

Skeletal Muscle Physiology

OVERVIEW

This chapter describes the way that muscle structures produce the desired function. Under the general classification of “physiology,” the chapter has been divided into three parts. First, we discuss the activation and contraction sequence of muscle, along with some functional consequences of this scheme. Next, the two basic mechanical properties of muscle—the length-tension and force-velocity properties—are highlighted. The basis for all muscle contraction is presented as well as the details of the cross-bridge cycle. The manner in which architecture affects these mechanical properties is included. Finally, the topics of muscle fiber types and motor units are presented, which enables discussion of recruitment, locomotion, and fatigue.

INTRODUCTION

In this chapter, anatomy meets physiology. In other words, the rationale for the physical arrangement of the various muscle components will become apparent. An understanding of muscle physiology is predicated on a good understanding of muscle macro- and microanatomy. This chapter represents the payoff for having waded through the previous one. It should be noted that anatomic studies are rarely performed in isolation of physiologic studies and *vice versa*. In fact, anatomists routinely refer to physiologic data in describing the significance of their findings, and physiologists routinely refer to anatomic studies in proposing mechanisms for their observations. Thus the distinction between muscle anatomy and physiology is often one of orientation. Significant cross-referencing between muscle anatomic and physiologic studies will be required as we continue our discussion of skeletal muscle structure and function.

PART 1: FIBER ACTIVATION

EXCITATION-CONTRACTION COUPLING

Our discussion of skeletal muscle physiology begins with the process of muscle activation itself. It is well known that peripheral nerves innervate

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skeletal muscles and that neural activation precedes muscle contraction. The precise process by which this neural activation signal culminates in muscle contraction is known as excitation-contraction coupling, or EC coupling (Figure 2.1). EC coupling is viewed as a sequence of events, each of which is necessary for contraction to occur. If any single step of EC coupling is impaired, muscle contraction does not occur normally. This impairment might be interpreted as muscle paralysis or fatigue. However, such a general classification is not useful unless the underlying cause is known (Ebashi *et al.*, 1980).

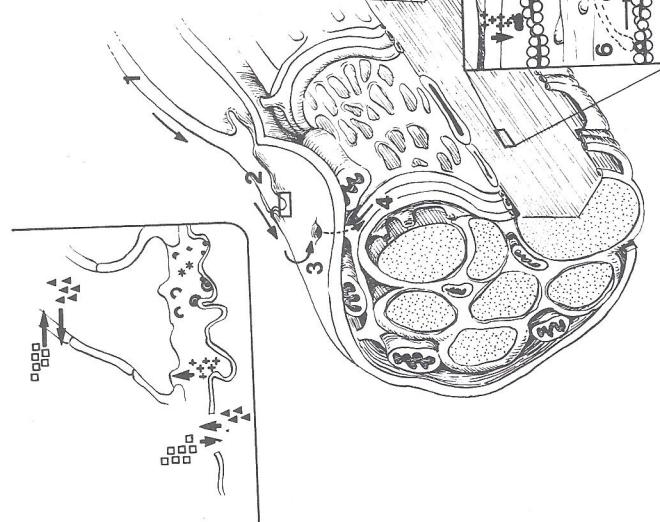


Figure 2.1. Sequence of events in excitation-contraction coupling of a nervous impulse to muscle contraction. **1**, Action potential conducted by nerve to muscle (squares represent Na^+ ions entering nerve, triangles represent K^+ ions leaving nerve to conduct the action potential). **2**, Nervous impulse transmitted across neuromuscular junction to muscle fiber (crosses represent ACh , and asterisks represent the entering nerve end). **3**, Action potential conducted along fiber surface. **4**, Enzyme acetylcholinesterase degrading ACh . **5**, Action potential conducted deep into fiber via the T-system. **6**, Cross-bridge produces force and filament sliding. **7**, Cross-bridge relax due to lack of Ca^{++} filament activation. **8**, Ca^{++} released from SR to activate actin filament. **9**, Ca^{++} pumped back into SR.

Action Potential—the First Step

The first step in the EC coupling chain is the generation of the peripheral nerve action potential. The action potential results from depolarization of the peripheral nerve axon that innervates the muscle. In addition to a signal from the CNS, the axon may be depolarized in a number of ways, including trauma to the peripheral nerve or application of an external electrical stimulating device. In any case, the resulting action potentials that propagate down the peripheral nerve are identical. The action potential arrives at the neuromuscular junction, the interface between muscle and nerve. The neuromuscular junction is itself a complex structure. The nerve ends in a small indentation on the muscle fiber surface, known as the synaptic cleft.

Acetylcholine Release—the Neurotransmitter

The end of the nerve contains packets of the neurotransmitter acetylcholine (ACh), which causes muscle fiber excitation. ACh is synthesized by the cell body of the motor nerve and transported down the axon where it is stored at nerve endings for later use. Following nerve depolarization, a quantum or unit of ACh is released into the small space between the muscle and nerve, the synaptic cleft (Figure 2.1). ACh then diffuses across the synaptic cleft and binds to the ACh receptor, which is integrated into the muscle membrane (refer to the discussion of synaptogenesis in Chapter 1, page 12). ACh binding results in depolarization of the muscle fiber sarcolemma and an action potential that propagates from the neuromuscular junction outward in all directions.

Transverse Tubular System and Sarcoplasmic Reticulum Involvement in Excitation-Contraction Coupling

At various intervals along the fiber surface, the action potential encounters invaginations of the sarcolemma that extend into the fiber—the transverse tubular system (T-system; Figure 2.1; Peachey and Franzini-Armstrong, 1983). The action potential is conducted deep into the fiber by the T-system. The interface between the “outside world” of the muscle fiber and the “inside world” of the contractile apparatus occurs at the next step where the T-system signals the sarcoplasmic reticulum (SR) to release calcium. The precise mechanism for this communication is not completely understood. However, it is believed that the SR feet, which anchor the terminal region of the SR to the T-system, are involved in some way. An important observation is that the lumen of the T-system contains *extracellular* fluid while the lumen of the SR contains *intracellular* fluid. Thus extracellular fluid is actually contained deep within the muscle fiber!

Calcium Release Results in Muscle Contraction

With the calcium signal, the actin-myosin calcium ion in the region of the myofilaments (Figure 3.1) this release process is extremely fast. The consequence of the activation process (*i.e.*, the muscle twitch) lies far behind the activation process itself. For example, let us suppose that the entire EC coupling process requires 100 msec. If, after the first impulse, we deliver a second impulse before 100 msec have elapsed, the muscle will be signaled to contract before it has fully relaxed. In other words, the second impulse will be superimposed somewhat on part of the cycle initiated by the first one, resulting in summation. Because the two events have summated due to their relative temporal relationship, this process is referred to as temporal summation.

The physiologic effects of temporal summation are quite dramatic. One effect of the first stimulus is to cause the contracting sarcomeres to "stretch out" the passive structures that lie in series with them (*e.g.*, tendons or passive sarcomeres). When the second impulse "arrives at the scene," it is not required to stretch out any of these structures and causes a greater force to be generated at the ends of the muscle fiber. Thus two impulses that are delivered to a muscle fiber and separated by only about 50 msec result in more force than the same two pulses delivered to the muscle but separated by more time. If a "train" of such pulses (say, 50 pulses in a row) is delivered to the muscle, separated in time by different amounts, this results in a tetanic contraction, and the resulting force is quite different (Figure 2.2). Higher forces result when stimuli are delivered at higher frequencies since there is less time for relaxation (frequency = 1/interpulse interval; low intervals correspond to high frequencies). Notice, in Figure 2.2, that at relatively low frequencies (*e.g.*, 10 Hz), the contractile record almost completely relaxes between successive pulses. This is referred to as an *unfused contraction*, because it is still possible to distinguish individual contractile events within the force record. However, note that as stimulation frequency increases, the tetanic record becomes more fused, until at very high frequencies (*e.g.*, 100 Hz), the contractile record becomes a *fused contraction*. A fused tetanic contraction appears as such because the repeated calcium release onto the myofilaments is much faster than the rate at which the myofilaments can relax.

