Electromyographic changes during strength training and detraining. *Med Sci Sports Exercise* 15: 455–460, 1983.

311. HAKKINEN K, KOMI PV, AND ALEN M. Effect of explosive type strength training on isometric force- and relaxation-time, electromyographic and muscle fibre characteristics of leg extensor muscles. *Acta Physiol Scand* 125: 587–600, 1985.

312. HALES JP AND GANDEVIA SC. Assessment of maximal voluntary contraction with twitch interpolation: an instrument to measure twitch responses. *J Neurosci Methods* 25: 97–102, 1988.

313. HANNERZ J. An electrode for recording single motor unit activity during strong muscle contractions. *Electroencephalogr Clin Neurophysiol* 37: 179–181, 1974.

314. HANNERZ J AND GRIMBY L. The afferent influence on the voluntary firing range of individual motor units in man. *Muscle Nerve* 2: 414–422, 1979.

315. HAOUZI P, HILL JM, LEWIS BK, AND KAUFMAN MP. Responses of group III and IV muscle afferents to distension of the peripheral vascular bed. *J Appl Physiol* 87: 545–553, 1999.

316. HARRIDGE SD, KRYGER A, AND STENSGAARD A. Knee extensor strength, activation, and size in very elderly people following strength training. *Muscle Nerve* 22: 831–839, 1999.

317. HARRIDGE SD, MAGNUSSON G, AND GORDON A. Skeletal muscle contractile characteristics and fatigue resistance in patients with chronic heart failure. *Eur Heart J* 17: 896–901, 1996.

318. HASSMÉN P, BLOMSTRAND E, EKBLOM B, AND NEWSHOLME EA. Branched-chain amino acid supplementation during 30-km competitive run: mood and cognitive performance. *Nutrition* 10: 405–410, 1994.

319. HATTORI S, NAOI M, AND NISHINO H. Striatal dopamine turnover during treadmill running in the rat: relation to the speed of running. *Brain Res Bull* 35: 41–49, 1994.

320. HAYWARD L, BREITBACH D, AND RYMER WZ. Increased inhibitory effects on close synergists during muscle fatigue in the decerebrate cat. *Brain Res* 440: 199–203, 1988.

321. HAYWARD L, WESSELMAN U, AND RYMER WZ. Effects of muscle fatigue on mechanically sensitive afferents of slow conduction velocity in the cat triceps surae. *J Neurophysiol* 65: 360–370, 1991.

322. HECKMAN CJ. Computer-simulations of the effects of different synaptic input systems on the steady-state input-output structure of the motoneuron pool. *J Neurophysiol* 71: 1727–1739, 1994.

323. HELLSING G AND LINDSTROM L. Rotation of synergistic activity during isometric jaw closing muscle contraction in man. *Acta Physiol Scand* 118: 203–207, 1983.

324. HENNEMAN E AND MENDELL LM. Functional organization of motoneuron pool and its inputs. In: *Handbook of Physiology. The Nervous System. Motor Control.* Bethesda, MD: Am Physiol Soc, 1981, sect. 1, vol. II, pt. 1, chapt. 11, p. 423–508.

325. HENNEMAN E, SOMJEN G, AND CARPENTER DO. Excitability and inhibitability of motoneurons of different sizes. *J Neurophysiol* 28: 599–620, 1965.

326. HERBERT RD, DEAN C, AND GANDEVIA SC. Effects of real and imagined training on voluntary muscle activation during maximal isometric contractions. *Acta Physiol Scand* 163: 361–368, 1998.

327. HERBERT RD AND GANDEVIA SC. Muscle activation in unilateral and bilateral efforts assessed by motor nerve and cortical stimulation. *J Appl Physiol* 80: 1351–1356, 1996.

328. HERBERT RD AND GANDEVIA SC. Twitch interpolation in human muscles: mechanisms and implications for measurement of voluntary activation. *J Neurophysiol* 82: 2271–2283, 1999.

329. HERBERT RD, GANDEVIA SC, AND ALLEN GM. Sensitivity of twitch interpolation. *Muscle Nerve* 20: 521–523, 1997.

330. HETTINGER T. *Physiology of Strength*. Springfield, IL: Thomas, 1961.

331. HICKIE IB, HOOKER AW, HADZI-PAVLOVIC D, BENNETT BK, WILSON AJ, AND LLOYD AR. Fatigue in selected primary care settings: sociodemographic and psychiatric correlates. *Med J Aust* 164: 585–588, 1996.

332. HILL AV. *Muscular Activity.* Baltimore, MD: Williams & Wilkins, 1926. p. 115.

333. HOBBS SF AND MCCLOSKEY DI. Effects of blood pressure on force production in cat and human muscle. *J Appl Physiol* 63: 834–839, 1987.

334. HOFFMAN-GOETZ L AND PEDERSEN BK. Exercise and the immune system: a model of the stress response? *Immunol Today* 15: 382–387, 1994.

335. HOLMGREN H, LARSSON LE, AND PEDERSEN S. Late muscular responses to transcranial cortical stimulation in man. *Electroencephalogr Clin Neurophysiol* 75: 161–172, 1990.

336. HOLMQVIST B AND LUNDBERG A. Differential supraspinal control of synaptic actions evoked by volleys in the flexion eflex afferents in alpha motoneurones. *Acta Physiol Scand* 54 Suppl 186: 1–51, 1961.

337. HORCHOLLE-BOSSAVIT G, JAMI L, PETIT J, VEJSADA R, AND ZYTNICKI D. Ensemble discharge from Golgi tendon organs of cat peroneus tertius muscle. *J Neurophysiol* 64: 813–821, 1990.

337a. HORTOBÁGYI T, DEMPSEY L, FRASER D, ZHENG G, HAMILTON G, LAMBERT J, AND DOHM L. Images in muscle strength, muscle fiber size and myofibrillar gene expression after immobilization and retraining in humans. *J Physiol (Lond)* 524: 293–304, 2000.

338. HOUK J AND HENNEMAN E. Responses of Golgi tendon organs to active contractions of the soleus muscle of the cat. *J Neurophysiol* 30: 466–481, 1967.

339. HOUNSGAARD J, HULTBORN H, JESPERSEN B, AND KIEHN O. Bistability of alpha-motoneurones in the decerebrate cat and in the acute spinal cat after intravenous 5-hydroxytryptophan. *J Physiol (Lond)* 405: 345–367, 1988.

340. HOUNSGAARD J AND KIEHN O. Calcium spikes and calcium plateaux evoked by differential polarization in dendrites of turtle motoneurones in vitro. *J Physiol (Lond)* 468: 245–259, 1993.

341. HOWARD JD AND ENOKA RM. Maximum bilateral contractions are modified by neurally mediated interlimb effects. *J Appl Physiol* 70: 306–316, 1991.

342. HOWELL JN, FUGLEVAND AJ, WALSH ML, AND BIGLAND-RITCHIE B. Motor unit activity during isometric and concentric-eccentric contractions of the human first dorsal interosseus muscle. *J Neurophysiol* 74: 901–904, 1995.

343. HULTBORN H, ILLERT M, NIELSEN J, PAUL A, BALLEGAARD M, AND WIESE H. On the mechanism of the post-activation depression of the H-reflex in human subjects. *Exp Brain Res* 108: 450–462, 1996.

344. HULTBORN H, KATZ R, AND MACKEL R. Distribution of recurrent inhibition within a motor nucleus. II. Amount of recurrent inhibition in motoneurones to fast and slow units. *Acta Physiol Scand* 134: 363–374, 1988.

345. HULTBORN H, MEUNIER S, PIERROT-DESEILLIGNY E, AND SHINDO M. Changes in presynaptic inhibition of Ia fibres at the onset of voluntary contraction in man. *J Physiol (Lond)* 389: 757–772, 1987.

346. HULTBORN H AND PIERROT-DESEILLIGNY E. Changes in recurrent inhibition during voluntary soleus contractions in man studied by an H-reflex technique. *J Physiol (Lond)* 297: 229–251, 1979.

347. HULTMAN E AND SJOHOLM H. Electromyogram, force and relaxation time during and after continuous electrical stimulation of human skeletal muscle in situ. *J Physiol (Lond)* 339: 33–40, 1983.

348. HULTMAN E AND SJOHOLM H. Energy metabolism and contraction force of human skeletal muscle in situ during electrical stimulation. *J Physiol (Lond)* 345: 525–532, 1983.

349. HURLEY MV AND NEWHAM DJ. The influence of arthrogenous muscle inhibition on quadriceps rehabilitation of patients with early, unilateral osteoarthritic knees. *Br J Rheumatol* 32: 127–131, 1993.

350. HURLEY MV, SCOTT DL, REES J, AND NEWHAM DJ. Sensorimotor changes and functional performance in patients with knee osteoarthritis. *Ann Rheum Dis* 56: 641–648, 1997.

351. HUTTON RS AND NELSON DL. Stretch sensitivity of Golgi tendon organs in fatigued gastrocnemius muscle. *Med Sci Sports Exercise* 18: 69–74, 1986.

352. IGGO A. Non-myelinated afferent fibres from mammalian skeletal muscle. *J Physiol (Lond)* 155: 52–53, 1961.

353. IKAI M AND FUKUNAGA T. A study on training effect on strength per unit cross-sectional area of muscle by means of ultrasonic measurement. *Int Z Angew Physiol* 28: 173–180, 1970.

354. IKAI M AND STEINHAUS AH. Some factors modifying the expression of human strength. *J Appl Physiol* 16: 157–163, 1961.

355. IKAI M, YABE K, AND ISCHII K. Muskelkraft und muskulare ermudung bei willkurllicher anspannung und elektrischer reizund des muskels. *Sportarzt Sportmedizin* 5: 197, 1967.

356. ILES JF. Evidence for cutaneous and corticospinal modulation of presynaptic inhibition of Ia afferents from the human lower limb. *J Physiol (Lond)* 491: 197–207, 1996.

357. INGHILLERI M, BERARDELLI A, CRUCCU G, AND MANFREDI M. Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. *J Physiol (Lond)* 466: 521–534, 1993.

358. JACOBS BL AND AZMITIA EC. Structure and function of the brain serotonin system. *Physiol Rev* 72: 165–229, 1992.

359. JACOBS BL AND FORNAL CA. 5-HT and motor control: a hypothesis. *Trends Neurosci* 16: 346–352, 1993.

360. JACOBSEN S, WILDSCHIODTZ G, AND DANNESKIOLD-SAMSOE B. Isokinetic and isometric muscle strength combined with transcutaneous electrical muscle stimulation in primary fibromyalgia syndrome. *J Rheumatol* 18: 1390–1393, 1991.

361. JAKOBI JM AND CAFARELLI E. Neuromuscular drive and force production are not altered during bilateral contractions. *J Appl Physiol* 84: 200–206, 1998.

362. JAMES C, SACCO P, AND JONES DA. Loss of power during fatigue of human leg muscles. *J Physiol (Lond)* 484: 237–246, 1995.

363. JAMI L. Golgi tendon organs in mammalian skeletal muscle: functional properties and central actions. *Physiol Rev* 72: 623–666, 1992.

364. JANKOWSKA E. Interneuronal relay in spinal pathways from proprioceptors. *Prog Neurobiol* 38: 335–378, 1992.

365. JANKOWSKA E AND MCCREA D. Shared reflex pathways from Ib tendon organ afferents and Ia muscle spindle afferents in the cat. *J Physiol (Lond)* 338: 99–111, 1983.

366. JANKOWSKA E AND PADEL Y. On the origin of presynaptic depolarization of group I muscle afferents in Clarke's column in the cat. *Brain Res* 295: 195–201, 1984.

367. JANKOWSKA E, PADEL Y, AND TANAKA R. Disynaptic inhibition of spinal motoneurones from the motor cortex in the monkey. *J Physiol (Lond)* 258: 467–487, 1976.

368. JANKOWSKA E AND SCHOMBURG ED. A Leu-enkephalin depresses transmission from muscle and skin non-nociceptors to first-order feline spinal neurones. *J Physiol (Lond)* 510: 513–525, 1998.

369. JANSSON E, SJÖDIN B, AND TESCH P. Changes in muscle fibre type distribuiton in man after physical training. *Acta Physiol Scand* 104: 235–237, 1978.

370. JARIC S, BLESIC S, MILANOVIC S, RADOVANOVIC S, LJUBISAVLJEVIC M, AND ANASTASIJEVIC R. Changes in movement final position associated with agonist and antagonist muscle fatigue. *Eur J Appl Physiol* 80: 467–471, 1999.

