PART III Muscle Physiology

CHAPTER 8

Contractile Properties of Muscle Cells

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CHAPTER OUTLINE

KEY CONCEPTS

1. Muscle is classified into three categories, based on anatomic location, histological structure, and mode of control. The categories may overlap.
2. Skeletal (striated) muscle is used for voluntary movement of the skeleton.
3. Smooth muscle controls and aids the function of visceral organs.
4. Cardiac muscle provides the motive power for circulation of the blood.
5. The contractile proteins of muscle are arranged into two overlapping sets of myofilaments, one predominantly myosin-containing (thick), and one predominantly actin-containing (thin).
6. In skeletal and cardiac muscle, the myofilaments are arranged into sarcomeres, the fundamental organizational unit of the contractile machinery.
7. Crossbridges are projections of myosin filaments that make mechanical contact with actin filaments.
8. The myofilament arrangement and crossbridge contacts in smooth muscle occur without an organized sarcomere structure.
9. Changes in the length of a skeletal muscle result in changes in the degree of overlap of the myofilaments.
10. The crossbridge cycle is a series of chemical reactions that transform the energy stored in ATP into mechanical energy that produces muscle contraction.
11. ATP has two functions in the crossbridge cycle: to provide the energy for contraction, and to allow the myosin crossbridges to release from the actin filaments.
12. Overall muscle force and shortening occur as a result of the cumulative effects of millions of crossbridges acting to move myofilaments past one another.
13. Crossbridge interaction and the events of the crossbridge cycle are regulated by the action of calcium ions, which are stored in the sarcoplasmic reticulum when the muscle is at rest.
14. The release and uptake of calcium ions by the sarcoplasmic reticulum of skeletal muscle are controlled by the membrane potential of the muscle fibers.
15. The energy for muscle contraction is derived from both aerobic and anaerobic metabolism; muscle can adapt its function depending on the availability of oxygen.

Muscle tissue is responsible for most of our interactions with the external world. These familiar functions include moving, speaking, and a host of other everyday actions. Less familiar, but no less important, are the internal functions of muscle. It pumps our blood and regulates its flow, it moves our food as it is being digested and causes the expulsion of wastes, and it serves as a critical regulator of numerous internal processes.

Muscle contraction is a cellular phenomenon. The shortening of a whole muscle results from the shortening of its individual cells, and the force a muscle produces is the sum of forces produced by its cells. Activation of a whole muscle involves activating its individual cells, and muscle relaxation involves a return of the cells to their resting state. The study of muscle function must, therefore, include an investigation of the cellular processes that cause and regulate muscle contraction.

As the great variety of its functions might imply, muscle is a highly diverse tissue. But in spite of its wide range of anatomic and physiological specializations, there is an underlying similarity in the way muscles are constructed and in their mechanism of contraction. This chapter discusses some fundamental aspects of muscle contraction expressed in all types of muscle. Chapters 9 and 10 consider the important specializations of structure and function that belong to particular kinds of muscle.

THE ROLES OF MUSCLE

Different types of muscle fall naturally into categories that are related to their anatomic and physiological properties. Within each major category are subclassifications that further specify differences among the muscle types. As with any classification scheme, some exceptions are inevitable and some categories overlap. For this reason, three sets of criteria are commonly used.

Muscles Are Grouped in Three Major Categories

Muscles may be grouped according to

- Their location in relation to other body structures
- Their histological (tissue) structure
- The way their action is controlled

These classifications are not mutually exclusive.

Throughout the three chapters on muscle, the highlighted categories in Figure 8.1 will be the preferred usage. The alternative categories are still useful, however, because in some instances they express more precisely the special attributes of a certain muscle type. The inconsistencies in classification are likewise useful in describing the characteristics of specific muscles.

Skeletal Muscle: Interactions With the External Environment. As its name implies, **skeletal muscle** is usually associated with bones of the skeleton. It is responsible for large and forceful movements, such as those involved in walking, running, and lifting heavy objects, as well as for small and delicate movements that position the eyeballs or allow the manipulation of tiny objects. Some skeletal muscle is specialized for the long-term maintenance of tension; for example, muscles of the torso involved in maintaining an upright posture can be active for many hours without undue fatigue. Other skeletal muscles, such as those in the upper arm, are better adapted for making rapid and forceful movements, but these fatigue rather rapidly when required to lift and hold heavy loads.