1. Generation of the peripheral nerve action potential
2. Release of ACh from the nerve terminal
3. Binding of ACh to the muscle fiber ACh receptor
4. Depolarization of the sarcolemma after ACh receptor binding
5. Conduction of the action potential into the fiber by the T-system
6. Signaling of the SR by the T-system to release calcium
7. Binding of calcium to the regulatory protein troponin, permitting actin-myosin interaction
8. Force generation resulting from actin-myosin interaction
9. Pumping of calcium back into the SR when neural activation ceases, resulting in inhibition of actomyosin interaction and muscle relaxation

TEMPORAL SUMMATION

A well-known muscle contractile property follows directly from an understanding of the EC coupling sequence presented above. First, it should be obvious that the time required for activation, contraction, and then relaxation to

occur is finite. That is, excitation (with accompanying calcium release) is relatively rapid (on the order of about 5 msec) while contraction and relaxation are relatively slow (on the order of about 100 msec). The mechanical consequence of the activation process (*i.e.*, the muscle twitch) lies far behind the activation process itself. For example, let us suppose that the entire EC coupling process requires 100 msec. If, after the first impulse, we deliver a second impulse before 100 msec have elapsed, the muscle will be signaled to contract before it has fully relaxed. In other words, the second impulse will be superimposed somewhat on part of the cycle initiated by the first one, resulting in summation. Because the two events have summated due to their relative temporal relationship, this process is referred to as temporal summation.

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Rate Coding: The Physiologic Significance of Temporal Summation

The variation in force obtained by altering activation frequency is known as frequency or rate coding. Because muscle force varies as a function of activation frequency, this is one method the CNS can use to alter muscle force. If high forces are required at the periphery, the CNS can deliver high-frequency pulses. Conversely, if only low forces are required, the CNS can deliver low-frequency

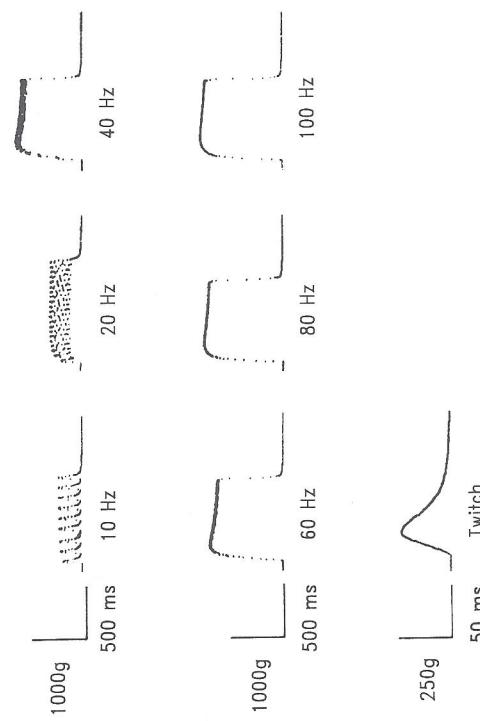


Figure 2.2. Contractile records from a rabbit tibialis anterior muscle demonstrating fusion of mechanical twitches as stimulation frequency increases (temporal summation). Note different tension calibration bars for tetani (upper panels) and twitch (lower panel). (From Lieber RL, Smith DE, Hargens AR. Real-time acquisition and data analysis of skeletal muscle contraction in a multi-user environment. *Comp Prog Biomed* 1986;29:259–265.)

varies with its starting length (see review by Podolsky and Shoenberg, 1983). The isometric length-tension curve is generated by maximally stimulating a skeletal muscle at a variety of discrete lengths and measuring the tension generated at each length. When maximum tetanic tension at each length is plotted against length, a relationship such as that shown in Figure 2.3 is usually obtained. While a general description of this relationship was established early in the history of biologic science, the precise structural basis for the length-tension relationship in skeletal muscle was not elucidated until the sophisticated mechanical experiments of the early 1960s were performed. It was these experiments that defined the precise relationship between myofilament overlap and tension generation, which we refer to today as the length-tension relationship. In its most basic form, the length-tension relationship states that tension generation in skeletal muscle is a direct function of the magnitude of overlap between the actin and myosin filaments.

Sarcomere Length-Tension Relationship

In the late 1950s and early 1960s, Andrew Huxley, Albert Gordon, and Fred Julian, working in England (Gordon *et al.*, 1966), and Paul Edman, working in

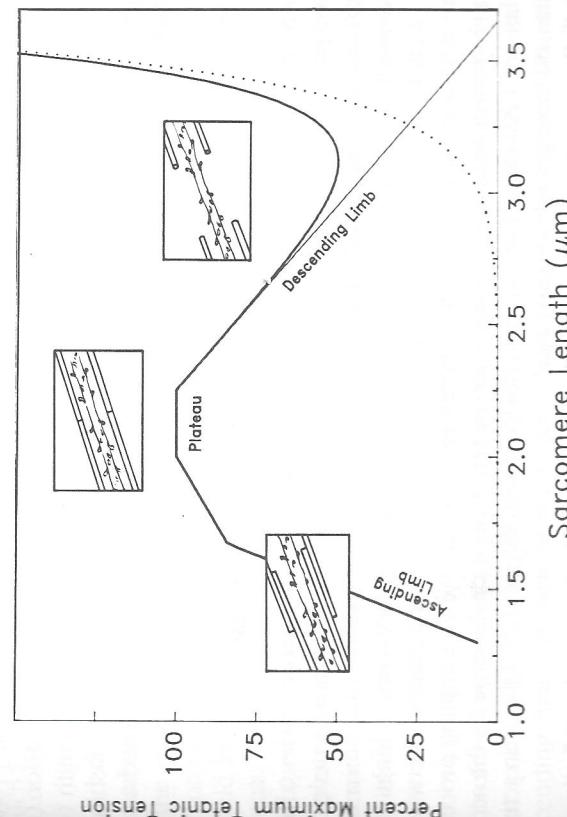


Figure 2.3. The sarcomere length-tension curve for frog skeletal muscle obtained using sequential isometric contractions in single muscle fibers. Insets show schematic arrangement of myofilaments in different regions of the length-tension curve. Dotted line represents passive muscle tension.

pulses. Of course, this type of effect is very difficult to demonstrate directly. In a very technical procedure involving single motor unit recording, ventral root recording, and muscle tension recording *in situ* during locomotion (as well as some fancy postexperimental data processing), Andy Hoffer and colleagues were able to demonstrate what they interpreted to be rate coding, which occurred during normal locomotion (Hoffer *et al.*, 1981 and 1987). We shall see, however, that the control of muscle force by the CNS is very much more sophisticated than this. The area of study that includes the control of muscles by the nervous system is known as neuromotor control (Binder and Mendell, 1990), which will be discussed in the chapters to follow. Suffice it to say for the present that muscle and nerve properties are matched in a very sophisticated fashion in order to accomplish a particular task. Rate coding is only one of the methods by which this match is accomplished.

PART 2: SKELETAL MUSCLE MECHANICS

LENGTH-TENSION RELATIONSHIP: ISOMETRIC MUSCLE CONTRACTION

Since the late 1800s, it has been known that the force developed by a muscle during isometric contraction (*i.e.*, when the muscle is not allowed to shorten)

Sweden (Edman, 1966), defined what might be one of the most explicit structure-function relationships in all of biology. It was obvious to these investigators that in order to determine the detailed structural basis for the length-tension relationship, isolated, intact single skeletal muscle fibers would be required. The muscle used was that of the frog since a great deal was known at the time about its structure, and intact single fibers could be isolated. Picture this: The experiments I am about to describe were performed on tissue (single muscle cells) approximately 8 mm long and 75 μm in diameter! That's small!

Andrew Huxley (who by this time had already received the Nobel prize with Alan Hodgkin for determining the mechanism of the nerve action potential) invented a mechanical version of his voltage clamp apparatus that was used in the nerve studies. This apparatus was designed to keep a small segment of the fiber at a constant length (and therefore keep a region of the fiber at a constant sarcomere length). This enabled him to make a unique correlation between muscle tension and sarcomere length. It was much easier said than done because it turned out that "isometric" force generation in the single fiber was anything but isometric! Sarcomeres in the end region of the fiber tended to stretch sarcomeres in the central region, and thus the apparatus Huxley developed was absolutely critical.

The results of the classic experiments by Gordon, Huxley, and Julian (1966) are summarized in Figure 2.3. In this figure, muscle relative tetanic tension (as a percentage of maximum) is plotted as a function of sarcomere length (in μm). This was one case where anatomy met physiology in dramatic fashion, because knowledge of the precise anatomic lengths of the myosin and actin filaments was crucial for understanding the basis of this relationship.

did tension slowly increase? Over the range of sarcomere lengths from 2.2–3.65 μm , as sarcomere length decreases, the number of cross-bridges between actin and myosin increases, resulting in increased force. This region of the length-tension curve is known as the descending limb.