371. JENSEN BR, PILEGAARD M, AND SJOGAARD G. Motor unit recruitment and rate coding in response to fatiguing shoulder abductions and subsequent recovery. *Eur J Appl Physiol* 83: 190–199, 2000.

372. JIMÉNEZ I, RUDOMIN P, AND SOLODKIN M. Mechanisms involved in the depolarization of cutaneous afferents produced by segmental and descending inputs in the cat spinal cord. *Exp Brain Res* 69: 195–207, 1987.

373. JOHANSSON HSP. Pathophysiological mechanisms involved in genesis and spread of muscular tension in occupational muscle pain and in chronic musculoskeletal pain syndromes: a hypothesis. *Med Hypotheses* 35: 196–203, 1991.

374. JOHNSON BD, BABCOCK MA, SUMAN OE, AND DEMPSEY JA. Exercise-induced diaphragmatic fatigue in healthy humans. *J Physiol (Lond)* 460: 385–405, 1993.

375. JONES DA, BIGLAND-RITCHIE B, AND EDWARDS RHT. Excitation frequency and muscle fatigue: mechanical responses during voluntary and stimulated contractions. *Eur J Neurol* 64: 401–413, 1979.

376. JONES DA AND RUTHERFORD OM. Human muscle strength training: the effects of three different regimens and the nature of the resultant changes. *J Physiol (Lond)* 391: 1–11, 1987.

377. JONES KE AND BAWA P. Computer simulation of the responses of human motoneurons to composite Ia EPSPS: effects of background firing rate. *J Neurophysiol* 77: 405–420, 1997.

378. JONES LA. Role of central and peripheral signals in force sensation during fatigue. *Eur J Neurol* 81: 497–503, 1983.

379. JONES LA. The senses of effort and force during fatiguing contractions. *Adv Exp Med Biol* 384: 305–313, 1995.

380. JONES LA AND HUNTER IW. Effect of fatigue on force sensation. *Eur J Neurol* 81: 640–650, 1983.

381. JOVANOVIC K, ANASTASIJEVIC R, AND VUCO J. Reflex effects on gamma fusimotor neurones of chemically induced discharges in small-diameter muscle afferents in decerebrate cats. *Brain Res* 521: 89–94, 1990.

382. JUEL C, BANGSBO J, GRAHAM T, AND SALTIN B. Lactate and potassium fluxes from human skeletal muscle during and after intense, dynamic, knee extensor exercise. *Acta Physiol Scand* 140: 147–159, 1990.

383. KANEKO K, KAWAI S, FUCHIGAMI Y, SHIRAISHI G, AND ITO T. Effect of stimulus intensity and voluntary contraction on corticospinal potentials following transcranial magnetic stimulation. *J Neurol Sci* 139: 131–136, 1996.

384. KANG Y, KANEKO T, OHISHI H, ENDO K, AND ARAKI T. Spatio-temporally differential inhibition of pyramidal cells in the cat motor cortex. *J Neurophysiol* 71: 280–293, 1994.

385. KASSER RJ AND CHENEY PD. Characteristics of corticomotoneuronal postspike facilitation and reciprocal suppression of EMG activity in the monkey. *J Neurophysiol* 53: 959–978, 1985.

386. KAUFMAN MP, LONGHURST JC, RYBICKI KJ, WALLACH JH, AND MITCHELL JH. Effects of static muscular contraction on impulse activity of groups III and IV afferents in cats. *J Appl Physiol* 55: 105–112, 1983.

387. KAUFMAN MP AND RYBICKI KJ. Discharge properties of group III and IV muscle afferents: their responses to mechanical and metabolic stimuli. *Circ Res* 61: 60–65, 1987.

388. KAUFMAN MP, RYBICKI KJ, WALDROP TG, AND ORDWAY GA. Effect of ischemia on responses of group III and IV afferents to contraction. *J Appl Physiol* 57: 644–650, 1984.

389. KAUFMAN MP, WALDROP TG, RYBICKI KJ, ORDWAY GA, AND MITCHELL JH. Effects of static and rhythmic twitch contractions on the discharge of group III and IV muscle afferents. *Cardiovasc Res* 18: 663–668, 1984.

390. KAWAKAMI Y, ABE T, KUNO SY, AND FUKUNAGA T. Training-induced changes in muscle architecture and specific tension. *Eur J Appl Physiol* 72: 37–43, 1995.

391. KAWAKAMI Y, AMEMIYA K, KANEHISA H, IKEGAWA S, AND FUKUNAGA T. Fatigue responses of human triceps surae muscles during repetitive maximal isometric contractions. *J Appl Physiol* 88: 1969–1975, 2000.

392. KAYSER B, BOKENKAMP R, AND BINZONI T. Alpha-motoneuron excitability at high altitude. *Eur J Appl Physiol* 66: 1–4, 1993.

393. KAYSER B, NARICI M, BINZONI T, GRASSI B, AND CERRETELLI P. Fatigue and exhaustion in chronic hypobaric hypoxia: influence of exercising muscle mass. *J Appl Physiol* 76: 634–640, 1994.

394. KELLGREN JH. Observations on referred pain arising from muscle. *Clin Sci* 3, 1938.

395. KEMM RE AND WESTBURY DR. Some properties of spinal gamma-motoneurones in the cat, determined by micro-electrode recording. *J Physiol (Lond)* 282: 59–71, 1978.

396. KENNEDY JC, ALEXANDER IJ, AND HAYES KC. Nerve supply of the human knee and its functional importance. *Am J Sports Med* 10: 329–335, 1982.

397. KENT-BRAUN JA. Central and peripheral contributions to muscle fatigue in humans during sustained maximal effort. *Eur J Appl Physiol* 80: 57–63, 1999.

398. KENT-BRAUN JA AND LE BLANC R. Quantitation of central activation failure during maximal voluntary contractions in humans. *Muscle Nerve* 19: 861–869, 1996.

399. KENT-BRAUN JA, SHARMA KR, WEINER MW, MASSIE B, AND MILLER RG. Central basis of muscle fatigue in chronic fatigue syndrome. *Neurology* 43: 125–131, 1993.

400. KENT-BRAUN JA, SHARMA KR, WEINER MW, AND MILLER RG. Effects of exercise on muscle activation and metabolism in multiple sclerosis. *Muscle Nerve* 17: 1162–1169, 1994.

401. KERESHI S, MANZANO G, AND McCOMAS AJ. Impulse conduction velocities in human biceps brachii muscles. *Eur J Neurol* 80: 652–662, 1983.

402. KERNELL D AND HULTBORN H. Synaptic effects on recruitment gain: a mechanism of importance for the input-output relations of motoneurone pools? *Brain Res* 507: 176–179, 1990.

403. KERNELL D AND MONSTER AW. Motoneurone properties and motor fatigue An intracellular study of gastrocnemius motoneurones of the cat. *Exp Brain Res* 46: 197–204, 1982.

404. KERNELL D AND MONSTER AW. Time course and properties of late adaptation in spinal motoneurones of the cat. *Exp Brain Res* 46: 191–196, 1982.

405. KIEHN O AND EKEN T. Prolonged firing in motor units: evidence of plateau potentials in human motoneurons? *J Neurophysiol* 78: 3061–3068, 1997.

406. KIRSCH RF AND RYMER WZ. Neural compensation for muscular fatigue: evidence for significant force regulation in man. *J Neurophysiol* 57: 1893–1910, 1987.

407. KIRSCH RF AND RYMER WZ. Neural compensation for fatigue-induced changes in muscle stiffness during perturbations of elbow angle in human. *J Neurophysiol* 68: 449–470, 1992.

408. KISCHKA U, RADKO F, FELLENBERG T, AND HESS CW. Facilitation of motor evoked potentials from magnetic brain stimulation in man: a comparative study of different target muscles. *J Clin Neurophysiol* 10: 505–512, 1993.

409. KITAI TA AND SALE DG. Specificity of joint angle in isometric training. *Eur J Appl Physiol* 58: 744–748, 1989.

410. KLEIM JA, LUSSNIG E, SCHWARZ ER, COMERY TA, AND GREENOUGH WT. Synaptogenesis and Fos expression in the motor cortex of the adult rat after motor skill learning. *J Neurosci* 16: 4529–4535, 1996.

411. KNIFFKI KD, MENSE S, AND SCHMIDT RF. Responses of group IV afferent units from skeletal muscle to stretch, contraction and chemical stimuli. *Exp Brain Res* 31: 511–522, 1978.

412. KNIFFKI KD, SCHOMBURG ED, AND STEFFENS H. Effects from fine muscle and cutaneous afferents on spinal locomotion in cats. *J Physiol (Lond)* 319: 543–554, 1981.

413. KNIFFKI KD, SCHOMBURG ED, AND STEFFENS H. Synaptic responses of lumbar alpha-motoneurones to chemical algesic stimulation of skeletal muscle in spinal cats. *Brain Res* 160: 549–552, 1979.

414. KNIFFKI KD, SCHOMBURG ED, AND STEFFENS H. Synaptic effects from chemically activated fine muscle afferents upon α-motoneurones in decerebrate and spinal cats. *Brain Res* 206: 361–370, 1981.

415. KOMI PV, VIITASALO JT, RAURAMAA R, AND VIHKO V. Effect of isometric strength training of mechanical, electrical, and metabolic aspects of muscle function. *Eur J Appl Physiol* 40: 45–55, 1978.

416. KOUCHTIR N, PERRIER JF, ZYTNICKI D, AND JAMI L. Contraction-induced excitation in cat peroneal motoneurons. *J Neurophysiol* 73: 974–982, 1995.

417. KOUTEDAKIS Y, FRISCHKNECHT R, VRBOVA G, SHARP NC, AND BUDGETT R. Maximal voluntary quadriceps strength patterns in Olympic overtrained athletes. *Med Sci Sports Exercise* 27: 566–572, 1995.

418. KRANZ H, ADORJANI C, AND BAUMGARTNER G. The effect of nociceptive cutaneous stimuli on human motoneurons. *Brain* 96: 571–590, 1973.

419. KRANZ H, WILLIAMS AM, CASSELL J, CADDY DJ, AND SILBERSTEIN RB. Factors determining the frequency content of the electromyogram. *J Appl Physiol* 55: 392–399, 1983.

420. KREMER E AND LEV-TOV A. GABA-receptor-independent dorsal root afferents depolarization in the neonatal rat spinal cord. *J Neurophysiol* 79: 2581–2592, 1998.

421. KRNJEVIC K, RANDIC M, AND STRAUGHAN DW. An inhibitory process in the cerebral cortex. *J Physiol (Lond)* 184: 16–48, 1966.

422. KRNJEVIC K, RANDIC M, AND STRAUGHAN DW. Nature of a cortical inhibitory process. *J Physiol (Lond)* 184: 49–77, 1966.

423. KROLL W. Isometric cross-transfer effects under conditions of central facilitation. *J Appl Physiol* 20: 297–300, 1965.

424. KUGELBERG E, EKLUND K, AND GRIMBY L. An electromyographic study of the nociceptive reflexes of the lower limb. Mechanism of the plantar responses. *Brain* 83: 394–409, 1960.

425. KUIACK S AND McCOMAS AJ. Transient hyperpolarization of non-contracting muscle fibres in anaesthetized rats. *J Physiol (Lond)* 454: 609–618, 1992.

426. KUJIRAI T, CARAMIA MD, ROTHWELL JC, DAY BL, THOMPSON PD, FERBERT A, WROE S, ASSELMAN P, AND MARSDEN CD. Corticocortical inhibition in human motor cortex. *J Physiol (Lond)* 471: 501–593, 1993.

427. KUKULKA CG AND CLAMANN HP. Comparison of the recruitment and discharge properties of motor units in human brachial biceps and adductor pollicis during isometric contractions. *Brain Res* 219: 45–55, 1981.

428. KUKULKA CG, MOORE MA, AND RUSSELL AG. Changes in human α-motoneuron excitability during sustained maximum isometric contractions. *Neurosci Lett* 68: 327–333, 1986.

429. KUMAZAWA T AND MIZUMURA K. Thin-fiber receptors responding to mechanical, chemical, and thermal stimulation in the skeletal muscle of the dog. *J Physiol (Lond)* 273: 179–194, 1977.