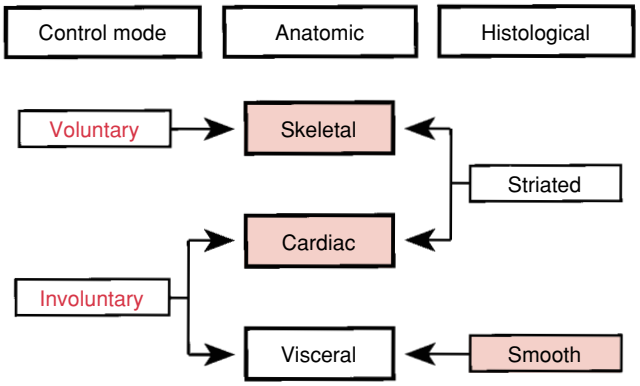

FIGURE 8.1 **Classification of types of muscles.** The categories overlap in different ways, depending on the criteria being used.

Whatever its specialization, skeletal muscle serves as the link between the body and the external world. Much of this interaction, such as walking or speaking, is under *voluntary* control. Other actions, such as breathing or blinking the eyelids, are largely automatic, although they can be consciously suppressed for brief periods of time. All skeletal muscle is externally controlled; it cannot contract without a signal from the somatic nervous system.

Not all skeletal muscle is attached to the skeleton. The human tongue, for example, is made of skeletal muscle that does not move bones closer together. Among mammals, perhaps the most striking example of this exception is the trunk of the elephant, in which skeletal muscles are arranged in a structure capable of great dexterity even though no articulated bones are involved in its movement.

An important secondary function of skeletal muscle is the production of body heat. This may be desirable, as when one shivers to get warm. During heavy exercise, however, muscle contraction may be a source of excess heat that must be eliminated from the body.

All skeletal muscle has a striated appearance when viewed with a light microscope or an electron microscope (Fig. 8.2). The regular and periodic pattern of the cross-striations of skeletal muscle relates closely to the way it functions at a cellular level.

Smooth Muscle: Regulation of the Internal Environment. Of the many processes regulating the internal state of the human body, one of the most important is controlling the movement of fluids through the visceral organs and the circulatory system. Such regulation is the task of **smooth muscle**. Smooth muscle also has many individual specializations that suit it well to particular tasks. Some smooth muscle, such as that in **sphincters**, circular bands of muscle that can stop flow in tubular organs, can remain contracted for long periods while using its metabolic energy econom-

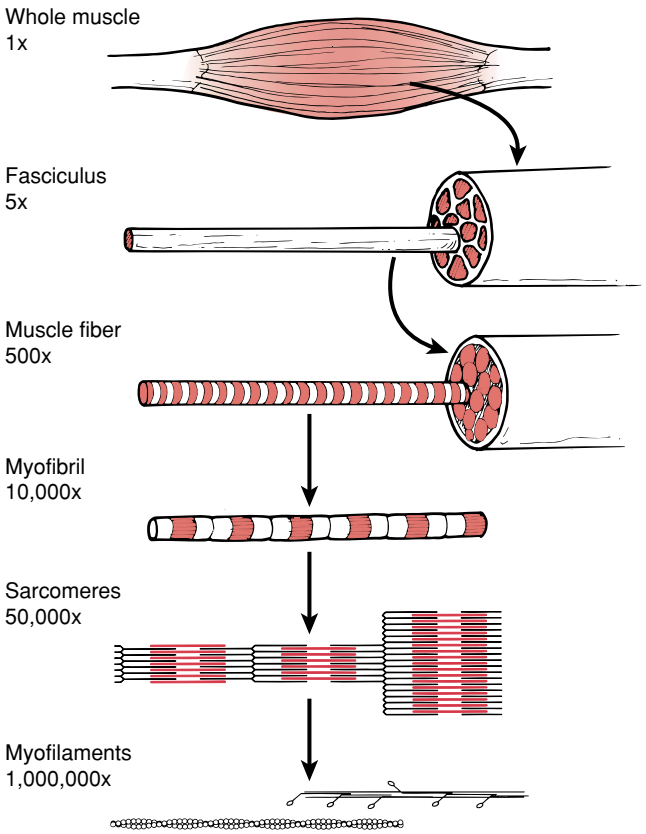

FIGURE 8.2 **Levels of complexity in the organization of skeletal muscle.** The approximate amount of magnification required to visualize each level is shown above each view.

ically. The muscle of the uterus, on the other hand, contracts and relaxes rapidly and powerfully during birth but is normally not very active during most of the rest of a woman's life. The economical use of energy is one of the most important general features of the physiology of smooth muscle.