Plateau Region of the Length-Tension Curve

As sarcomere length changed from 2.0 μm to 2.2 μm , muscle force remained constant. Again, this was a direct result of thick filament structure. Recall from Chapter 1 that the myosin filament is a polymeric arrangement of myosin molecules arranged in an antiparallel fashion. Because many myosin "backbones" (the light meromyosin portion of the myosin molecules) come together in the center of the myosin filament, there exists a bare region of the myosin molecule that is devoid of cross-bridges. You guessed it—the length of the bare region was 0.2 μm ! Thus while sarcomere length shortening over the range 2.2–2.0 μm results in greater filament overlap, it does not result in increased force generation since no additional cross-bridge connections are made. The region of the length-tension curve over which length change results in no change in force is known as the plateau region. The maximum tetanic tension of the muscle in this region is abbreviated P_O . The length at which P_O is attained is known as optimal length (L_O).

Ascending Limb of the Length-Tension Curve

At a sarcomere length of 2.0 μm , notice that the actin filaments from one side of the sarcomere juxtapose the actin filaments from the opposite side of the sarcomere (Figure 2.3). It might be predicted that shortening past this point would be impossible. However, as sarcomere length decreases below the plateau region, actin filaments from one side of the sarcomere double overlap with the actin filaments on the opposite side of the sarcomere. That is, at these lengths, actin filaments overlap both with themselves and with the myosin filament. Under these double-overlap conditions, the actin filament from one side of the sarcomere interferes with cross-bridge formation on the other side of the sarcomere, and this results in decreased muscle force output. This occurs from 2.0–1.87 μm , and this region is known as the shallow ascending limb of the length-tension curve. The word "shallow" distinguishes it from the next portion of the length-tension curve, which is known as the steep ascending limb, because at these very short lengths, the myosin filament actually begins to interfere with shortening as it abuts the sarcomere Z-disk, reducing force precipitously.

An interesting observation relative to muscle force generation at short lengths was made in the late sixties by Rüdel and Taylor (1971). They

As a muscle was highly stretched by the investigators to a sarcomere length of 3.65 μm , the muscle developed no active force. Why did the muscle develop zero force at this length? The answer lay in the observation that, since the myosin filament is 1.65 μm long and the actin filament is 2.0 μm in length, at a sarcomere length of 3.65 μm , there is no overlap (interdigitation) between the actin and myosin filaments. Therefore, although the EC coupling process might *permit* actin-myosin interaction by removing the inhibition on the actin filament, because no myosin cross-bridges are in the vicinity of the actin active sites, no force generation can occur.

As the muscle was allowed to shorten, overlap between actin and myosin was possible, and the amount of force generated by the muscle increased as sarcomere length decreased. Increasing force with decreasing sarcomere length occurred until the muscle reached a sarcomere length of 2.2 μm . Why

observed that when an intact muscle fiber was stimulated at very short sarcomere lengths (*i.e.*, sarcomere lengths on the ascending limb), electrical failure of the EC coupling apparatus occurred. This raised the question as to whether the decreased force at short sarcomere lengths was actually due to myofilament properties or was simply an electrical failure phenomenon. To address this question, Taylor and Rüdel (1970) ensured maximal single fiber activation by bathing the fiber in caffeine (which enhances calcium release from the SR) and obtained the same relationship as Gordon, Huxley, and Julian had obtained. Rick Moss repeated the experiment on small *pieces* of single muscle fibers, which were activated chemically using a calcium buffering system (Moss, 1979). Again, the same relationship was obtained. Thus while shortening deactivation as described by Rüdel and Taylor could occur, it did not seem to detract from the elegance and truth of the sarcomere length-tension relationship itself.

To summarize, the length-tension relationship states that muscle force varies as a function of sarcomere length (myofilament overlap). This is a physiologic property of the force-generating system and should not simply be viewed as an anatomic artifact. Recent experimental studies suggest that this length-tension relationship can be advantageous to the musculoskeletal torque-generating system, as will be described in Chapter 3.

Origin of the Passive Portion Length-Tension Curve

The solid line in Figure 2.3 represents the tension generated if a muscle is stretched to various lengths without stimulation. Note that near the optimal length, passive tension is almost zero. However, as the muscle is stretched to longer lengths, passive tension increases dramatically. These relatively long lengths can be attained physiologically, and therefore, passive tension can play a role in providing resistive force even in the absence of muscle activation. What is the origin of passive tension? Obviously, the structure(s) responsible for passive tension are outside of the cross-bridge itself since muscle activation is not required. Recent studies performed by Alan Magid have shown that the origin of passive muscle tension is actually *within* the myofibrils themselves. He demonstrated this by chemically stripping the sarclemma from a single muscle fiber and measuring passive tension (Magid and Law, 1985). Interestingly, a new structural protein has also been identified, which may be the source of this passive tension. The very large protein, creatively named “titin,” connects the thick myosin filaments end to end. This very large protein is also relatively fragile and thus has probably been missed in earlier studies because the laboratory techniques destroyed the protein. In addition to passively supporting the sarcomere, titin stabilizes

the myosin lattice so that high muscle forces do not disrupt the orderly hexagonal array. If titin is selectively destroyed, normal muscle contraction causes significant myofibrillar disruption (Horowitz and Podolsky, 1987).

Before leaving the length-tension relationship, let me present one caution: Never try to describe a shortening muscle using the length-tension relationship. In other words, looking at Figure 2.3, one might be tempted to predict that as a muscle shortens from a long length, force increases. However, one must remember that the length-tension relationship is strictly valid only for *isometric* contractions. Thus the curve represents the artificial connection of individual data points from isometric experiments. In order to describe *motion*, we will require an understanding of the force-velocity relationship, presented below.

FORCE-VELOCITY RELATIONSHIP: ISOTONIC MUSCLE CONTRACTION

Unlike the length-tension relationship, the force-velocity relationship does not have a precise, anatomically identifiable basis. The force-velocity relationship states that the force generated by a muscle is a function of its velocity. It can also be stated in the reverse, such that the velocity of muscle contraction is dependent on the force resisting the muscle. Historically, the force-velocity relationship was used to define the kinetic properties of the cross-bridges as well as the precise force-velocity relationship itself.

Experimental elucidation of the force-velocity relationship was first presented by A. V. Hill and Bernard Katz in their classic papers (Hill, 1938; Katz, 1939), but the current description of the force-velocity relationship has been ascribed to the physiologist A. V. Hill (see summary in Hill, 1970). Hill, in his decades of important muscle studies, generated an equation for the muscle force-velocity relationship that is still in use today. Interestingly, Andrew Huxley, in 1957, developed a theory of isotonic muscle contraction based on specific cross-bridge properties, which yielded the actual force-velocity relationship and explained the amount of energy used by a muscle during contraction at different velocities (Huxley, 1957; Hill, 1964). The beauty of this theory was its ability to explain both mechanical and energetic data.

Experimentally, the force-velocity relationship, like the length-tension relationship, is a curve that actually represents the results of many experiments plotted on the same graph. Experimentally, a muscle is stimulated maximally and allowed to shorten (or lengthen) against a constant load. The muscle velocity during shortening (or lengthening) is measured and then plotted against the resistive force. The general form of this relationship is plotted in Figure 2.4. On the horizontal axis we have plotted muscle velocity relative to maximum velocity (V_{max}) while on the vertical axis we have plotted muscle force relative to maximum force (P_O).