430. LAFLEUR J, ZYTNICKI D, HORCHOLLE-BOSSAVIT G, AND JAMI L. Depolarization of Ib afferent axons in the cat spinal cord during homonymous muscle contraction. *J Physiol (Lond)* 445: 345–354, 1992.

431. LAGHI F, TOPELI A, AND TOBIN MJ. Does resistive loading decrease diaphragmatic contractility before task failure? *J Appl Physiol* 85: 1103–1112, 1998.

432. LAGIER-TESSONNIER F, BALZAMO E, AND JAMMES Y. Comparative effects of ischemia and acute hypoxemia on muscle afferents from tibialis anterior in cats. *Muscle Nerve* 16: 135–141, 1993.

433. LAIDLAW DH, BILODEAU M, AND ENOKA RM. Steadiness is reduced and motor unit discharge is more variable in old adults. *Muscle Nerve* 23: 600–612, 2000.

434. LAKIE M AND ROBSON LG. Thixotropic changes in human muscle stiffness and the effects of fatigue. *Q J Exp Physiol* 73: 487–500, 1988.

435. LAMOTTE D'INCAMPS B, DESTOMBES J, THIESSON D, HELLIO R, LASERRE X, KOUCHTIR-DEVANNE N, JAMI L, AND ZYTNICKI D. Indications for GABA-immunoreactive axo-axonic contacts on the intraspinal arborization of a Ib fiber in the cat: a confocal microscope study. *J Neurosci* 18: 10030–10036, 1998.

436. LANG AH AND VALLBO AB. Motoneuron activation by low intensity tetanic stimulation of muscle afferents in man. *Eur J Neurol* 18: 383–391, 1967.

437. LAPORTE Y AND LLOYD DPC. Nature and significance of the reflex connections established by large afferent fibers of muscular origin. *Am J Physiol* 169: 609–621, 1952.

438. LATASH ML, YEE MJ, ORPETT C, SLINGO A, AND NICHOLAS JJ. Combining electrical muscle stimulation with voluntary contraction for studying muscle fatigue. *Arch Phys Med Rehabil* 75: 29–35, 1994.

439. LATIES VG AND WEISS B. The amphetamine margin in sports. *Federation Proc* 40: 2689–2692, 1981.

440. LATTANZIO PJ, PETRELLA RJ, SPROULE JR, AND FOWLER PJ. Effects of fatigue on knee proprioception. *Clin J Sport Med* 7: 22–27, 1997.

441. LEE RH AND HECKMAN CJ. Bistability in spinal motoneurons in vivo: systematic variations in rhythmic firing patterns. *J Neurophysiol* 80: 572–582, 1998.

442. LEE RH AND HECKMAN CJ. Enhancement of bistability in spinal motoneurons in vivo by the noradrenergic alpha1 agonist methoxamine. *J Neurophysiol* 81: 2164–2174, 1999.

443. LEGRAMANTE JM, RAIMONDI G, ADREANI CM, SACCO S, IELLAMO F, PERUZZI G, AND KAUFMAN MP. Group III muscle afferents evoke reflex depressor responses to repetitive muscle contractions in rabbits. *Am J Physiol Heart Circ Physiol* 278: H871–H877, 2000.

444. LEMON RM AND MANTEL GWH. The influence of changes in discharge frequency of corticospinal neurones on hand muscles in the monkey. *J Physiol (Lond)* 413: 351–378, 1989.

445. LEONARD CT, KANE J, PERDAEMS J, FRANK C, GRAETZER DG, AND MORITANI T. Neural modulation of muscle contractile properties during fatigue: afferent feedback dependence. *Electroencephalogr Clin Neurophysiol* 93: 209–217, 1994.

446. LIBET B, GLEASON CA, WRIGHT EW, AND PEARL DK. Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential). The unconscious initiation of a freely voluntary act. *Brain* 106: 623–642, 1983.

447. LIEPERT J, KOTTERBA S, TEGENTHOFF M, AND MALIN JP. Central fatigue assessed by transcranial magnetic stimulation. *Muscle Nerve* 19: 1429–1434, 1996.

448. LIND AR, BURSE R, ROCHELLE RH, RINEHART JS, AND PETROFSKY JS. Influence of posture on isometric fatigue. *J Appl Physiol* 45: 270–274, 1978.

449. LIND AR AND PETROFSKY JS. Amplitude of the surface electromyogram during fatiguing isometric contractions. *Muscle Nerve* 2: 257–264, 1979.

450. LIND AR AND PETROFSKY JS. Isometric tension from rotary stimulation of fast and slow cat muscles. *Muscle Nerve* 1: 213–218, 1978.

451. LINDH M. Increase of muscle strength from isometric quadriceps exercises at different knee angles. *Scand J Rehabil Med* 11: 33–36, 1979.

452. LINDSTROM L, KADEFORS R, AND PETERSEN I. An electromyographic index for localized muscle fatigue. *J Appl Physiol* 43: 750–754, 1977.

453. LIPPOLD OCJ. Oscillation in the stretch reflex arc and the origin of the rhythmical, 8–12 C-S component of physiological tremor. *J Physiol (Lond)* 206: 359–382, 1970.

454. LIPPOLD OCJ. The tremor in fatigue. *Ciba Found Symp* 82: 234–248, 1981.

455. LJUBISAVLJEVIC M AND ANASTASIJEVIC R. Fusimotor-induced changes in muscle spindle outflow and responsiveness in muscle fatigue in decerebrate cats. *Neuroscience* 63: 339–348, 1994.

456. LJUBISAVLJEVIC M, ANASTASIJEVIC R, AND TRIFUNJAGIC D. Changes in fusimotor discharge rate provoked by isotonic fatiguing muscle contractions in decerebrate cats. *Brain Res* 673: 126–132, 1995.

457. LJUBISAVLJEVIC M, JOVANOVIC K, AND ANASTASIJEVIC R. Changes in discharge rate of fusimotor neurones provoked by fatiguing contractions of cat triceps surae muscles. *J Physiol (Lond)* 445: 499–513, 1992.

458. LJUBISAVLJEVIC M, MILANOVIC S, RADOVANOVIC S, VUKCEVIC I, KOSTIC V, AND ANASTASIJEVIC R. Central changes in muscle fatigue during sustained submaximal isometric voluntary contraction as revealed by transcranial magnetic stimulation. *Electroencephalogr Clin Neurophysiol* 101: 281–288, 1996.

459. LLOYD AR, GANDEVIA SC, AND HALES JP. Muscle performance, voluntary activation, twitch properties and perceived effort in normal subjects and patients with the chronic fatigue syndrome. *Brain* 114: 85–98, 1991.

460. LOEB GE. Motoneurone task groups: coping with kinematic heterogeneity. *J Exp Biol* 115: 137–146, 1985.

461. LOEB GE. Hard lessons in motor control from the mammalian spinal cord. *Trends Neurosci* 10: 108–113, 1987.

462. LOISELLE DS AND WALMSLEY B. Cost of force development as a function of stimulus rate in rat soleus muscle. *Am J Physiol Cell Physiol* 243: C242–C246, 1982.

463. LOMBARD WP. Some of the influences which affect the power of voluntary muscular contractions. *J Physiol (Lond)* 13: 1–58, 1892.

464. LOMELÍ J, QUEVEDO J, LINARES P, AND RUDOMIN P. Local control of information flow in segmental and ascending collaterals of single afferents. *Nature* 395: 600–604, 1998.

465. LORING SH AND HERSHENSON MB. Effects of series compliance on twitches superimposed on voluntary contractions. *J Appl Physiol* 73: 516–521, 1992.

466. LOSCHER WN, CRESSWELL AG, AND THORSTENSSON A. Central fatigue during a long-lasting submaximal contraction of the triceps surae. *Exp Brain Res* 108: 305–314, 1996.

467. LOSCHER WN, CRESSWELL AG, AND THORSTENSSON A. Excitatory drive to the alpha-motoneuron pool during a fatiguing submaximal contraction in man. *J Physiol (Lond)* 491: 271–280, 1996.

468. LOSCHER WN, CRESSWELL AG, AND THORSTENSSON A. Recurrent inhibition of soleus alpha-motoneurons during a sustained submaximal plantar flexion. *Electroencephalogr Clin Neurophysiol* 101: 334–338, 1996.

469. LUNDBERG A AND VOORHOEVE P. Effects from the pyramidal tract on spinal reflex arcs. *Acta Physiol Scand* 56: 201–219, 1962.

470. LYLE N AND RUTHERFORD OM. A comparison of voluntary versus stimulated strength training of the human adductor pollicis muscle. *J Sports Sci* 16: 267–270, 1998.

471. LYONS MF, CADDEN SW, BAXENDALE RH, AND YEMM R. Twitch interpolation in the assessment of the maximum force-generating capacity of the jaw-closing muscles in man. *Arch Oral Biol* 41: 1161–1168, 1996.

472. MACDOUGALL JD, ELDER GC, SALE DG, MOROZ JR, AND SUTTON JR. Effects of strength training and immobilization on human muscle fibres. *Eur J Appl Physiol* 43: 25–34, 1980.

473. MACEFIELD G, GANDEVIA SC, AND BURKE D. Perceptual responses to microstimulation of single afferents innervating joints, muscles and skin of the human hand. *J Physiol (Lond)* 429: 113–129, 1990.

474. MACEFIELD G, HAGBARTH KE, GORMAN R, GANDEVIA SC, AND BURKE D. Decline in spindle support to alpha-motoneurones during sustained voluntary contractions. *J Physiol (Lond)* 440: 497–512, 1991.

475. MACEFIELD VG, FUGLEVAND AJ, AND BIGLAND-RITCHIE B. Contractile

properties of single motor units in human toe extensors assessed by intraneural motor axon stimulation. *J Neurophysiol* 75: 2509–2519, 1996.

476. MACEFIELD VG, FUGLEVAND AJ, HOWELL JN, AND BIGLAND-RITCHIE B. Discharge behaviour of single motor units during maximal voluntary contractions of a human toe extensor. *J Physiol (Lond)* 528: 227–234, 2000.

477. MACEFIELD VG, GANDEVIA SC, BIGLANDRITCHIE B, GORMAN RB, AND BURKE D. The firing rates of human motoneurones voluntarily activated in the absence of muscle afferent feedback. *J Physiol (Lond)* 471: 429–443, 1993.

478. MAIER MA, ILLERT M, KIRKWOOD PA, NIELSEN J, AND LEMON RN. Does a C_3-C_4 propriospinal system transmit corticospinal excitation in the primate? An investigation in the macaque monkey. *J Physiol (Lond)* 511: 191–212, 1998.

479. MANN MD AND FOLLETT KA. Excitability changes along pyramidal tract axons after sensory stimulation. *Eur J Neurol* 78: 685–702, 1982.

480. MANOHAR M. Blood flow to the respiratory and limb muscles and to abdominal organs during maximal exertion in ponies. *J Physiol (Lond)* 377: 25–35, 1986.

481. MARCHETTINI P, SIMONE DA, CAPUTI G, AND OCHOA JL. Pain from excitation of identified muscle nociceptors in humans. *Brain Res* 740: 109–116, 1996.

482. MARSDEN CD, MEADOWS JC, AND MERTON PA. Muscular wisdom. *J Physiol (Lond)* 200: 15P, 1969.

483. MARSDEN CD, MEADOWS JC, AND MERTON PA. Isolated single motor units in human muscle and their rate of discharge during maximal voluntary effort. *J Physiol (Lond)* 217: 12P–13P, 1971.

484. MARSDEN CD, MEADOWS JC, AND MERTON PA. "Muscular wisdom" that minimizes fatigue during prolonged effort in man: peak rates of motoneuron discharge and slowing of discharge during fatigue. *Adv Neurol* 39: 169–211, 1983.

485. MARSDEN CD, MERTON PA, AND MORTON HB. Servo action in the human thumb. *J Physiol (Lond)* 257: 1–44, 1976.

486. MASON P AND WILKINSON G. The prevalence of psychiatric morbidity. OPCS survey of psychiatric morbidity in Great Britain. *Br J Psychiat* 168: 1–3, 1996.

487. MATHIS J, DE QUERVAIN D, AND HESS CW. Dependence of the transcranially induced silent period on the 'instruction set' and the individual reaction time. *Electroencephalogr Clin Neurophysiol* 109: 426–435, 1998.

488. MATON B AND GAMET D. The fatigability of two agonistic muscles in human isometric voluntary submaximal contraction: an EMG study. II. Motor unit firing rate and recruitment. *Eur J Appl Physiol* 58: 369–374, 1989.