The contraction of smooth muscle is *involuntary*. Although contraction may occur in response to a nerve stimulus, many smooth muscles are also controlled by circulating hormones or contracted under the influence of local hormonal or metabolic influences quite independent of the nervous system. Some indirect voluntary control of smooth muscle may be possible through mental processes such as biofeedback, but this ability is rare and is not an important aspect of smooth muscle function.

While one of the terms describing smooth muscle—*visceral*—implies its location in internal organs, much smooth muscle is located elsewhere. The muscles that control the diameter of the pupil of the eye and accommodate the eye for near vision, cause body hair to become erect (pilomotor muscles), and control the diameter of blood vessels are all examples of smooth muscles that are not visceral.

Cardiac Muscle: Motive Power for Blood Circulation. **Cardiac muscle** provides the force that moves blood throughout the body and is found only in the heart. It shares, with skeletal muscle, a striated cell structure, but its contractions are involuntary; the heartbeat arises from within the cardiac muscle and is not initiated by the nervous system. The nervous system, however, does participate in regulating the rate and strength of heart muscle contractions. Chapter 10 considers the special properties of cardiac muscle.

Muscles Have Specialized Adaptations of Structure and Function

All of the above should emphasize the varied and specialized nature of muscle function. Skeletal muscle, with its large and powerful contractions; smooth muscle, with its slow and economical contractions; and cardiac muscle, with its unceasing rhythm of contraction—all represent specialized adaptations of a basic cellular and biochemical system. An understanding of both the common features and the diversity of different muscles is important, and it is useful to emphasize particular types of muscle when investigating a general aspect of muscle function. Skeletal muscle is often used as the "typical" muscle for purposes of discussion, and this convention is followed in this chapter where appropriate, with an effort to point out those features relative to muscle in general. Important adaptations of the general features found in specific muscle types are considered in Chapters 9 and 10.

THE FUNCTIONAL ANATOMY AND ULTRASTRUCTURE OF MUSCLE

In biology, as in architecture, it can be said that form follows function. Nowhere is this truism more relevant than in the study of muscle. Investigations using light and electron microscopy, x-ray and light diffraction, and other modern visualization techniques have shown the complex and highly ordered internal structure of skeletal muscle. Elegant mechanical experiments have revealed how this structure determines the ways muscle functions.

Muscle Structure Provides a Key to Understanding the Mechanism of Contraction

Skeletal muscle is a highly organized tissue (Fig. 8.3). A whole skeletal muscle is composed of numerous muscle cells, also called **muscle fibers.** A cell can be up to 100 μm in diameter and many centimeters long, especially in larger muscles. The fibers are multinucleate, and the nuclei occupy positions near the periphery of the fiber. Skeletal muscle has an abundant supply of **mitochondria,** which are vital for supplying chemical energy in the form of ATP to the contractile system. The mitochondria lie close to the contractile elements in the cells. Mitochondria are especially plentiful in skeletal muscle fibers specialized for rapid and powerful contractions.

Each muscle fiber is further divided lengthwise into several hundred to several thousand parallel **myofibrils.** Electron micrographs show that each myofibril has alternating light and dark bands, giving the fiber a striated (striped) appearance. As shown in Figure 8.3, the bands repeat at regular intervals. Most prominent of these is a dark band