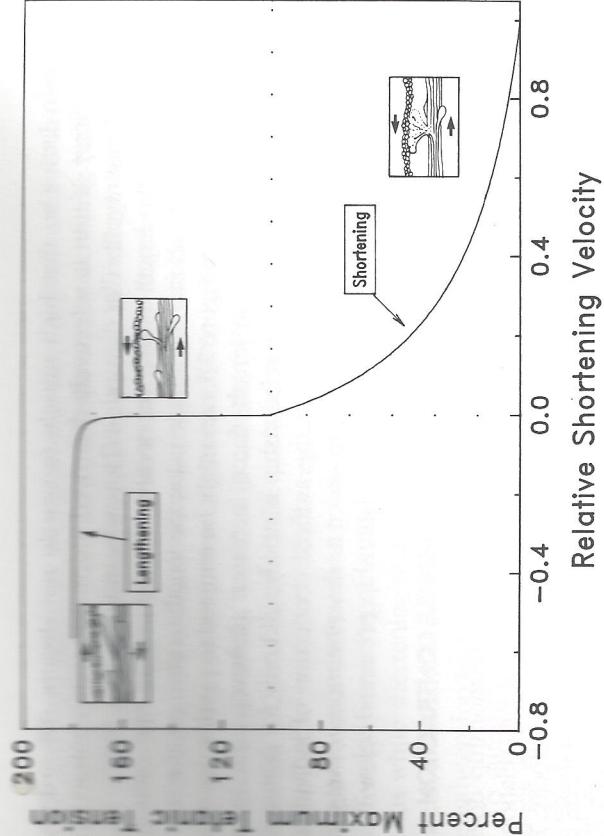


Figure 2.4. The muscle force-velocity curve for skeletal muscle obtained using sequential isotonic contractions in single fibers. Insets show schematic representation of cross-bridges. Note that force increases dramatically upon forced muscle lengthening.

Concentric Contractions—Muscle Actively Shortening

When a muscle is activated and required to lift a load that is less than its maximum tetanic tension, the muscle begins to shorten. Contractions that permit the muscle to shorten are known as concentric contractions. In concentric contractions, the force generated by the muscle is always less than the muscle's maximum (P_o). As the load the muscle is required to lift decreases, contraction velocity increases. This occurs until the muscle finally reaches its maximum contraction velocity, V_{max} . V_{max} is a parameter we can use to characterize muscle, which is related to both fiber type distribution and architecture. The mathematical form of the force-velocity relationship is a rectangular hyperbola and is given in Equation 2.1:

$$(P+a)v = b(P_o - P) \quad (2.1)$$

where a and b are constants derived experimentally (usually about 0.25), P is muscle force, P_o is maximum tetanic tension, and v is muscle velocity. This equation can be used to determine the relative muscle force that occurs as a muscle is allowed to shorten. Some of these values are presented below in Table 2.1. It is important to note that the force-velocity relationship is a steep

rectangular hyperbola. In other words, force drops off rapidly as velocity increases. For example, in a muscle that is shortening at only 1% of its maximum contraction velocity (extremely slow), tension drops by 5% relative to maximum isometric tension. Similarly, as contraction velocity increases to only 10% maximum (easily attainable physiologically), muscle force drops by 35%! Note that even when muscle force is only 50% maximum, muscle velocity is only 17% V_{max} . The take-home lesson is that as a muscle is allowed to shorten, force drops precipitously.

What is the physiologic basis of the force-velocity relationship? It has been determined that the cross-bridges between actin and myosin attach at a certain rate and detach at a certain rate (see below). These rates are referred to as *rate constants*. At any point in time, the force generated by a muscle depends on the number of cross-bridges attached. Because it takes a certain amount of time for the cross-bridges to attach (based on the rate constant of attachment), as filaments slide past one another faster and faster (*i.e.*, as the muscle shortens with increasing velocity), force decreases due to the lower number of cross-bridges attached. Conversely, as the relative filament velocity decreases (*i.e.*, as muscle velocity decreases), more cross-bridges have time to attach and to generate force, and thus force increases. This discussion is not meant to be a definitive description of the basis for the force-velocity relationship, only to provide some insight as to how cross-bridge rate constants can affect muscle force generation as a function of velocity.

Eccentric Contractions—Muscle Actively Lengthening

As the load on the muscle increases, it reaches a point where the external load is greater than the load which the muscle itself can generate. Thus the muscle is activated, but it is forced to lengthen due to the high external load.

Table 2.1.
Relative Muscle Force at Various Muscle Velocities

Relative Force	Velocity
100% P_o	0% V_{max}
95% P_o	1% V_{max}
90% P_o	2.2% V_{max}
75% P_o	6.3% V_{max}
50% P_o	16.6% V_{max}
25% P_o	37.5% V_{max}
10% P_o	64.3% V_{max}
5% P_o	79.1% V_{max}
0% P_o	100% V_{max}

This is referred to as an eccentric contraction (please remember that contraction in this context does not necessarily imply shortening!). There are two main features to note regarding eccentric contractions. First, the absolute tensions are very high relative to the muscle's maximum tetanic tension generating capacity. Second, the absolute tension is relatively independent of lengthening velocity. This suggests that skeletal muscles are very resistant to lengthening, a property which we shall see comes in very handy for many normal movement patterns (Chapter 3).

Eccentric contractions are currently under study for three main reasons: First, much of a muscle's normal activity occurs while it is actively lengthening, so that eccentric contractions are physiologically common. Second, muscle injury and soreness are selectively associated with eccentric contraction. Finally, muscle strengthening is greatest using exercises that involve eccentric contractions. These phenomena will be elaborated upon in Chapters 4 and 6.

LENGTH-TENSION-VELOCITY RELATIONSHIP

From the preceding discussion, it is apparent that muscle force changes due to changing length and/or due to changing velocity. It should not be surprising, therefore, to suggest that when muscle length *and* muscle velocity change simultaneously, it is still possible to define the muscle force produced. It should also not be surprising that while the length-tension and force-velocity relationships are useful, such isometric and isotonic conditions are almost never encountered in daily activities. However, the length-tension experiment can be viewed simply as a series of length-force-velocity experiments performed at constant (zero) velocity. Similarly, the force-velocity relationship can be viewed as a series of length-force-velocity experiments performed at constant length (L_0). The point shared between the classic force-velocity and length-tension curves is the point of maximum isometric tension (P_0) at zero velocity, resulting in a tension of P_0 . If both length and velocity simultaneously change, the result is the superposition of the two relationships.

The appearance of the length-tension-velocity relationship is shown in Figure 2.5. Don't let the three-dimensional nature of the relationship intimidate you. If the surface is viewed along one set of axes, it is simply a series of force-velocity curves at different lengths. When viewed along the other set of axes, it is simply a series of length-tension curves at different velocities. In this surface we have all possible combinations of muscle length and velocity and their resulting force. What can we conclude? For one thing, if muscle velocity is very high, force will be low no matter what the length. In other words, at high velocities, length is not very important. At low concentric

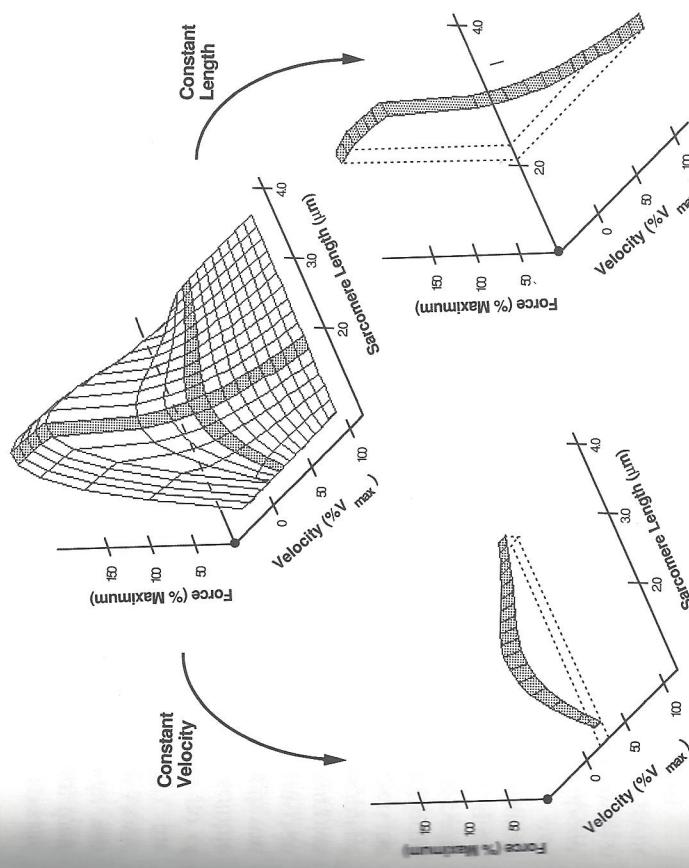


Figure 2.5. The hypothetical muscle length-force-velocity surface for skeletal muscle. Shaded regions represent a slice of the surface at either constant length or velocity. A slice of the surface at constant length is simply a force-velocity curve (compare with Figure 2.4). A slice of the surface at constant velocity is simply a length-tension curve (compare with Figure 2.3). (From Fridén J, Lieber RL. The structural and mechanical basis of exercise-induced muscle injury. *Med Sci Sports Exerc*, in press.)

velocities, muscle length becomes an important force modulator. At eccentric velocities, again muscle velocity dominates length as the determinant of force. This relationship is of course important in neuromotor control as we attempt to understand how muscle actions can be responsible for external movements observed. We will have more to say on this topic in Chapters 3 and 4.