489. MATTHEWS PB AND STEIN RB. The sensitivity of muscle spindle afferents to small sinusoidal changes of length. *J Physiol (Lond)* 200: 723–743, 1969.

490. MATTHEWS PBC. Observations on the automatic compensation of reflex gain on varying the pre-existing level of motor discharge in man. *J Physiol (Lond)* 374: 73–90, 1986.

491. MATTHEWS PBC. Relationship of firing intervals of human motor units to the trajectory of post-spike after-hyperpolarization and synaptic noise. *J Physiol (Lond)* 492: 597–628, 1996.

492. MATTHEWS PBC. Spindle and motoneuronal contributions to the phase advance of the human stretch reflex and the reduction of tremor. *J Physiol (Lond)* 498: 249–275, 1997.

493. MAUGHAN RJ, WATSON JS, AND WEIR J. Muscle strength and cross-sectional area in man: a comparison of strength-trained and untrained subjects. *Br J Sports Med* 18: 149–157, 1984.

494. MAUGHAN RJ, WATSON JS, AND WEIR J. Strength and cross-sectional area of human skeletal muscle. *J Physiol (Lond)* 338: 37–49, 1983.

495. MAXWELL DJ, OTTERSEN OP, AND STORM-MATHISEN J. Synaptic organization of excitatory and inhibitory boutons associated with spinal neurons which project through the dorsal columns of the cat. *Brain Res* 676: 103–112, 1995.

496. MAXWELL DJ AND RIDDELL JS. Axo-axonic synapses on terminals of identified group II muscle spindle afferent axons in the cat spinal cord. *Eur J Neurosci* 11: 2151–2159, 1999.

497. MAZZOCCHIO R AND ROSSI A. Further evidence for Renshaw inhibition in man. A combined electrophysiological and pharmacological approach. *Neurosci Lett* 106: 131–136, 1989.

498. MAZZOCCHIO R, ROSSI A, AND ROTHWELL JC. Depression of Renshaw recurrent inhibition by activation of corticospinal fibres in human upper and lower limb. *J Physiol (Lond)* 481: 487–498, 1994.

499. MCCARTNEY N, MOROZ D, GARNER SH, AND MCCOMAS AJ. The effects of strength training in patients with selected neuromuscular disorders. *Med Sci Sports Exercise* 20: 362–368, 1988.

500. MCCLOSKEY DI. Kinesthetic sensibility. *Physiol Rev* 58: 763–820, 1978.

501. MCCLOSKEY DI, COLEBATCH JG, POTTER EK, AND BURKE D. Judgements about onset of rapid voluntary movements in man. *J Neurophysiol* 49: 851–863, 1983.

502. MCCLOSKEY DI, EBELING P, AND GOODWIN GM. Estimation of weights and tensions and apparent involvement of a "sense of effort." *Eur J Neurol* 42: 220–232, 1974.

503. MCCOMAS AJ. Human neuromuscular adaptations that accompany changes in activity. *Med Sci Sports Exercise* 26: 1498–1509, 1994.

504. MCCOMAS AJ, KERESHI S, AND QUINLAN J. A method for detecting functional weakness. *J Neurol Neurosurg Psychiat* 46: 280–282, 1983.

505. MCCOMAS AJ, MILLER RG, AND GANDEVIA SC. Fatigue brought on by malfunction of the central and peripheral nervous systems. *Adv Exp Med Biol* 384: 495–512, 1995.

506. MCDONAGH MJ, HAYWARD CM, AND DAVIES CTM. Isometric training in human elbow flexor muscles The effects on voluntary and electrically evoked forces. *J Bone Joint Surg Br* 65: 355–358, 1983.

507. MCDONAGH MJN AND DAVIES CTM. Adaptive response of mammalian skeletal muscle to exercise with high loads. *Eur J Appl Physiol* 52: 139–155, 1984.

508. MCFADDEN LK AND MCCOMAS AJ. Late depression of muscle excitability in humans after fatiguing stimulation. *J Physiol (Lond)* 496: 851–855, 1996.

509. MCKAY WB, TUEL SM, SHERWOOD AM, STOKIC DS, AND DIMITRIJEVIC MR. Focal depression of cortical excitability induced by fatiguing muscle contraction: a transcranial magnetic stimulation study. *Exp Brain Res* 105: 276–282, 1995.

510. MCKAY WB, STOKIC DS, SHERWOOD AM, VRBOVA G, AND DIMITRIJEVIC MR. Effect of fatiguing maximal voluntary contraction on excitatory and inhibitory responses elicited by transcranial magnetic motor cortex stimulation. *Muscle Nerve* 19: 1017–1024, 1996.

511. MCKENZIE DK, ALLEN GM, BUTLER JE, AND GANDEVIA SC. Task failure with lack of diaphragm fatigue during inspiratory resistive loading in human subjects. *J Appl Physiol* 82: 2011–2019, 1997.

512. MCKENZIE DK, ALLEN GM, AND GANDEVIA SC. Reduced voluntary drive to the human diaphragm at low lung volumes. *Respir Physiol* 105: 69–76, 1996.

513. MCKENZIE DK AND BELLEMARE F. Respiratory muscle fatigue. *Adv Exp Med Biol* 384: 401–414, 1995.

514. MCKENZIE DK, BIGLAND-RITCHIE B, GORMAN RB, AND GANDEVIA SC. Central and peripheral fatigue of human diaphragm and limb muscles assessed by twitch interpolation. *J Physiol (Lond)* 454: 643–656, 1992.

515. MCKENZIE DK AND GANDEVIA SC. Recovery from fatigue of human diaphragm and limb muscles. *Respir Physiol* 84: 49–60, 1991.

516. MCKENZIE DK, PLASSMAN BL, AND GANDEVIA SC. Maximal activation of the human diaphragm but not inspiratory intercostal muscles during static inspiratory efforts. *Neurosci Lett* 89: 63–68, 1988.

517. MEEUSEN R, SMOLDERS I, SARRE S, DE MEIRLEIR K, KEIZER H, SERNEELS M, EBINGER G, AND MICHOTTE Y. Endurance training effects on neurotransmitter release in rat striatum: an in vivo microdialysis study. *Acta Physiol Scand* 159: 335–341, 1997.

518. MEINCK HM, PIESIUR-STREHLOW B, AND KOEHLER W. Some principles of flexor reflex generation in human leg muscles. *Electroencephalogr Clin Neurophysiol* 52: 140–150, 1981.

519. MENGSHOEL AM, SAUGEN E, FORRE O, AND VOLLESTAD NK. Muscle fatigue in early fibromyalgia. *J Rheumatol* 22: 143–150, 1995.

520. MENSE S. Nervous outflow from skeletal muscle following chemical noxious stimulation. *J Physiol (Lond)* 267: 75–88, 1977.

521. MENSE S AND MEYER H. Bradykinin-induced modulation of the response behaviour of different types of feline group III and IV muscle receptors. *J Physiol (Lond)* 398: 49–63, 1988.

522. MENSE S AND SCHMIDT RF. Activation of group IV afferent units from skeletal muscle by algesic agents. *Brain Res* 72: 305–310, 1974.

523. MENSE S AND STAHNKE M. Responses in muscle afferent fibres of

slow conduction velocity to contractions and ischaemia in the cat. *J Physiol (Lond)* 342: 383–397, 1983.

524. MERTON PA. Voluntary strength and fatigue. *J Physiol (Lond)* 123: 553–564, 1954.

525. MERTON PA. Problems of muscular fatigue. *Br Med Bull* 12: 219–221, 1956.

526. MERTON PA, HILL DK, AND MORTON HB. Indirect and direct stimulation of fatigued human muscle. *Ciba Found Symp* 82: 120–129, 1981.

527. MERTON PA AND MORTON HB. Stimulation of the cerebral cortex in the intact human subject. *Nature* 285: 227, 1980.

528. MERTON PA AND PAMPIGLIONE G. Strength and fatigue. *Nature* 166: 1950.

529. MEUNIER S AND PIERROT-DESEILLIGNY E. Gating of the afferent volley of the monosynaptic stretch reflex during movement in man. *J Physiol (Lond)* 419: 753–763, 1989.

530. MIER A, BROPHY C, MOXHAM J, AND GREEN M. Twitch pressures in the assessment of diaphragm weakness. *Thorax* 44: 990–996, 1989.

531. MILLAN MJ. Serotonin (5-HT) and pain: a reappraisal of its role in the light of receptor multiplicity. *Semin Neurosci* 7: 409–419, 1995.

532. MILLER RG, MIRKA A, AND MAXFIELD M. Rate of tension development in isometric contractions of a human hand muscle. *Eur J Neurol* 73: 267–285, 1981.

533. MILLER TA, ALLEN GM, AND GANDEVIA SC. Muscle force, perceived effort, and voluntary activation of the elbow flexors assessed with sensitive twitch interpolation in fibromyalgia. *J Rheumatol* 23: 1621–1627, 1996.

534. MILLS KR. Power spectral analysis of electromyogram and compound muscle action potential during muscle fatigue and recovery. *J Physiol (Lond)* 326: 401–409, 1982.

535. MILLS KR AND THOMSON CCB. Human muscle fatigue investigated by transcranial magnetic stimulation. *Neuroreport* 6: 1966–1968, 1995.

536. MILNER-BROWN HS, STEIN RB, AND LEE RG. Synchronization of human motor units: possible roles of exercise and supraspinal reflexes. *Electroencephalogr Clin Neurophysiol* 38: 245–254, 1975.

537. MILNER-BROWN HS, STEIN RB, AND YEMM R. The orderly recruitment of human motor units during voluntary isometric contractions. *J Physiol (Lond)* 230: 359–370, 1973.

538. MITTLEMAN KD, RICCI MR, AND BAILEY SP. Branched-chain amino acids prolong exercise during heat stress in men and women. *Med Sci Sports Exercise* 30: 83–91, 1998.

539. MORITANI T AND DEVRIES HA. Neural factors versus hypertrophy in the time course of muscle strength gain. *Am J Phys Med* 58: 115–130, 1979.

540. MOSSO A. *Fatigue.* London: Swan Sonnenschein, 1904.

541. MUIR RB AND PORTER R. The effect of a preceding stimulus on temporal facilitation at corticomotoneuronal synapses. *J Physiol (Lond)* 228: 749–763, 1973.

542. MUNSON JB, FOEHRING RC, MENDELL LM, AND GORDON T. Fast-to-slow conversion following chronic low-frequency activation of medial gastrocnemius muscle in cats. II. Motoneuron properties. *J Neurophysiol* 77: 2605–2615, 1997.

543. NAESS K AND STORM-MATHISEN A. Fatigue of sustained tetanic contractions. *Acta Physiol Scand* 44: 363–383, 1955.

544. NAKAMURA H, KITAGAWA H, KAWAGUCHI Y, AND TSUJI H. Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. *J Physiol (Lond)* 498: 817–823, 1997.

545. NARDONE A AND SCHIEPPATI M. Shift of activity from slow to fast muscle during voluntary lengthening contractions of the triceps surae muscles in humans. *J Physiol (Lond)* 395: 363–381, 1988.

546. NARDONE A, TARANTOLA J, GIORDANO A, AND SCHIEPPATI M. Fatigue effects on body balance. *Electroencephalogr Clin Neurophysiol* 105: 309–320, 1997.

547. NARICI MV, ROI GS, LANDONI L, MINETTI AE, AND CERRETELLI P. Changes in force, cross-sectional area and neural activation during strength training and detraining of the human quadriceps. *Eur J Appl Physiol* 59: 310–319, 1989.

548. NELSON DL AND HUTTON RS. Dynamic and static stretch responses in muscle spindle receptors in fatigued muscle. *Med Sci Sports Exercise* 17: 445–450, 1985.

549. NEWELL SZ, MCKENZIE DK, AND GANDEVIA SC. Inspiratory and skeletal muscle strength and endurance and diaphragmatic activation in patients with chronic airflow limitation. *Thorax* 44: 903–912, 1989.

550. NEWHAM DJ, DAVIES JM, AND MAYSTON MJ. Voluntary force generation and activation in the knee muscles of stroke patients with mild spastic hemiparesis. *J Physiol (Lond)* 483: 128P, 1995.