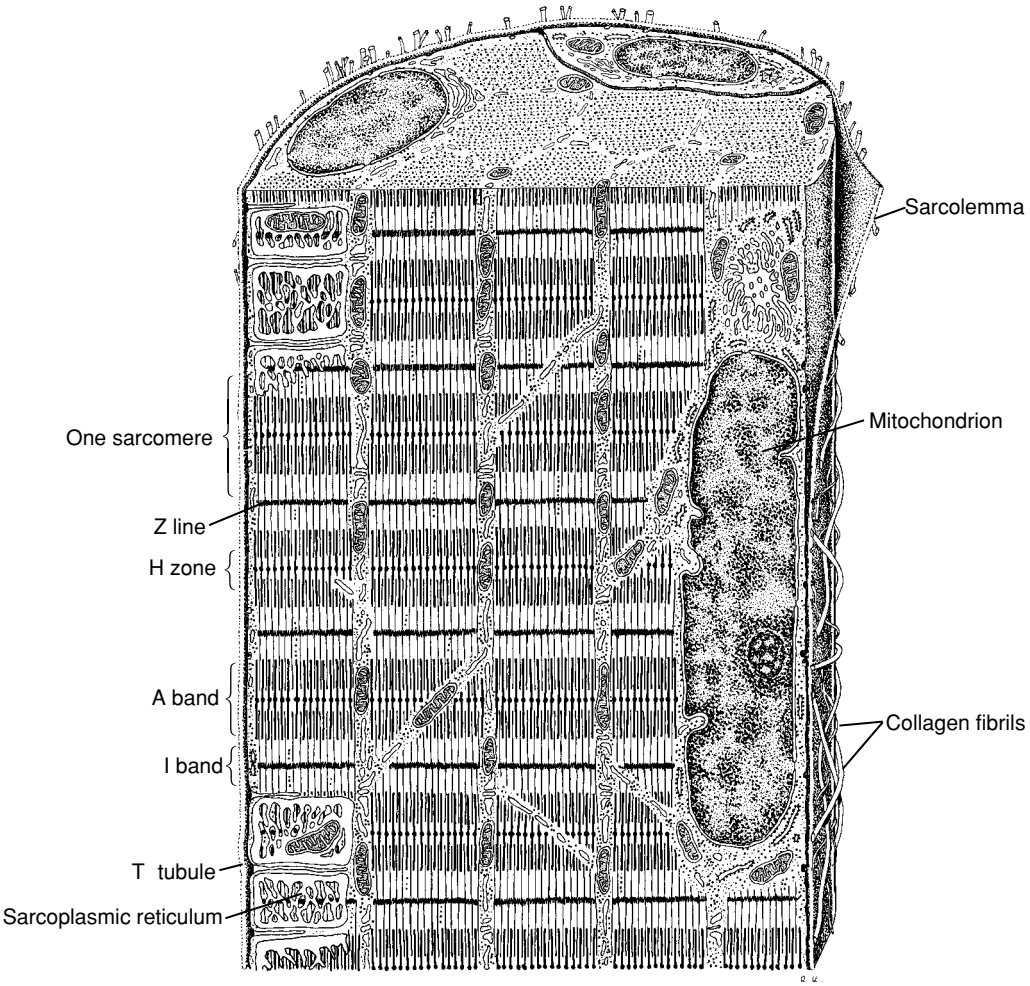

FIGURE 8.3 **The ultrastructure of skeletal muscle, a reconstruction based on electron micrographs.** (From Krstic RV. General Histology of the Mammal. New York: Springer-Verlag, 1984.)

called an **A band.** It is divided at its center by a narrow, lighter-colored region called an **H zone.** In many skeletal muscles, a prominent **M line** is found at the center of the H zone. Between the A bands lie the less dense **I bands.** (The letters *A* and *I* stand for anisotropic and isotropic; the bands are named for their appearance when viewed with polarized light.) Crossing the center of the I band is a dark structure called a **Z line** (sometimes termed a *Z disk* to emphasize its three-dimensional nature). The filaments of the I band attach to the Z line and extend in both directions into the adjacent A bands. This pattern of alternating bands is repeated over the entire length of the muscle fiber. The fundamental repeating unit of these bands is called a **sarcomere** and is defined as the space between (and including) two successive Z lines (Fig. 8.4).

Closer examination of a sarcomere shows the A and I bands to be composed of two kinds of parallel structures called **myofilaments.** The I band contains **thin filaments,** made primarily of the protein **actin**, and A bands contain **thick filaments** composed of the protein **myosin.**

Thin Myofilaments. Each thin (actin-containing) filament consists of two strands of macromolecular subunits entwined about each other (Fig. 8.5). The strands are composed of repeating subunits (monomers) of the globular protein **G-actin** (molecular weight, 41,700). These slightly ellipsoid molecules are joined front to back into long chains that wind about each other, forming a helical structure—**F-actin** (or filamentous actin)—that undergoes a half-turn every seven G-actin monomers. In the groove formed down the length of the helix, there is an end-to-end series of fibrous protein molecules (molecular weight, 50,000) called **tropomyosin.** Each tropomyosin molecule extends a distance of seven G-actin monomers along the F-actin groove. Near one end of each tropomyosin molecule is a protein complex called **troponin,** composed of three attached subunits: troponin-C (Tn-C), troponin-T (Tn-T), and troponin-I (Tn-I). The **Tn-C subunit** is capable of binding calcium ions, the **Tn-T subunit** attaches the complex to tropomyosin, and the **Tn-I subunit** has an inhibitory function. The troponin-tropomyosin complex regulates the contraction of skeletal muscle.