THE CROSS-BRIDGE CYCLE

We have alluded to cyclic interaction between actin and myosin in our structural discussion in Chapter 1 and in explaining the force-velocity curve above. How were such hypotheses generated? Much of our understanding of the mechanism of muscle contraction has come in large part from excellent biochemical studies performed from the 1950s to the mid-1970s (Webb and

While both of these ultrastructural differences hold true generally, again, there is a continuum of Z-disk widths and M-band bridging pattern, so that it is not a simple task to measure a Z-disk width or observe an M-band and then to unambiguously type the fiber. It appears that in about 80% of the fibers, M-band width provides a good indication of fiber type.

THE MOTOR UNIT

Introduction

To this point, we have discussed the properties of whole skeletal muscles and their composite muscle fibers. However, during normal activities, muscle fibers are activated by their composite nerves. What determines the distribution of muscle fibers that are normally activated during a particular task? How does the nervous system determine the force generated by a particular muscle? How are muscle fiber properties tailored to the task at hand? The answer to all of these questions requires an understanding of the anatomy and physiology of the motor unit (Burke, 1981).

Motor Unit Anatomy

While the functional unit of force generation is the sarcomere (actually, the half-sarcomere due to sarcomere symmetry), the functional unit of *movement* is the motor unit. A motor unit is defined as an α -motoneuron plus the muscle fibers it innervates. Motoneurons have their cell bodies in the ventral root of the spinal cord. The cell body is responsible for synthesis of the various nutrients responsible for maintenance of neuronal integrity. The long projection that extends from the cell body is known as the axon. Each cell body projects one axon through the ventral root, and this axon extends along with many other axons projecting from other cell bodies (together these axons are known as a peripheral nerve), to innervate a particular muscle. As the axon (or neuron) approaches the muscle, it branches many times (from just a few to hundreds of branches), and normally each small terminal branch innervates a single muscle fiber (see Chapter 1 for a description for the way in which this anatomic arrangement arises).

Thus a whole muscle contains many motor units, each of which contains a single motoneuron and its composite muscle fibers. The number of muscle fibers belonging to a motor unit (*i.e.*, the innervation ratio) as well as the number of motor units within a whole muscle vary widely. We will discuss the significance of innervation ratio and motor unit number in the next section.

One might guess that all of the muscle fibers within a motor unit might be located in a cluster within the muscle. This is not the case and actually would

represent a pathologic condition. Although muscle fibers belonging to a particular motor unit are scattered over subregions of the muscle, fibers from one motor unit are interspersed among fibers of other motor units. The functional consequence of this dispersion is that the forces generated by a unit will be spread over a larger tissue area. This probably minimizes mechanical stress in focal regions within the muscle.

Identification of Muscle Fibers Belonging to a Motor Unit

A prerequisite to any discussion of motor unit properties is a general understanding of the methods used for identification of muscle fibers within a motor unit. Currently, it is not possible to stain for various motor units in the same way that is done for muscle fibers. Motor unit identification methods must identify muscle fibers that are all innervated by the same α -motoneuron. Thus one logical place to begin identifying motor units is the ventral root of the spinal cord, where the motoneurons originate.

Experimentally, the spinal cord can be surgically exposed, and the many motoneurons that exit the ventral root delicately teased apart. These ventral root filaments (actually motor neuron axons) can then be activated individually to stimulate only the fibers belonging to that unit. If the entire peripheral nerve is stimulated, many units and fibers are activated. Even when isolating ventral root filaments, it is possible to isolate, for example, two very small axons that appear to be the same axon. Thus certain tests are performed to ensure that, indeed, a single axon has been isolated.

The main test is to stimulate the filament and record the tension generated by the fibers in that unit. If a single axon were isolated, all muscle fibers belonging to the unit would contract at a single stimulation intensity. If the intensity is increased, and muscle force increases, then more than one axon has been isolated. This is because different axons have different thresholds for activation (see below). This criterion is known as the all-or-none response. If a unit demonstrates an all-or-none response, it is assumed that all of the fibers belong to a single motor unit. In an alternate method, the motoneuron cell body can be impaled by a microelectrode and stimulated to activate all terminal axon branches along with the motor unit muscle fibers.

Now that we are certain that a single axon and its composite fibers have been isolated, how do we identify those fibers? The ideal method would be to somehow "see" fibers that were actively contracting and ignore those that were not. Presently, this is not possible. However, we can trick the active fibers into making themselves visible by stimulating them in a certain way. We can't see active fibers, but we can sometimes see the results of what active fibers do. For example, as a muscle fiber is repetitively stimulated in a way that forces it to generate force anaerobically, it uses intracellular glycogen preferentially as

a fuel source. It is a straightforward procedure to stain a muscle cross-section for glycogen. Thus if we force muscle fibers to perform anaerobic metabolism, glycogen will be depleted from the activated fibers and will remain in the nonactivated fibers. This "glycogen depletion" method for isolating motor units was pioneered by Edström and Kugelberg (1968) and has been of critical importance in current motor unit studies.

It is clear that the glycogen depletion method is not without ambiguity. The most obvious problem is developing stimulation protocols that force those muscle fibers that have a choice of aerobic or anaerobic metabolism to choose anaerobic metabolism. Thus the method itself tends to select for the easily identified fibers (the FG fibers) and select against identification of the highly oxidative fibers which have little anaerobic capacity (the SO fibers). This has implications in determining, by glycogen depletion, how many fibers belong to a motor unit. Values for innervation ratio obtained by glycogen depletion would tend to overestimate the number of FG fibers and underestimate the number of SO fibers belonging to a unit.

As a side note, an alternative method is to "feed" radioactive glucose to the muscle and then stimulate it repetitively. The active cells transport the glucose into the cell, thereby labeling them. This method has the advantage that it is not necessary to selectively activate the glycolytic pathway.

Motor Unit Physiologic Properties

Many of the classic motor unit physiology experiments were performed in the late 1960s and early 1970s. The work often cited is that of Bob Burke and his colleagues (Burke, 1967 and 1981). These investigators isolated single cat hindlimb motor units (using intracellular motoneuron stimulation) and measured numerous electrophysiologic properties of the motoneuron and mechanical properties of the motor units within the whole muscle. Interestingly (and fortunately), they found that motor units could generally be classified into three categories based on several physiologic properties of the contracting fibers (Figure 2.8). In other words, motor units were most easily classified based on the physiologic properties of their muscle fibers. These physiologic properties were (a) the motor unit twitch tension, (b) the fatigability of the unit in response to a specific stimulation protocol, and (c) the behavior of the tetanic tension record at an intermediate stimulation frequency. These will be discussed sequentially.

MOTOR UNIT TWITCH TENSION

Early motor unit studies revealed that in response to a single electrical impulse, some units developed very high twitch tensions while others

developed relatively low twitch tensions and still others generated intermediate tensions. The exact basis for this difference was not clear. However, the units with low twitch tensions also tended to have slow contraction times while those with higher tensions tended to have fast contractions. This provided some of the first evidence that the different properties of motor units might have profound physiologic significance (Figure 2.13).