551. NEWHAM DJ, HARRISON RA, AND CLARK CG. Skeletal muscle function after major abdominal surgery. *Hum Nutr Clin Nutr* 41: 363–371, 1987.

552. NEWHAM DJ AND HSIAO SF. Detection and estimation of voluntary activation with percutaneous electrical stimulation of the human quadriceps at 1 and 100 Hz. *J Physiol (Lond)* 491: 71P, 1996.

553. NEWHAM DJ, MCCARTHY T, AND TURNER J. Voluntary activation of human quadriceps during and after isokinetic exercise. *J Appl Physiol* 71: 2122–2126, 1991.

554. NHLBI. Workshop on Respiratory Muscle Fatigue. *Am Rev Respir Dis* 142: 474–480, 1990.

555. NIELSEN B. Heat stress and acclimation. *Ergonomics* 37: 49–58, 1994.

556. NIELSEN B, HALES STRANGE S JR, CHRISTENSEN NJ, WARBERG J, AND SALTIN B. Human circulatory and thermoregulatory adaptations with heat acclimation and exercise in a hot, dry environment. *J Physiol (Lond)* 460: 467–485, 1993.

557. NIELSEN J AND PETERSEN N. Is presynaptic inhibition distributed to corticospinal fibres in man? *J Physiol (Lond)* 477: 47–58, 1994.

558. NIELSEN J, PETERSEN N, DEUSCHL B, AND BALLEGAARD M. Task-related changes in the effect of magnetic brain stimulation on spinal neurones in man. *J Physiol (Lond)* 471: 223–243, 1993.

559. NIEMAN DC. Immune response to heavy exertion. *J Appl Physiol* 82: 1385–1394, 1997.

560. NORDSTROM MA, ENOKA RM, REINKING RM, CALLISTER RC, AND STUART DG. Reduced motor unit activation of muscle spindles and tendon organs in the immobilized cat hindlimb. *J Appl Physiol* 78: 901–913, 1995.

561. NORDSTROM MA AND MILES TS. Instability of motor unit firing rates during prolonged isometric contractions in human masseter. *Brain Res* 549: 268–274, 1991.

562. NORREGAARD J, LYKKEGAARD JJ, BULOW PM, AND DANNESKIOLD-SAMSOE B. The twitch interpolation technique for the estimation of true quadriceps muscle strength. *Clin Physiol* 17: 523–532, 1997.

563. NUDO RJ, MILLIKEN GW, JENKINS WM, AND MERZENICH MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *J Neurosci* 16: 785–807, 1996.

564. O'HAGAN F, TSUNODA N, SALE DG, AND MACDOUGALL JD. Elbow flexor evoked twitch contractile properties in untrained men and women and male bodybuilders. *Eur J Appl Physiol* 66: 240–245, 1993.

565. OHTSUKI T. Decrease in human voluntary isometric arm strength induced by simultaneous bilateral exertion. *Behav Brain Res* 7: 165–178, 1983.

566. OLYAEI GR AND BAXENDALE RH. The effects of fatiguing voluntary activity of the quadriceps muscle on the soleus H reflex excitability in man. *J Physiol (Lond)* 483: 81P, 1995.

567. OSTROWSKI K, HERMANN C, BANGASH A, SCHJERLING P, NIELSEN JN, AND PEDERSEN BK. A trauma-like elevation of plasma cytokines in humans in response to treadmill running. *J Physiol (Lond)* 513: 889–894, 1998.

568. PAINTAL AS. Functional analysis of group III afferent fibers of mammalian muscle. *J Physiol (Lond)* 152: 250–270, 1960.

569. PAINTAL AS. The mechanism of excitation of type J receptors, and the J reflex. In: *Breathing: Hering-Breuer Centenary Symposium,* edited by Porter R. London: Churchill, 1970, p. 59–71.

570. PALMER E AND ASHBY P. Corticospinal projections to upper limb motoneurones in humans. *J Physiol (Lond)* 448: 397–412, 1992.

571. PARTRIDGE DL. Signal-handling characteristics of load-moving skeletal muscle. *Am J Physiol* 210: 1178–1191, 1966.

572. PASCUAL-LEONE A, GRAFMAN J, AND HALLETT M. Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science* 263: 1287–1289, 1994.

573. PATTON HD AND AMASSIAN VE. Single- and multiple-unit analysis of cortical stage of pyramidal tract activation. *J Neurophysiol* 17: 345–363, 1954.

574. PATTON HD AND AMASSIAN VE. The pryamidal tract: its excitation and

functions. In: *Handbook of Physiology. Neurophysiology*. Washington, DC: Am Physiol Soc, 1960, sect. 1, vol. II, p. 837–861.

575. PEARSON KG AND COLLINS DF. Reversal of the influence of group Ib afferents from plantaris on activity in medial gastrocnemius muscle during locomotor activity. *J Neurophysiol* 70: 1009–1017, 1993.

576. PEDERSEN BK AND HOFFMAN-GOETZ L. Exercise and the immune system: regulation, integration, and adaptation. *Physiol Rev* 80: 1055–1081, 2000.

577. PEDERSEN J, LJUBISAVLJEVIC M, BERGENHEIM M, AND JOHANSSON H. Alterations in information transmission in ensembles of primary muscle spindle afferents after muscle fatigue in heteronymous muscle. *Neuroscience* 84: 953–959, 1998.

578. PEDERSEN J, LONN J, HELLSTROM F, DJUPSJOBACKA M, AND JOHANSSON H. Localized muscle fatigue decreases the acuity of the movement sense in the human shoulder. *Med Sci Sports Exercise* 31: 1047–1052, 1999.

579. PETERS EJD AND FUGLEVAND AJ. Cessation of human motor unit discharge during sustained maximal voluntary contraction. *Neurosci Lett* 274: 66–70, 1999.

580. PETIT J, SCOTT JJ, AND REYNOLDS KJ. Tendon organ sensitivity to steady-state isotonic contraction of in-series motor units in feline peroneus tertius muscle. *J Physiol (Lond)* 500: 227–233, 1997.

581. PETTOROSSI VE DELLA TORRE G, BORTOLAMI R, AND BRUNETTI O. The role of capsaicin-sensitive muscle afferents in fatigue-induced modulation of the monosynaptic reflex in the rat. *J Physiol (Lond)* 515: 599–607, 1999.

582. PHILLIPS CG. Epicortical electrical mapping of motor areas in primates. *Ciba Found Symp* 132: 5–20, 1987.

583. PHILLIPS CG AND PORTER R. *Corticospinal Neurones: Their Role in Movement*. London: Academic, 1977. p. v-xii.

584. PICKAR JG, HILL JM, AND KAUFMAN MP. Dynamic exercise stimulates group III muscle afferents. *J Neurophysiol* 71: 753–760, 1994.

585. PICKAR JG, HILL JM, AND KAUFMAN MP. Stimulation of vagal afferents inhibits locomotion in mesencephalic cats. *J Appl Physiol* 74: 103–110, 1993.

586. PIERCE JP AND MENDELL LM. Quantitative ultrastructure of Ia boutons in the ventral horn: scaling and positional relationships. *J Neurosci* 13: 4748–4763, 1993.

587. PIERROT-DESEILLIGNY E. Transmission of the cortical command for human voluntary movement through cervical propriospinal premotoneurons. *Prog Neurobiol* 48: 489–517, 1996.

588. PITSILADIS YP AND MAUGHAN RJ. The effects of exercise and diet manipulation on the capacity to perform prolonged exercise in the heat and in the cold in trained humans. *J Physiol (Lond)* 517: 919–930, 1999.

589. POPPELE RE AND BOWMAN RJ. Quantitative description of linear behavior of mammalian muscle spindles. *J Neurophysiol* 33: 59–72, 1970.

590. PORTER R. Early facilitation at corticomotoneuronal synapses. *J Physiol (Lond)* 207: 733–745, 1970.

591. POWERS RK AND BINDER MD. Effects of low-frequency stimulation on the tension-frequency relations of fast-twitch motor units in the cat. *J Neurophysiol* 66: 905–918, 1991.

592. POWERS RK AND BINDER MD. Summation of motor unit tensions in the tibialis posterior muscle of the cat under isometric and nonisometric conditions. *J Neurophysiol* 66: 1838–1846, 1991.

593. POWERS RK, SAWCZUK A, MUSICK JR, AND BINDER MD. Multiple mechanisms of spike-frequency adaptation in motoneurones. *J Physiol (Paris)* 93: 101–114, 1999.

594. PRATT CA. Evidence of positive force feedback among hindlimb extensors in the intact standing cat. *J Neurophysiol* 73: 2578–2583, 1995.

595. PRIORI A, BERARDELLI A, INGHILLERI M, PEDACE F, GIOVANNELLI M, AND MANFREDI M. Electrical stimulation over muscle tendons in humans. Evidence favouring presynaptic inhibition of Ia fibres due to the activation of group III tendon afferents. *Brain* 121: 373–380, 1998.

596. PROCHAZKA A. Proprioceptive feedback and movement regulation. In: *Handbook of Physiology. Exercise: Regulation and Integration of Multiple Systems*. Bethesda, MD: Am Physiol Soc, 1996, sect. 12, chapt. 3, p. 89–127.

597. PROCHAZKA A AND WAND P. Tendon organ discharge during voluntary movements in cats. *J Physiol (Lond)* 303: 385–390, 1980.

598. PROCHAZKA A, WESTERMAN RA, AND ZICCONE SP. Ia afferent activity during a variety of voluntary movements in the cat. *J Physiol (Lond)* 268: 423–448, 1977.

599. PROSKE U. The Golgi tendon organ. Properties of the receptor and reflex action of impulses arising from tendon organs. *Int Rev Physiol* 25: 127–171, 1981.

600. PROSKE U, MORGAN DL, AND GREGORY JE. Thixotropy in skeletal muscle and in muscle spindles: a review. *Prog Neurobiol* 41: 705–721, 1993.

601. PSEK JA AND CAFARELLI E. Behavior of co-active muscles during fatigue. *J Appl Physiol* 74: 170–175, 1993.

602. RACK PM AND WESTBURY DR. The effects of length and stimulus rate on tension in the isometric cat soleus muscle. *J Physiol (Lond)* 204: 443–460, 1969.

603. RAJ H, SINGH VK, ANAND A, AND PAINTAL AS. Sensory origin of lobeline-induced sensations: a correlative study in man and cat. *J Physiol (Lond)* 482: 235–246, 1995.

604. RANATUNGA KW, SHARPE B, AND TURNBULL B. Contractions of a human skeletal muscle at different temperatures. *J Physiol (Lond)* 390: 383–395, 1987.

605. RANKIN LL, ENOKA RM, VOLZ KA, AND STUART DG. Coexistence of twitch potentiation and tetanic force decline in rat hindlimb muscle. *J Appl Physiol* 65: 2687–2695, 1988.

606. REFSHAUGE KM, KILBREATH SL, AND GANDEVIA SC. Movement detection at the distal joint of the human thumb and fingers. *Exp Brain Res* 122: 85–92, 1998.

607. REID C. The mechanism of voluntary muscular fatigue. *J Physiol (Lond)* 29: 17–42, 1928.

608. REKLING JC, FUNK GD, BAYLISS DA, DONG XW, AND FELDMAN JL. Synaptic control of motoneuronal excitability. *Physiol Rev* 80: 767–852, 2000.

609. RIBEIRO-DA-SILVA A. Substantia gelatinosa of the spinal cord. In: *The Rat Nervous System*, edited by Paxinos G. London: Academic, 1995, p. 47–59.

610. RICE CL, VOLLMER TL, AND BIGLAND-RITCHIE B. Neuromuscular responses of patients with multiple sclerosis. *Muscle Nerve* 15: 1123–1132, 1992.

611. RICH C AND CAFARELLI E. Submaximal motor unit firing rates after 8 wk of isometric resistance training. *Med Sci Sports Exercise* 32: 190–196, 2000.

612. RIDDELL JS AND HADIAN M. Field potentials generated by group II muscle afferents in the lower-lumbar segments of the feline spinal cord. *J Physiol (Lond)* 522: 97–108, 2000.

613. RIDDELL JS AND HADIAN M. Interneurones in pathways from group II muscle afferents in the lower-lumbar segments of the feline spinal cord. *J Physiol (Lond)* 522: 109–123, 2000.

614. RIDDING MC, TAYLOR JL, AND ROTHWELL JC. The effect of voluntary contraction on cortico-cortical inhibition in human motor cortex. *J Physiol (Lond)* 487: 541–548, 1995.