Thick Myofilaments. Thick (myosin-containing) filaments are also composed of macromolecular subunits (Fig. 8.6). The fundamental unit of a thick filament is

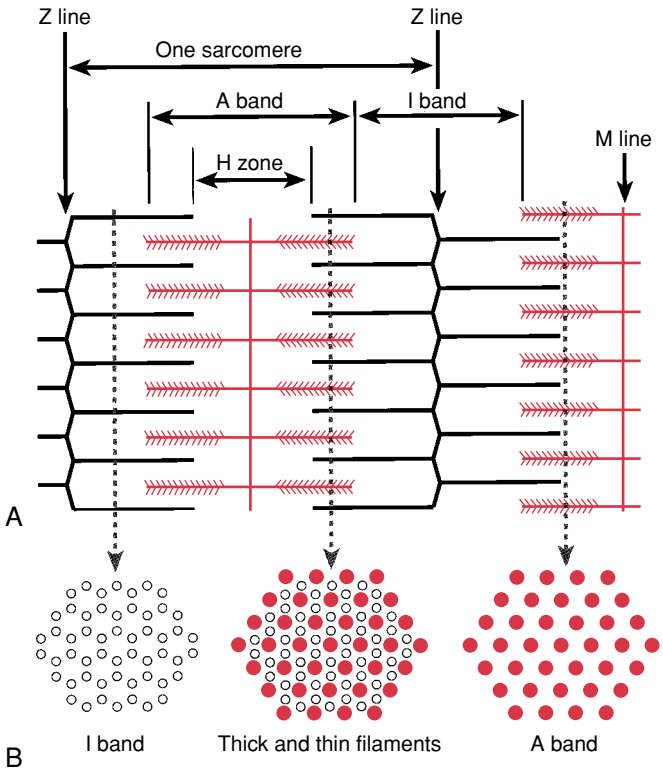

FIGURE 8.4 **Nomenclature of the skeletal muscle sarcomere.** **A,** The arrangement of the elements in a sarcomere. **B,** Cross sections through selected regions of the sarcomere, showing the overlap of myofilaments at different parts of the sarcomere.

myosin (molecular weight, approximately 500,000), a complex molecule with several distinct regions. Most of the length of the molecule consists of a long, straight portion, often called the "tail" region, composed of **light meromyosin** (LMM). The remainder of the molecule, **heavy meromyosin** (HMM), consists of a protein chain that terminates in a globular head portion. The head portion, called the **S1 region** (or subfragment 1), is responsible for the enzymatic and chemical activity that results in muscle contraction. It contains an **actin-binding site,** by which it can interact with the thin filament, and an **ATP-binding site** that is involved in the supply of energy for the actual process of contraction. The chain portion of HMM, the **S2 region** (or subfragment 2), serves as a flexible link between the head and tail regions. Associated with the S1 region are two loosely attached peptide chains of a much lower molecular weight. The **essential light chain** is necessary for myosin to function, and the **regulatory light chain** can be phosphorylated during muscle activity and modulates muscle function. Functional myosin molecules are paired; their tail and S2 regions are wound about each other along their lengths, and the two heads (each bearing its two light chains and its own ATP- and actin-binding sites) lie adjacent to each other. The molecule, with its attached light chains, exists as a functional dimer, but the degree of functional independence of the two heads is not yet known with certainty.

The assembly of individual myosin dimers into thick filaments involves close packing of the myosin molecules such that their tail regions form the "backbone" of the thick filament, with the head regions extending outward in a helical fashion. A myosin head projects every 60 degrees around the circumference of the filament, with each one displaced 14.4 nm further along the filament. The effect is like that of a bundle of golf clubs bound tightly by the handles, with the heads projecting from the bundle. The myosin molecules are packed so that they are tail-to-tail in the center of the thick filament and extend outward from the center in both directions, creating a bare zone (i.e., no heads protruding) in the middle of the filament (see Figs. 8.4 and 8.6).