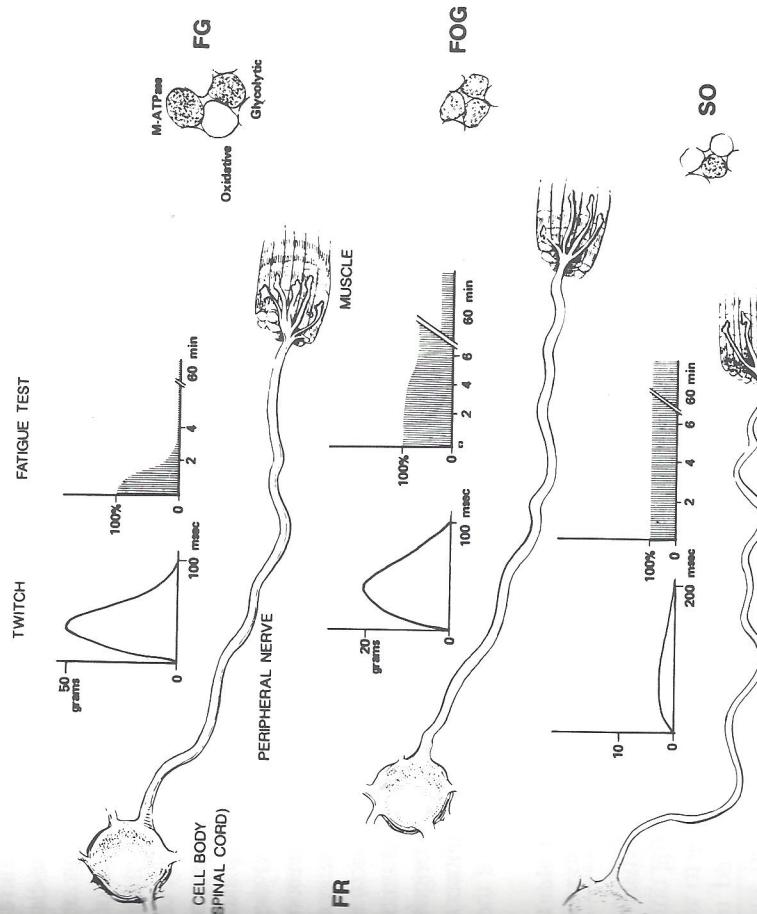


Figure 2.13. Schematic representation of the anatomic, physiologic, and histochemical properties of the three motor units types. FG units (top) have large axons that innervate many large muscle fibers. The units generate large tensions but fatigue rapidly (tension record insets). FR units (middle) have moderately sized axons that innervate many muscle fibers. The units generate moderate tensions and do not fatigue a great deal. S units (bottom) are composed of small axons that innervate a few small fibers. The units generate low forces but maintain force for a long time. Schematic diagram of histochemical staining pattern is shown on right of figure (c.f., Figure 2.11). (Adapted from Edington and Edgerton, 1976.)

MOTOR UNIT FATIGUE INDEX

A second functional property used to distinguish between the various motor units was their "fatigue index," or how much the muscle tension declined upon repetitive stimulation. It was important in these early studies to choose a stimulation frequency that fatigued the muscle fibers themselves. As mentioned, the long chain of events in excitation-contraction coupling can be interrupted at any point, resulting in a force decrease. If our purpose is to identify muscle fibers of a motor unit, we must be sure that the fatigue measured is muscle fiber fatigue and not fatigue, say, of the nerve or neuromuscular junction. Experimentally, the electrical activity of the muscle fibers was measured during repetitive stimulation to guarantee that the activation pulses were reaching the muscle fibers. The fatigue index test required stimulation of the motor unit at approximately 40 Hz (generating about half-maximum tension) for one-third of a second, allowing the muscle to relax for two-thirds of a second, and then repeating the sequence. Thus every second, the motor unit received a burst of 40-Hz pulses. This sequence has been slightly modified by other investigators but is still basically used by many to identify the fatigue index of muscles and motor units. The stimulation protocol was continued for 2 minutes and the muscle tension measured. If the motor unit was highly fatigable, the tension dropped significantly compared to the initial tension. If the unit was not fatigable, the tension dropped only slightly or not at all. Using this approach, it was observed that units could be classified as highly fatigable (defined as units that generated less than 25% of the initial tension after 2 minutes), fatigue resistant (units that generated over 75% of the initial tension after 2 minutes), and fatigue intermediate (units that generated between 25% and 75% of the initial tension after 2 minutes; Figure 2.13).

As we demonstrated with muscle fiber types, we see that motor units also come only in three flavors: Those that have a fast contraction time, a low fatigue index, and sag are known as fast fatigable units (abbreviated FF). Those that have a fast contraction time, a high fatigue index, and demonstrate sag are known as fast fatigue-resistant units (abbreviated FR). Finally, those that have slow contraction times, a high fatigue index, and no sag are known as slow units (abbreviated S).

Motor Unit Histochemistry

The alert student may already have an idea of what is to come. The issue to be addressed at this point is, What determines the physiologic properties of the motor units? (Hint: Compare Tables 2.4 and 2.7.) Using the glycogen depletion method, Burke and his colleagues identified the muscle fibers belonging to various motor units using the histochemical procedures previously described (Figure 2.13). It was determined that motor units of different types were composed of muscle fibers of different types. The correspondence between motor units and muscle fibers was as would be expected based on their physiologic properties. The FF motor units were composed of FG muscle fibers, the FR motor units were composed of FOG muscle fibers, and the S units were composed of SO muscle fibers (Table 2.8). I must add a caution following this discussion. It is often stated in the motor unit literature that muscle fibers within a motor unit are *exactly* the same. While it is true that they are the same fiber type, we know that all fibers of a given type are not exactly the same. Recent quantitative studies of the oxidative capacity of

Table 2.7.
Three Motor Unit Types Obtained Using Physiologic Measurements

Motor Unit Designation	Twitch Tension	Twitch Contraction Time	Fatigue Index	"Sag" Present?
FF	High	Fast	Low	Yes
FR	Moderate	Fast	High	Yes
S	Low	Slow	High	No

MOTOR UNIT "SAG" PROPERTY

At this point, we have two classification criteria for motor units: twitch tension and fatigue index. A final and less well understood criterion for motor unit classification is based on the nature of the tension record in response to an unfused tetanic contraction. In some units, the tension was observed to increase smoothly, while in other units, the tension record first increased, and then decreased or "sagged" slightly. The presence or absence of "sag," while not clearly understood in origin, became the final classification criterion. In a manner completely analogous to muscle fiber type classification, these three properties when measured in motor units result in eight potential motor unit types. However, again in a manner analogous to muscle fiber types, only three types of motor units were commonly observed. A summary of these types is shown in Table 2.7.

Table 2.8.
Correspondence between Motor Unit and Muscle Fiber Types

Motor Unit Designation	Muscle Fiber Type in the Motor Unit
Fast fatigable (FF)	Fast glycolytic (FG)
Fast fatigue-resistant (FR)	Fast oxidative-glycolytic (FOG)
Slow (S)	Slow oxidative (SO)

different muscle fibers within the same unit reveal a surprising degree of variability between fibers (Martin *et al.*, 1988). These data suggest that while the α -motoneuron certainly influences motor unit properties, it does not absolutely determine them. This result has significant implications in studies of muscle plasticity (adaptation), which we will discuss in Chapters 4 and 5.

Determinant of Motor Unit Tension

As previously described, different motor unit types develop different tensions. Generally, fast motor units develop higher tensions than the slow motor units. Why is this? We might presume that because fast motor units are composed of fast muscle fibers that fast muscle fibers generate more tension than slow muscle fibers. On the other hand, perhaps fast and slow fibers generate the same tension, but fast units simply have a greater *number* of fibers than slow units. Perhaps still, fast and slow units have the same number of fibers of equal intrinsic strength, but the fast fibers are *larger* and therefore generate more tension. Which (if any) of these possibilities is the reason for the differences in muscle tension?

As you might imagine, determination of the number of fibers belonging to a motor unit (innervation ratio) is very difficult experimentally. We mentioned that experimental identification of muscle fibers belonging to a unit requires the glycogen depletion method, which tends to select for FG fibers (FF units) and against SO fibers (S units). This is the first problem. However, even after these fibers have been glycogen depleted, it is technically difficult to find them all within the muscle, especially if the muscle has a pennated architecture. Burke and others used a series of indirect calculations that attempt to account for the various anatomic features (innervation ratio, specific tension, and fiber size). They concluded that fast muscle fibers within a motor unit have a much larger specific tension than slow muscle fibers and have a somewhat higher innervation ratio (Burke, 1981). Unfortunately, it has not been possible to explain the difference in specific tension of fast and slow muscle fibers based on known structural features. However, using a different approach, Sue Bodine, working in Reggie Edgerton's laboratory, *directly measured* innervation ratio in a muscle with longitudinally oriented fibers (the cat tibialis anterior) and, using a stepwise regression model, demonstrated that the major reason that motor units generate different tensions is that high-tension motor units have a greater number of fibers (Bodine *et al.*, 1987). In addition, these high-tension units tend to have larger fibers within them (Figure 2.13). These two factors taken together suggest that motor unit tension is determined primarily by the number and size of the fibers within the unit and not as much by intrinsic differences (specific tension) between the fibers themselves.