615. RIEK S AND BAWA P. Recruitment of motor units in human forearm extensors. *J Neurophysiol* 68: 100–108, 1992.

616. ROBINSON LR, MUSTOVIC EH, LIEBER PS, HAIDET PM, IRGANG JJ, MCLANE T, AND NICHOLAS JJ. A technique for quantifying and determining the site of isometric muscle fatigue in the clinical setting. *Arch Phys Med Rehabil* 71: 901–904, 1990.

617. RODE G, ROSSETTI Y, AND BOISSON D. Inverse relationship between sensation of effort and muscular force during recovery from pure motor hemiplegia: a single-case study. *Neuropsychologia* 34: 87–95, 1996.

618. ROICK H, VAN GIESEN HJ, AND BENECKE R. On the origin of the post-excitatory inhibition seen after transcranial magnetic brain stimulation in awake human subjects. *Exp Brain Res* 94: 489–498, 1993.

619. ROSSI A AND DECCHI B. Changes in Ib heteronymous inhibition to soleus motoneurones during cutaneous and muscle nociceptive stimulation in humans. *Brain Res* 774: 55–61, 1997.

620. ROSSI A, DECCHI B, AND GINANNESCHI F. Presynaptic excitability changes of group Ia fibres to muscle nociceptive stimulation in humans. *Brain Res* 818: 12–22, 1999.

621. ROTHMULLER C AND CAFARELLI E. Effect of vibration on antagonist muscle coactivation during progressive fatigue in humans. *J Physiol (Lond)* 485: 857–864, 1995.

622. ROTHWELL J, BURKE D, HICKS R, STEPHEN J, WOODFORTH I, AND CRAWFORD M. Transcranial electrical stimulation of the motor cortex in

man: further evidence for the site of activation. *J Physiol (Lond)* 481: 243–250, 1994.

623. ROTHWELL JC. Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. *J Neurosci Methods* 74: 113–122, 1997.

624. ROTTO DM AND KAUFMAN MP. Effect of metabolic products of muscular contraction on discharge of group III and IV afferents. *J Appl Physiol* 64: 2306–2313, 1988.

625. ROTTO DM, SCHULTZ HD, LONGHURST JC, AND KAUFMAN MP. Sensitization of group III muscle afferents to static contraction by arachidonic acid. *J Appl Physiol* 68: 861–867, 1990.

626. ROUSSOS C, FIXLEY M, GROSS D, AND MACKLEM PT. Fatigue of inspiratory muscles and their synergic behavior. *J Appl Physiol* 46: 897–904, 1979.

627. ROUSSOS CS AND MACKLEM PT. Diaphragmatic fatigue in man. *J Appl Physiol* 43: 189–197, 1977.

628. ROWELL LB, O'LEARY DS, AND KELLOGG DL. Integration of cardiovascular control systems in dynamic exercise. In: *Handbook of Physiology. Exercise: Regulation and Integration of Multiple Systems.* Bethesda, MD: Am Physiol Soc, 1996, sect. 12, chapt. 17, p. 770–838.

629. RUBE N AND SECHER NH. Effect of training on central factors in fatigue following two- and one-leg static exercise in man. *Acta Physiol Scand* 141: 87–95, 1991.

630. RUDOMIN P, JIMENEZ I, SOLODKIN M, AND DUENAS S. Sites of action of segmental and descending control of transmission on pathways mediating PAD of Ia- and Ib-afferent fibers in cat spinal cord. *J Neurophysiol* 50: 743–769, 1983.

631. RUDOMIN P AND SCHMIDT RF. Presynaptic inhibition in the vertebrate spinal cord revisited. *Exp Brain Res* 129: 1–37, 1999.

632. RUTHERFORD OM AND JONES DA. The role of learning and coordination in strength training. *Eur J Appl Physiol* 55: 100–105, 1986.

633. RUTHERFORD OM, JONES DA, AND NEWHAM DJ. Clinical and experimental application of the percutaneous twitch superimposition technique for the study of human muscle activation. *J Neurol Neurosurg Psychiat* 49: 1288–1291, 1986.

634. RUTHERFORD OM AND WHITE PD. Human quadriceps strength and fatiguability in patients with post viral fatigue. *J Neurol Neurosurg Psychiat* 54: 961–964, 1991.

635. SACCO P, THICKBROOM GW, THOMPSON ML, AND MASTAGLIA FL. Changes in corticomotor excitation and inhibition during prolonged submaximal muscle contractions. *Muscle Nerve* 20: 1158–1166, 1997.

636. SAHLIN K, TONKONOGI M, AND SODERLUND K. Energy supply and muscle fatigue in humans. *Acta Physiol Scand* 162: 261–266, 1998.

637. SALE DG. Neural adaptation to resistance training. *Med Sci Sports Exercise* 20: S135–S145, 1988.

638. SALE DG. Neural adaptations to strength training. In: *Strength and Power in Sport*, edited by Komi P. Oxford, UK: Blackwell, 1992, p. 249–265.

639. SALE DG, MACDOUGALL JD, UPTON AR, AND MCCOMAS AJ. Effect of strength training upon motoneuron excitability in man. *Med Sci Sports Exercise* 15: 57–62, 1983.

640. SALE DG, MCCOMAS AJ, MACDOUGALL JD, AND UPTON AR. Neuromuscular adaptation in human thenar muscles following strength training and immobilization. *J Appl Physiol* 53: 419–424, 1982.

641. SALTIN B AND GOLLNICK PD. Skeletal muscle adaptability: significance for metabolism and performance. In*: Handbook of Physiology. Skeletal Muscle.* Bethesda, MD: Am Physiol Soc, 1983, sect. 10, chapt. 19, p. 555–631.

642. SAMII A, CANOS M, IKOMA K, WASSERMAN EM, AND HALLETT M. Absence of facilitation or depression of motor evoked potentials after contralateral homologous muscle activation. *Electroencephalogr Clin Neurophysiol* 105: 241–245, 1997.

643. SAMII A, WASSERMAN EM, AND HALLETT M. Decreased postexercise facilitation of motor evoked potentials in patients with cerebellar degeneration. *Neurology* 49: 538–542, 1997.

644. SAMII A, WASSERMAN EM, AND HALLETT M. Post-exercise depression of motor evoked potentials as a function of exercise duration. *Electroencephalogr Clin Neurophysiol* 105: 352–356, 1997.

645. SAMII A, WASSERMAN EM, IKOMA K, MERCURI B, GEORGE MS, O'FALLON A, DALE JK, STRAUS SE, AND HALLETT M. Decreased postexercise facilitation of motor evoked potentials in patients with chronic fatigue syndrome or depression. *Neurology* 47: 1410–1414, 1996.

646. SAMII A, WASSERMAN EM, IKOMA K, MERCURI B, AND HALLETT M. Characterization of postexercise facilitation of motor evoked potentials to transcranial magnetic stimulation. *Neurology* 46: 1376–1382, 1996.

647. SANDERCOCK TG, FAULKNER JA, ALBERS JW, AND ABBRECHT PH. Single motor unit and fiber action potentials during fatigue. *J Appl Physiol* 58: 1073–1079, 1985.

648. SANDERCOCK TG AND HECKMAN CJ. Doublet potentiation during eccentric and concentric contractions of cat soleus muscle. *J Appl Physiol* 82: 1219–1228, 1997.

649. SAVARD GK, ARESKOG NH, AND SALTIN B. Maximal muscle activation is not limited by pulmonary ventilation in chronic hypoxia. *Acta Physiol Scand* 157: 187–190, 1996.

650. SAWCZUK A, POWERS RK, AND BINDER MD. Intrinsic properties of motoneurons. Implications for muscle fatigue. *Adv Exp Med Biol* 384: 123–134, 1995.

651. SAWCZUK A, POWERS RK, AND BINDER MD. Spike frequency adaptation studied in hypoglossal motoneurons of the rat. *J Neurophysiol* 73: 1799–1810, 1995.

652. SAXTON JM, CLARKSON PM, JAMES R, MILES M, WESTERFER M, CLARK S, AND DONNELLY AE. Neuromuscular dysfunction following eccentric exercise. *Med Sci Sports Exercise* 27: 1185–1193, 1995.

653. SCHANTZ PG, MORITANI T, KARLSON E, JOHANSSON E, AND LUNDH A. Maximal voluntary force of bilateral and unilateral leg extension. *Acta Physiol Scand* 136: 185–192, 1989.

654. SCHIEPPATI M AND CRENNA P. From activity to rest: gating of excitatory autogenetic afferences from the relaxing muscle in man. *Exp Brain Res* 56: 448–457, 1984.

655. SCHMIED A AND FETZ EE. Activity-related changes in electrical thresholds of pyramidal tract axons in the behaving monkey. *Exp Brain Res* 65: 352–360, 1987.

656. SCHMIED A, IVARSSON C, AND FETZ EE. Short-term synchronization of motor units in human extensor digitorum communis muscle: relation to contractile properties and voluntary control. *Exp Brain Res* 97: 159–172, 1993.

657. SCHOMBURG ED. Enkephalinergic and monoaminergic control of segmental pathways from flexor reflex afferents. In: *Neural Control of Movement*, edited by Ferrell WR and Proske U. New York: Plenum, 1995, p. 103–107.

658. SCHOMBURG ED, STEFFENS H, AND KNIFFKI KD. Contribution of group III and IV muscle afferents to multisensorial spinal motor control in cats. *Neurosci Res* 33: 195–206, 1999.

659. SCHWINDT PC AND CALVIN WH. Equivalence of synaptic and injected current in determining the membrane potential trajectory during motoneuron rhythmic firing. *Brain Res* 59: 389–394, 1973.

660. SCHWINDT PC AND CRILL WE. Factors influencing motoneuron rhythmic firing: results from a voltage-clamp study. *J Neurophysiol* 48: 875–890, 1982.

661. SCRIPTURE EW, SMITH TL, AND BROWN EM. On the education of muscular control and power. In: *Studies from the Yale Psychological Laboratory*, edited by Scripture EW. New Haven: Yale University, 1893, p. 114–119.

662. SEARS TA AND STAGG D. Short-term synchronization of intercostal motoneurone activity. *J Physiol (Lond)* 263: 357–381, 1976.

662a. SECHER NH AND PETERSEN S. Fatigue of voluntary contractions in normal and myaesthenic human subjects. *Acta Physiol Scand* 122: 243–248, 1984.

663. SECHER NH, RUBE N, AND ELERS J. Strength of two- and one-leg extension in man. *Acta Physiol Scand* 134: 333–339, 1988.

664. SEGER JY AND THORSTENSSON A. Electrically evoked eccentric and concentric torque-velocity relationships in human knee extensor muscles. *Acta Physiol Scand* 169: 63–69, 2000.

665. SEJERSTED OM AND SJOGAARD G. Dynamics and consequences of potassium shifts in skeletal muscle and heart during exercise. *Physiol Rev* 80: 1411–1481, 2000.

666. SELIGA R, BHATTACHARYA A, SUCCOP P, WICKSTROM R, SMITH D, AND WILLEKE K. Effect of work load and respirator wear on postural stability, heart rate, and perceived exertion. *Am Ind Hyg Assoc J* 52: 417–422, 1991.

667. SEMMLER JG AND NORDSTROM MA. Motor unit discharge and force

tremor in skill- and strength-trained individuals. *Exp Brain Res* 119: 27–38, 1998.

668. SEMMLER JG, NORDSTROM MA, AND WALLACE CJ. Relationship between motor unit short-term synchronization and common drive in human first dorsal interosseous muscle. *Brain Res* 767: 314–320, 1997.

669. SHAHANI BT AND YOUNG RR. Human flexor reflexes. *J Neurol Neurosurg Psychiat* 34: 616–627, 1971.

670. SHARMA KR, KENT-BRAUN J, MYNHIER MA, WEINER MW, AND MILLER RG. Excessive muscular fatigue in the postpoliomyelitis syndrome. *Neurology* 44: 642–646, 1994.

671. SHARPE MH AND MILES TS. Position sense at the elbow after fatiguing contractions. *Exp Brain Res* 94: 179–182, 1993.

672. SHEEAN GL, MURRAY NM, ROTHWELL JC, MILLER DH, AND THOMPSON AJ. An electrophysiological study of the mechanism of fatigue in multiple sclerosis. *Brain* 120: 299–315, 1997.

673. SHEPHARD RJ, BOUHLEL E, VANDEWALLE H, AND MONOD H. Muscle mass as a factor limiting physical work. *J Appl Physiol* 64: 1472–1479, 1988.

674. SIMILOWSKI T, YAN S, GAUTHIER AP, MACKLEM PT, AND BELLEMARE F. Contractile properties of the human diaphragm during chronic hyperinflation. *N Engl J Med* 325: 917–923, 1991.

675. SIMONE DA, MARCHETTINI P, CAPUTI G, AND OCHOA JL. Identification of muscle afferents subserving sensation of deep pain in humans. *J Neurophysiol* 72: 883–889, 1994.

676. SINKJAER T, ANDERSEN JB, LADOUCEUR M, CHRISTENSEN LOD, AND NIELSEN JB. Major role for sensory feedback in soleus EMG activity in the stance phase of walking in man. *J Physiol (Lond)* 523: 817–827, 2000.

677. SINOWAY LI, HILL JM, PICKAR JG, AND KAUFMAN MP. Effects of contraction and lactic acid on the discharge of group III muscle afferents in cats. *J Neurophysiol* 69: 1053–1059, 1993.

678. SIRIN AV AND PATLA AE. Myoelectric changes in the triceps surae muscles under sustained contractions. Evidence for synergism. *Eur J Appl Physiol* 56: 238–244, 1987.

679. SKINNER HB, WYATT MP, HODGDON JA, CONARD DW, AND BARRACK RL. Effect of fatigue on joint position sense of the knee. *J Orthop Res* 4: 112–118, 1986.

680. SMITH JL, HUTTON RS, AND ELDRED E. Postcontraction changes in sensitivity of muscle afferents to static and dynamic stretch. *Brain Res* 78: 193–202, 1974.

681. SMUTZ WP, KONGSAYREEPONG A, HUGHES RE, NIEBUR G, COONEY WP, AND AN KN. Mechanical advantage of the thumb muscles. *J Biomech* 31: 565–570, 1998.

682. SOHN MK, GRAVEN-NIELSEN T, ARENDT-NIELSEN L, AND SVENSSON P. Inhibition of motor unit firing during experimental muscle pain in humans. *Muscle Nerve* 23: 1219–1226, 2000.

683. SPARTO PJ, PARNIANPOUR M, REINSEL TE, AND SIMON S. The effect of fatigue on multijoint kinematics and load sharing during a repetitive lifting test. *Spine* 22: 2647–2654, 1997.

684. SPENCER JD, HAYES KC, AND ALEXANDER IJ. Knee joint effusion and quadriceps reflex inhibition in man. *Arch Phys Med Rehabil* 65: 171–177, 1984.

685. SPIELMANN JM, LAOURIS Y, NORDSTROM MA, ROBINSON GA, REINKING RM, AND STUART DG. Adaptation of cat motoneurons to sustained and intermittent extracellular activation. *J Physiol (Lond)* 464: 75–120, 1993.

686. STEENSBERG A, VAN HALL G, OSADA T, SACCHETTI M, SALTIN B, AND PEDERSEN BK. Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. *J Physiol (Lond)* 529: 237–242, 2000.

687. STEFAN K, KUNESCH E, COHEN LG, BENECKE R, AND CLASSEN J. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain* 123: 572–584, 2000.

688. STEPHENS JA, HARRISON LM, MAYSTON MJ, CARR LJ, AND GIBBS J. The sharing principle. *Prog Brain Res* 123: 419–426, 1999.

689. STERNER RL, PINCIVERO DM, AND LEPHART SM. The effects of muscular fatigue on shoulder proprioception. *Clin J Sport Med* 8: 96–101, 1998.

690. STOKES MJ, COOPER RG, AND EDWARDS RH. Normal muscle strength and fatigability in patients with effort syndromes. *Br Med J* 297: 1014–1017, 1988.

691. STOKIC DS, MCKAY WB, SCOTT L, SHERWOOD AM, AND DIMITRIJEVIC MR.

692. STROJNIK V. Muscle activation level during maximal voluntary effort. *Eur J Appl Physiol* 72: 144–149, 1995.

693. STRÜDER HK, HOLLMANN W, PLATEN P, DONIKE M, GOTZMANN A, AND WEBER K. Influence of paroxetine, branched-chain amino acids and tyrosine on neuroendocrine system responses and fatigue in humans. *Horm Metab Res* 30: 188–194, 1998.

694. STUART DG, MOSHER CC, GERLACH RL, AND REINKING RM. Mechanical arrangement and transducing properties of Golgi tendon organs. *Exp Brain Res* 14: 274–292, 1972.

695. SUTER E, HERZOG W, AND HUBER A. Extent of motor unit activation in the quadriceps muscles of healthy subjects. *Muscle Nerve* 19: 1046–1048, 1996.

696. SUTTON REEVES JT, WAGNER PD, GROVES BM, CYMERMAN A JR, MALCONIAN MK, ROCK PB, YOUNG PM, WALTER SD, AND HOUSTON CS. Operation Everest II: oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol* 64: 1309–1321, 1988.

697. SUZUKI J, TANAKA R, YAN S, CHEN R, MACKLEM PT, AND KAYSER B. Assessment of abdominal muscle contractility, strength, and fatigue. *Am J Respir Crit Care Med* 159: 1052–1060, 1999.

698. TAKAISHI T, YASUDA Y, ONO T, AND MORITANI T. Optimal pedaling rate estimated from neuromuscular fatigue for cyclists. *Med Sci Sports Exercise* 28: 1492–1497, 1996.

699. TANII K, SADOYAMA T, SANJO Y, AND KOGI K. Appearance of effort-depending changes in static local fatigue. *J Human Ergol* 2: 31–45, 1973.

700. TAYLOR J, BUTLER JE, AND GANDEVIA SC. Magnetic stimulation of the descending tracts in human subjects. *Proc Aust Neurosci Soc* 11: 48P, 2000.

701. TAYLOR JL, ALLEN GM, BUTLER JE, AND GANDEVIA SC. Effect of contraction strength on responses in biceps brachii and adductor pollicis to transcranial magnetic stimulation. *Exp Brain Res* 117: 472–478, 1997.

702. TAYLOR JL, ALLEN GM, BUTLER JE, AND GANDEVIA SC. Supraspinal fatigue during intermittent maximal voluntary contractions of the human elbow flexors. *J Appl Physiol* 89: 305–313, 2000.

703. TAYLOR JL, BUTLER JE, ALLEN GM, AND GANDEVIA SC. Changes in motor cortical excitability during human muscle fatigue. *J Physiol (Lond)* 490: 519–528, 1996.

704. TAYLOR JL, BUTLER JE, AND GANDEVIA SC. Altered responses of human elbow flexors to peripheral nerve and cortical stimulation during a sustained maximal voluntary contraction. *Exp Brain Res* 127: 108–115, 1999.

705. TAYLOR JL, PETERSEN N, BUTLER JE, AND GANDEVIA SC. Ischaemia after exercise does not reduce responses of human motoneurones to cortical or corticospinal tract stimulation. *J Physiol (Lond)*. In press.

706. TERGAU F, GEESE R, BAUER A, BAUR S, PAULUS W, AND REIMERS CD. Motor cortex fatigue in sports measured by transcranial magnetic double stimulation. *Med Sci Sports Exercise* 32: 1942–1948, 2000.

707. THOMAS CK. Fatigue in human thenar muscles paralysed by spinal cord injury. *J Electromyogr Kinesiol* 7: 15–26, 1997.

708. THOMAS CK, BIGLAND-RICHIE B, AND JOHANSSON RS. Force-frequency relationships of human thenar motor units. *J Neurophysiol* 65: 1509–1516, 1991.

709. THOMAS CK, BROTON JG, AND CALANCIE B. Motor unit forces and recruitment patterns after cervical spinal cord injury. *Muscle Nerve* 20: 212–220, 1997.

710. THOMAS CK, JOHANSSON RS, AND BIGLAND-RITCHIE B. Attempts to physiologically classify human thenar motor units. *J Neurophysiol* 65: 1501–1508, 1991.

711. THOMAS CK, JOHANSSON RS, AND BIGLAND-RITCHIE B. Pattern of pulses that maximize force output from single human thenar motor units. *J Neurophysiol* 82: 3188–3195, 1999.

712. THOMAS CK, WOODS JJ, AND BIGLAND-RITCHIE B. Impulse propagation and muscle activation in long maximal voluntary contractions. *J Appl Physiol* 67: 1835–1842, 1989.

713. THOMPSON S, GREGORY JE, AND PROSKE U. Errors in force estimation can be explained by tendon organ desensitization. *Exp Brain Res* 79: 365–372, 1990.

714. TÖRK I AND HORNUNG JP. Raphe nuclei and the serotonergic system. The intracortical inhibition of lower limb motor-evoked potentials after paired transcranial magnetic stimulation. *Exp Brain Res* 117: 437–443, 1997.

In: *The Human Nervous System*, edited by Paxinos G. San Diego, CA: Academic, 1990, p. 1011–1022.

715. Triggs WJ, Cros D, MacDonell RA, Chiappa KH, Fang J, and Day BJ. Cortical and spinal motor excitabiity during the transcranial magnetic stimulation silent period in humans. *Brain Res* 628: 39–48, 1993.

716. Trott JR. The effect of low amplitude muscle vibration on the discharge of fusimotor neurones in the decerebrate cat. *J Physiol (Lond)* 255: 635–649, 1976.

717. Tsuboi T, Sato T, Egawa K, and Miyazaki M. The effect of fatigue caused by electrical induction or voluntary contraction on Ia inhibition in human soleus muscle. *Neurosci Lett* 197: 72–74, 1995.

717a. Turker KS and Powers RK. Effects of large excitatory and inhibitory inputs on motoneuron discharge rate and probability. *J Neurophysiol* 82: 829–840, 1999.

718. Ugawa Y, Rothwell JC, Day BL, Thompson PD, and Marsden CD. Percutaneous electrical stimulation of corticospinal pathways at the level of the pyramidal decussation in humans. *Ann Neurol* 29: 418–427, 1991.

719. Ugawa Y, Uesaka Y, Terao Y, Hanajima R, and Kanazawa I. Magnetic stimulation of the descending and ascending tracts at the foramen magnum level. *Electroencephalogr Clin Neurophysiol* 105: 128–131, 1997.

720. Uncini A, Treviso M, Di Muzio A, Simone P, and Pullman S. Physiological basis of voluntary activity inhibition induced by transcranial cortical stimulation. *Electroencephalogr Clin Neurophysiol* 89: 211–220, 1993.

721. Upton AR, McComas AJ, and Sica RE. Potentiation of "late" responses evoked in muscles during effort. *J Neurol Neurosurg Psychiat* 34: 699–711, 1971.

722. Urbach D and Awiszus F. Effects of transcranial magnetic stimulation on results of the twitch interpolation technique. *Muscle Nerve* 23: 1125–1128, 2000.

723. Vagg R, Mogyoros I, Kiernan MC, and Burke D. Activity-dependent hyperpolarization of human motor axons produced by natural activity. *J Physiol (Lond)* 507: 919–925, 1998.

724. Vallbo AB. Slowly adapting muscle receptors in man. *Acta Physiol Scand* 78: 315–333, 1970.

725. Vallbo AB. Muscle spindle response at the onset of isometric voluntary contractions in man. Time difference between fusimotor and skeletomotor effects. *J Physiol (Lond)* 218: 405–431, 1971.

726. Vallbo AB. Afferent discharge from human muscle spindles in non-contracting muscles. Steady state impulse frequency as a function of joint angle. *Acta Physiol Scand* 90: 303–318, 1974.

727. Vallbo AB. Human muscle spindle discharge during isometric voluntary contractions. Amplitude relations between spindle frequency and torque. *Acta Physiol Scand* 90: 319–336, 1974.

728. Van Boxtel A. Differential effects of low-frequency depression, vibration-induced inhibition, and posttetanic potentiation on H-reflexes and tendon jerks in the human soleus muscle. *J Neurophysiol* 55: 551–568, 1986.

729. Van Cutsem M, Duchateau J, and Hainaut K. Changes in single motor unit behaviour contribute to the increase in contraction speed after dynamic training in humans. *J Physiol (Lond)* 513: 295–305, 1998.

730. Vander Linden DW, Kukulka CG, and Soderberg GL. The effect of muscle length on motor unit discharge characteristics in human tibialis anterior muscle. *Exp Brain Res* 84: 210–218, 1991.