The final chapter in this story has not yet been written. The take-home lesson is that our best evidence to date is that fast and slow muscle fibers within a motor unit have about the same specific tension, but that fiber size and innervation ratio differ significantly between motor unit types.

MOTOR UNIT RECRUITMENT

In our discussion of temporal summation, we mentioned that the nervous system can vary muscle force output by varying the stimulation frequency to the muscle fibers. This phenomenon is termed temporal summation. However, muscle force can also be varied by changing the number of motor units that are active at a given time. For relatively low-force contractions, few motor units are activated, while for higher force contractions, more units are activated. The process by which motor units are added as muscle force increases is known as recruitment. What factors determine the point during a contraction that a motor unit is recruited?

A classic study was performed in the 1960s by Elwood Henneman and colleagues whereby motoneuron electrical activity was measured as a muscle was slowly stretched, and therefore tension slowly increased. The increase in passive tension applied to a muscle caused more motor units to be recruited (Binder and Mendell, 1990; Henneman *et al.*, 1965; Figure 2.14). Henneman found that, at very low forces, electrical spikes were observed on the nerve, which were very low amplitude. (It was already known at the time that the amplitude of the spike is related to the size of the axon.) As muscle force increased, the size of the spikes also increased in a very orderly fashion. In other words, as force continued to increase, the units recruited always had larger and larger spikes. The entire process was reversed as force decreased. Henneman and colleagues interpreted this result to mean that at low muscle force levels motor units with small axons were first recruited, and, as force increased, larger and larger axons were recruited. This became known as the "size principle" and provided an anatomic basis for the orderly recruitment of motor units to produce a smooth contraction. Based on other studies, it was determined that, generally, small motor axons innervated slow motor units and larger motor axons innervated fast motor units. In fact, the FF units had the largest axons of all.

VOLUNTARY MOTOR UNIT RECRUITMENT

Essentially all of the data presented above were obtained from animal studies of isolated motor units. What evidence is there that human motor unit properties and recruitment patterns are similar? Obviously, it is not possible

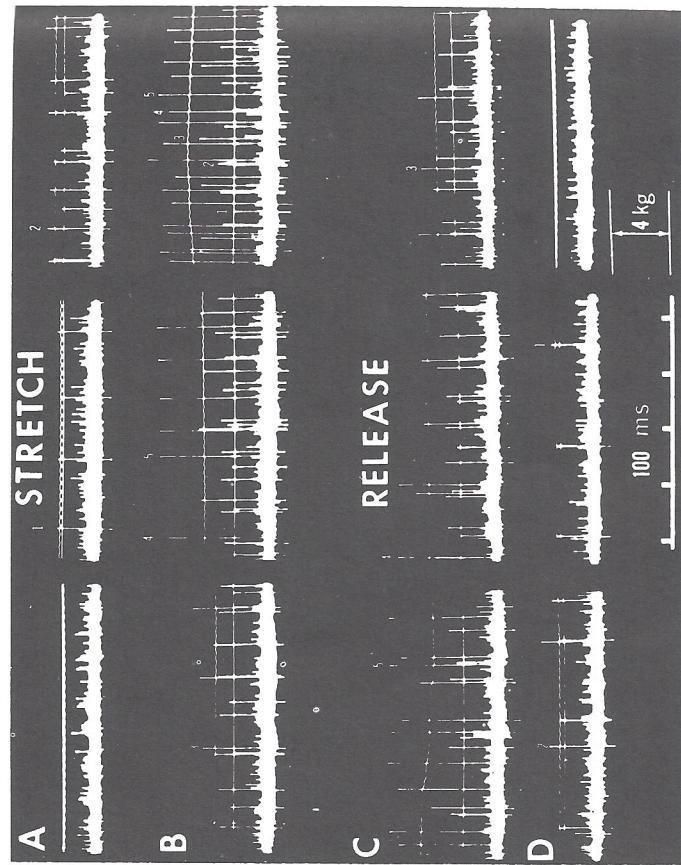


Figure 2.14. Demonstration of orderly recruitment according to the size principle. As the muscle is passively stretched, axons of various sizes (labeled **1** to **5**) are recruited. A continuous line across each trace represents muscle passive tension. As tension decreases (**bottom panel**), units drop out in the reverse order of recruitment. (From Henneman E, Somjen G, Carpenter DO. Functional significance of cell size in spinal motoneurons. *J Neurophysiol* 1965;28:560-580.)

to perform the identical experiments in humans. However, one method has been developed to study human motor unit properties that has validated many of the results from animal studies.

In the early 1970s, Milner-Brown and his colleagues, developed an ingenious method for measuring the contractile properties of human motor units (Milner-Brown *et al.*, 1973). The experimental apparatus consisted of small needle electrodes placed in the muscle of interest, a force transducer placed on the joint of interest, and surface electrodes to measure muscle electrical activity (Figure 2.15).

After placing the small electrodes in the muscle of interest, Milner-Brown *et al.*, asked the subject to attempt to activate voluntarily a single motor unit! With a little practice and feedback, this task can be performed. During these low-level voluntary activations, motor unit spike trains were recorded from

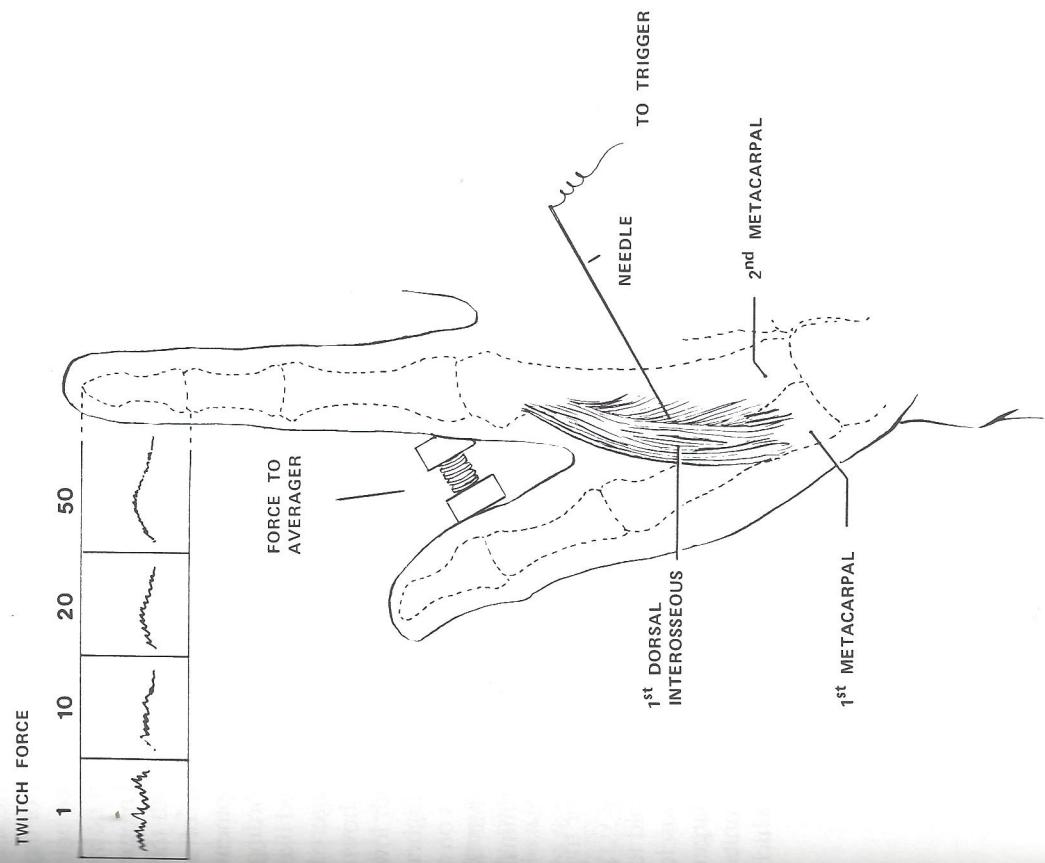


Figure 2.15. Experimental method for demonstration of human motor unit properties according to the spike-triggered averaging method. A needle is placed into the first dorsal interosseous muscle to record motor unit spikes and connected to a trigger. After each spike, finger abduction force is recorded. Many records are recorded (**upper panels**), which decreases background noise and reveals motor unit twitch tension.

the intramuscular electrodes. As voluntary activation level increased, the size of the motor unit spikes also increased. However, the really slick part of the experiment was the manner in which the investigators measured motor unit tension. At very low contraction levels, the force recorded was a very noisy force record—nothing like the smooth twitches recorded from animal motor units. Milner-Brown *et al.*, thus synchronized the force recording with the intramuscular electrical spikes recorded. Thus each time a spike of a particular size was recorded, they triggered their force recording equipment to measure tension. As more and more spikes triggered the recording equipment, the force records were averaged to yield records that looked like muscle twitches (Figure 2.16)! This technique was named spike-triggered averaging for obvious reasons. Using this technique, it has also been shown that at low levels of voluntary effort, slow contracting motor units with low tensions are recruited. As effort increases, faster motor units with higher tensions are recruited (Figure 2.17). Numerous subsequent experiments on a variety of muscles have essentially verified these initial studies. Thus it appears that the size principle is applicable to human as well as animal subjects.