731. Vandervoort AA and McComas AJ. Contractile changes in opposing muscles of the human ankle joint with aging. *J Appl Physiol* 61: 361–367, 1986.

732. Vandervoort AA, Quinlan J, and McComas AJ. Twitch potentiation after voluntary contraction. *Eur J Neurol* 81: 141–152, 1983.

733. Vandervoort AA, Sale DG, and Moroz J. Comparison of motor unit activation during unilateral and bilateral leg extension. *J Appl Physiol* 56: 46–51, 1984.

734. Vandervoort AA, Sale DG, and Moroz JR. Strength-velocity relationship and fatiguability of unilateral versus bilateral arm extension. *Eur J Appl Physiol* 56: 201–205, 1987.

735. Van Hall G, Raaymakers JSH, Saris WHM, and Wagenmakers AJM. Ingestion of branched-chain amino acids and tryptophan during sustained exercise in man: failure to affect performance. *J Physiol (Lond)* 486: 789–794, 1995.

736. Van Keulen L. Autogenetic recurrent inhibition of individual spinal motoneurones of the cat. *Neurosci Lett* 21: 297–300, 1981.

737. Van Zuylen EJ, Gielen CC, and Denier Van Der Gon JJ. Coordination and inhomogeneous activation of human arm muscles during isometric torques. *J Neurophysiol* 60: 1523–1548, 1988.

738. Varnier M, Sarto P, Martines D, Lora L, Carmignoto F, Leese G, and Naccarato R. Effect of infusing branched-chain amino acid during incremental exercise with reduced muscle glycogen content. *Eur J Appl Physiol* 69: 26–31, 1994.

739. Veasey SC, Fornal CA, Metzler CW, and Jacobs BL. Response of serotonergic caudal raphe neurons in relation to specific motor activities in freely moving cats. *J Neurosci* 15: 5346–5359, 1995.

740. Veasey SC, Fornal CA, Metzler CW, and Jacobs BL. Single-unit responses of serotonergic dorsal raphe neurons to specific motor challenges in freely moving cats. *Neuroscience* 79: 161–169, 1997.

741. Voigt M, Jakobsen J, and Sinkjaer T. Non-noxious stimulation of the glenohumeral joint capsule elicits strong inhibition of active shoulder muscles in conscious human subjects. *Neurosci Lett* 254: 105–108, 1998.

742. Vollestad NK, Sejersted I, and Saugen E. Mechanical behavior of skeletal muscle during intermittent voluntary isometric contractions in humans. *J Appl Physiol* 83: 1557–1565, 1997.

743. Vollestad NK, Sejersted OM, Bahr R, Woods JJ, and Bigland-Ritchie B. Motor drive and metabolic responses during repeated submaximal contractions in humans. *J Appl Physiol* 64: 1421–1427, 1988.

744. Von Giesen HJ, Roick H, and Benecke R. Inhibitory actions of motor cortex following unilateral brain lesions as studied by magnetic brain stimulation. *Exp Brain Res* 99: 84–96, 1994.

745. Wall PD and Woolf CJ. Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. *J Physiol (Lond)* 356: 443–456, 1984.

746. Waller AD. *An Introduction to Human Physiology*. London: Londmans, Green, 1891.

747. Walmsley B, Graham B, and Nicol MJ. Serial E-M and simulation study of presynaptic inhibition along a group of Ia collateral in the spinal cord. *J Neurophysiol* 74: 616–623, 1995.

747a. Wang L-Y and Kaczmarek LK. High-frequency firing helps replenish the readily releasable pool of synaptic vesicles. *Nature* 394: 384–388, 1998.

748. West JB, Boyer SJ, Graber DJ, Hackett PH, Maret KH, Milledge JS, Peters RMJ, Pizzo CJ, Samaja M, and Sarnquist FH. Maximal exercise at extreme altitudes on Mount Everest. *J Appl Physiol* 55: 688–698, 1983.

749. Westerblad H and Lannergren J. Slowing of relaxation during fatigue in single mouse muscle fibres. *J Physiol (Lond)* 434: 323–336, 1991.

749a. Westgaard RH and De Luca CJ. Motor unit substitution in long duration contractions of human trapezius muscle. *J Neurophysiol* 82: 501–504, 1999.

750. Westing SH, Seger JY, and Thorstensson A. Effects of electrical stimulation on eccentric and concentric torque-velocity relationships during knee extension in man. *Acta Physiol Scand* 140: 17–22, 1990.

751. Willis D. Dorsal root potentials and dorsal root reflexes: a double-edged sword. *Exp Brain Res* 124: 395–421, 1999.

752. Wilson LR, Gandevia SC, and Burke D. Discharge of human muscle spindle afferents innervating ankle dorsiflexors during target isometric contractions. *J Physiol (Lond)* 504: 221–232, 1997.

753. Wilson LR, Gandevia SC, and Burke D. Increased resting discharge of human spindle afferents following voluntary contractions. *J Physiol (Lond)* 488: 833–840, 1995.

754. Wilson SA, Lockwood RJ, Thickbroom GW, and Mastaglia FL. The muscle silent period following transcranial magnetic cortical stimulation. *J Neurol Sci* 114: 216–222, 1993.

755. Wilson SA, Thickbroom GW, and Mastaglia FL. Topography of excitatory and inhibitory muscle responses evoked by transcranial magnetic stimulation in the human motor cortex. *Neurosci Lett* 154: 52–56, 1993.

756. Wilson WM and Maughan RJ. Evidence for a possible role of 5-hydroxytryptamine in the genesis of fatigue in man: administration of paroxetine, a 5-HT re-uptake inhibitor, reduces the capacity to perform prolonged exercise. *Exp Physiol* 77: 921–924, 1992.

757. WINDHORST U. *How Brain-like Is the Spinal Cord?* Berlin: Springer-Verlag, 1988, p. 334.

758. WINDHORST U AND BOORMAN G. Overview: potential role of segmental motor circuitry in muscle fatigue. *Adv Exp Med Biol* 384: 241–258, 1995.

759. WINDHORST U, BOORMAN G, AND KIRMAYER D. Renshaw cells and recurrent inhibition: comparison of responses to cyclic inputs. *Neuroscience* 67: 225–233, 1995.

760. WINDHORST U, KIRMAYER D, SOIBELMAN F, MISRI A, AND ROSE R. Effects of neurochemically excited group III-IV muscle afferents on motoneuron afterhyperpolarization. *Neuroscience* 76: 915–929, 1997.

761. WINDHORST U AND KOKKOROYIANNIS T. Interaction of recurrent inhibitory and muscle spindle afferent feedback during muscle fatigue. *Neuroscience* 43: 249–259, 1991.

762. WINDHORST U, MEYER-LOHMANN J, KIRMAYER D, AND ZOCHODNE D. Renshaw cell responses to intra-arterial injection of muscle metabolites into cat calf muscles. *Neurosci Res* 27: 235–247, 1997.

763. WIRTSHAFTER D, STRATFORD TR, AND PITZER MR. Studies on the behavioral activation produced by stimulation of GABA$_B$ receptors in the median raphe nucleus. *Behav Brain Res* 59: 83–93, 1993.

764. WOLPAW JR. Operant conditioning of primate spinal reflexes: the H-reflex. *J Neurophysiol* 57: 443–459, 1987.

765. WOOD L, FERRELL WR, AND BAXENDALE RH. Pressures in normal and acutely distended human knee joints and effects on quadriceps maximal voluntary contractions. *Q J Exp Physiol* 73: 305–314, 1988.

766. WOOD SA, GREGORY JE, AND PROSKE U. The influence of muscle spindle discharge on the human H reflex and the monosynaptic reflex in the cat. *J Physiol (Lond)* 497: 279–290, 1996.

767. WOODS JJ, FURBUSH F, AND BIGLAND-RITCHIE B. Evidence for a fatigue-induced reflex inhibition of motoneuron firing rates. *J Neurophysiol* 58: 125–137, 1987.

768. WRIGHT JR, MCCLOSKEY DI, AND FITZPATRICK RC. Effects of muscle perfusion pressure on fatigue and systemic arterial pressure in human subjects. *J Appl Physiol* 86: 845–851, 1999.

769. WU T, SOMMER M, TERGAU F, AND PAULUS W. Lasting influence of repetitive transcranial magnetic stimulation on intracortical excitability in human subjects. *Neurosci Lett* 287: 37–40, 2000.

770. YAKSH TL. Pharmacology and mechanisms of opioid analgesic activity. *Acta Anaesthiol Scand* 41: 94–111, 1997.

771. YANG JF, STEIN RB, AND JAMES KB. Contribution of peripheral afferents to the activation of the soleus muscle during walking in humans. *Exp Brain Res* 87: 679–687, 1991.

772. YOUNG K, MCDONAGH MJ, AND DAVIES CT. The effects of two forms of isometric training on the mechanical properties of the triceps surae in man. *Pflügers Arch* 405: 384–388, 1985.

773. YUE G AND COLE KJ. Strength increases from the motor program: comparison of training with maximal voluntary and imagined muscle contractions. *J Neurophysiol* 67: 1114–1123, 1992.

774. YUE GH, BILODEAU M, HARDY PA, AND ENOKA RM. Task-dependent effect of limb immobilization on the fatigability of the elbow flexor muscles in humans. *Exp Physiol* 82: 567–592, 1997.

775. ZAJAC FE. Muscle and tendon: properties, models, scaling, and application to biomechanics and motor control. *Crit Rev Biomed Eng* 17: 359–411, 1989.

776. ZAJAC FE AND YOUNG JL. Properties of stimulus trains producing maximum tension-time area per pulse from single motor units in medial gastrocnemius muscle of the cat. *J Neurophysiol* 43: 1206–1220, 1980.

777. ZANETTE G, BONATO C, POLO A, TINAZZI M, MANGANOTTI P, AND FIASCHI A. Long-lasting depression of motor-evoked potentials to transcranial magnetic stimulation following exercise. *Exp Brain Res* 107: 80–86, 1995.

778. ZEDKA M, PROCHAZKA A, KNIGHT B, GILLARD D, AND GAUTHIER M. Voluntary and reflex control of human back muscles during induced pain. *J Physiol (Lond)* 520: 591–604, 1999.

779. ZIEMANN U, CHEN R, COHEN LG, AND HALLETT M. Dextromethorphan decreases the excitability of the human motor cortex. *Neurology* 51: 1320–1324, 1998.

780. ZIEMANN U, ISHII K, BORGHERESI A, YASEEN Z, BATTAGLIA F, HALLETT M, CINCOTTA M, AND WASSERMANN EM. Dissociation of the pathways mediating ipsilateral and contralateral motor-evoked potentials in human hand and arm muscles. *J Physiol (Lond)* 518: 895–906, 1999.

781. ZIEMANN U, TERGAU F, WASSERMANN EM, WISCHER S, HILDEBRANDT J, AND PAULUS W. Demonstration of facilitatory I wave interaction in the human motor cortex by paired transcranial magnetic stimulation. *J Physiol (Lond)* 511: 181–190, 1998.

781a. ZIJDEWIND I AND KERNELL D. Bilateral interactions during contractions of intrinsic hand muscles. *J Neurophysiol* 85: 1907–1913, 2001.

782. ZIJDEWIND I, KERNELL D, AND KUKULKA CG. Spatial differences in fatigue-associated electromyographic behaviour of the human first dorsal interosseus muscle. *J Physiol (Lond)* 483: 499–509, 1995.

783. ZIJDEWIND I, ZWARTS MJ, AND KERNELL D. Influence of a voluntary fatigue test on the contralateral homologous muscle in humans? *Neurosci Lett* 253: 41–44, 1998.

784. ZIJDEWIND I, ZWARTS MJ, AND KERNELL D. Fatigue-associated changes in the electromyogram of the human first dorsal interosseous muscle. *Muscle Nerve* 22: 1432–1436, 1999.

785. ZWARTS MJ AND ARENDT-NIELSEN L. The influence of force and circulation on average muscle fibre conduction velocity during local muscle fatigue. *Eur J Appl Physiol* 58: 278–283, 1988.

786. ZYTNICKI D, LAFLEUR J, HORCHOLLE-BOSSAVIT G, LAMY F, AND JAMI L. Reduction of Ib autogenetic inhibition in motoneurons during contractions of an ankle extensor muscle in the cat. *J Neurophysiol* 64: 1380–1389, 1990.