Using all of this information, the following scheme was proposed for the manner in which motor units are recruited voluntarily (Figure 2.18): At very low exertion levels, the smallest axons (which have the lowest threshold to activation) are first activated. Most of these small axons innervate SO muscle fibers within S units. As voluntary effort increases, most of the next-larger axons are recruited, which activates the FOG fibers belonging to FR units. Finally, during maximal efforts, the largest axons are activated, most of which

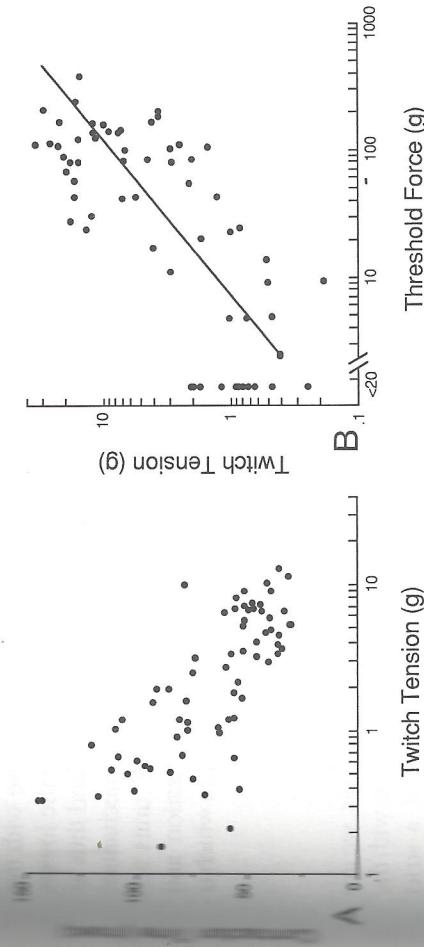


Figure 2.17. **A,** Human motor unit twitch contraction time as a function of twitch tension recorded by spike-triggered averaging. Note that as contractile tension increases, contraction time decreases. This suggests that the motor units with larger tension have faster contractile speed, as predicted by the size principle. **B,** Human motor unit twitch tension as a function of threshold voltage. As threshold increases, larger units are recruited, as predicted by the size principle. (Data from Milner-Brown *et al.*, 1973.)

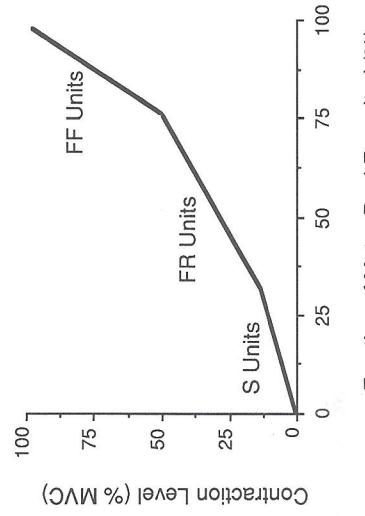


Figure 2.18. Schematic demonstration of predicted orderly recruitment of motor units during voluntary activity as a function of contractile force. At lower forces S units are recruited, while as force increases FR and FF units are recruited. (Adapted from Edgerton VR, Roy RR, Bodine SC, Sacks RD. The matching of neuronal and muscular physiology. In: Borer KT, Edgington DW, White TP, eds. Frontiers of exercise biology. Illinois: Human Kinetics Publishers, 1993.)

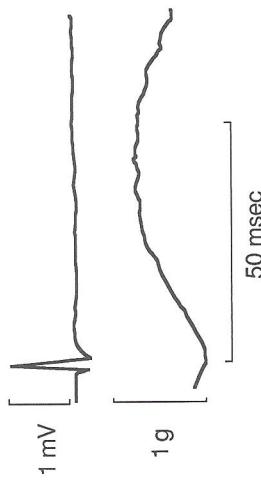
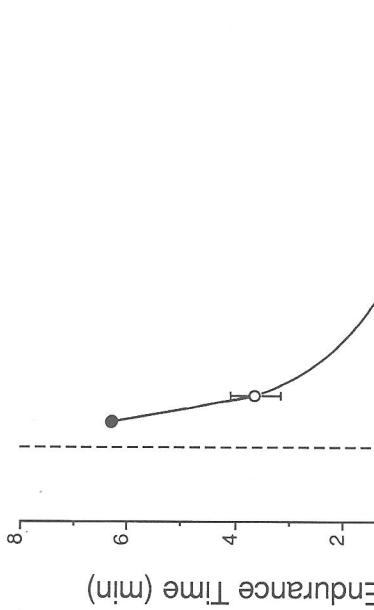


Figure 2.16. Single twitch recorded from human first dorsal interosseous muscle using spike-triggered averaging. Top record is the action potential, and bottom record is averaged twitch record. Note that this twitch looks very much like that obtained from isolated muscle (c.f., Figure 2.2). (Adapted from Milner-Brown HS, Stein RB, Yemm R. The contractile properties of human motor units during voluntary isometric contraction. *J Physiol [Lond]*. 1973;228:285–306.)



Now that we have discussed fiber types, metabolism, and motor units, we are in a position to discuss the issue of fatigue. Nearly everyone is familiar with the feeling of muscle fatigue following prolonged exercise. However, a strict definition of fatigue has been more difficult to establish. This is due, in part, to the complex nature of voluntary contractions themselves. At least three major components are involved in the production of voluntary contractions (Figure 2.19): the CNS, the peripheral nerve, and neuromuscular junction, and the skeletal muscles. *A priori* any one of these systems might be involved in the fatigue process. We will examine several of the classic fatigue studies that add to our current understanding of muscle fatigue.

Intuitively, it is obvious that low forces can be maintained longer than high forces. In fact, this relationship was quantified for a number of human muscles (Rohmert, 1960). Subjects were asked to maintain a target force ranging from 5% to 100% of their maximum voluntary contraction (MVC) level. For contraction levels less than 15% MVC, subjects could maintain the target level indefinitely (>45 minutes). However, as the target force increased, endurance time rapidly decreased (Figure 2.20). How can these changes in endurance time be explained? Why does muscle force decrease? Which of the different systems (Figure 2.19) changes in response to prolonged contraction?

Substrate Depletion in Fatigue

We have seen that ATP is the immediate energy source for force generation in muscle. However, under normal conditions, skeletal muscle only contains enough ATP to fuel two or three maximal contractions! What happens as ATP levels suddenly drop following contraction? An ATP regenerating system is present in muscle that is composed of the high-energy molecule creatine

innervate FG fibers and make up FF units. An appealing aspect of this hypothesis is that the units most often activated (S units) are those with the greatest endurance. The FF units, which are rarely activated, have the lowest endurance. In addition, the S units develop the slowest tension, and thus as contractions begin, low tensions are generated. This provides a mechanism for smoothly increasing tension as first S, then FR, and then FF units are recruited. This exquisite interrelationship of anatomic specialization and physiologic function is just one more structure-function relationship, which is the hallmark of the neuromuscular system.

PHYSIOLOGIC BASIS OF FATIGUE

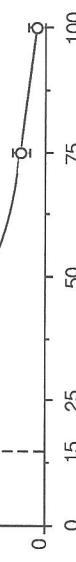


Figure 2.20. Relationship between endurance time and contraction intensity (% MVC). Note that forces lower than approximately 15% MVC can be maintained indefinitely (here defined as >45 minutes). As force increases, endurance time rapidly decreases. (Data from Rohmert, 1960.)