Other Muscle Proteins. In addition to the proteins directly involved in the process of contraction, there are several other important structural proteins. **Titin**, a large filamentous protein, extends from the Z lines to the bare

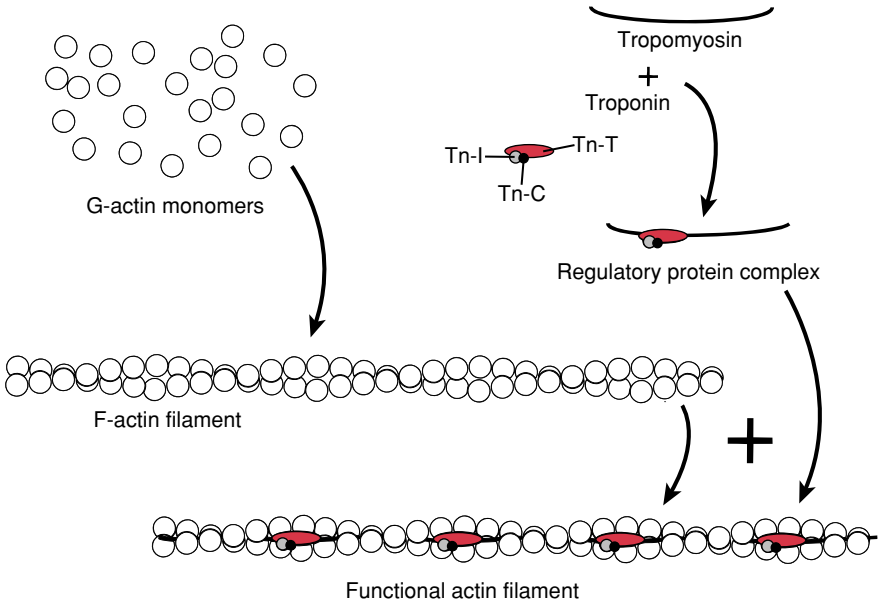

FIGURE 8.5 **The assembly of the thin (actin) filaments of skeletal muscle.** (See text for details.)

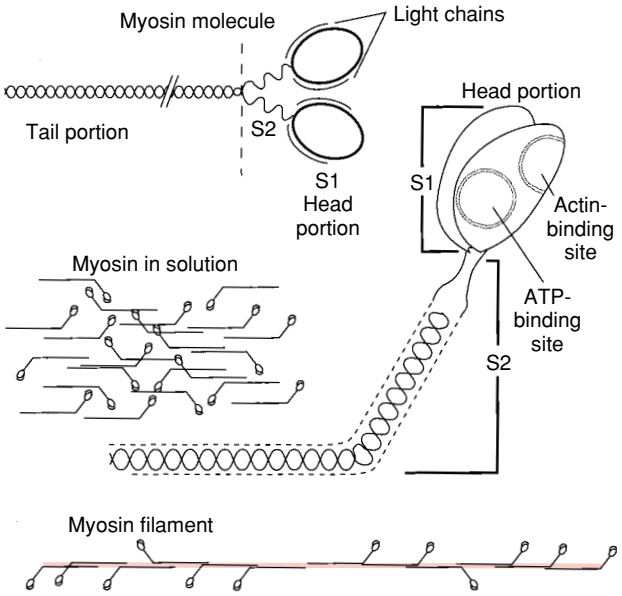

FIGURE 8.6 **The assembly of skeletal muscle thick filaments from myosin molecules.** (See text for details.)

portion of the myosin filaments and may help to prevent overextension of the sarcomeres and maintain the central location of the A bands. **Nebulin**, a filamentous protein that extends along the thin filaments, may play a role in stabilizing thin filament length during muscle development. The protein α-**actinin**, associated with the Z lines, serves to anchor the thin filaments to the structure of the Z line.

Dystrophin, which lies just inside the sarcolemma, participates in the transfer of force from the contractile system to the outside of the cells via membrane-spanning proteins called **integrins**. External to the cells, the protein **laminin** forms a link between integrins and the extracellular matrix. These proteins are disrupted in the group of genetic diseases collectively called **muscular dystrophy**, and their lack or malfunction leads to muscle degeneration and weakness and death (see Clinical Focus Box 8.1).

Polymyositis is an inflammatory disorder that produces damage to several or many muscles (Clinical Focus Box 8.2). The progressive muscle weakness in polymyositis usually develops more rapidly than in muscular dystrophy.

Skeletal Muscle Membrane Systems. Muscle cells, like other types of living cells, have a system of surface and in-

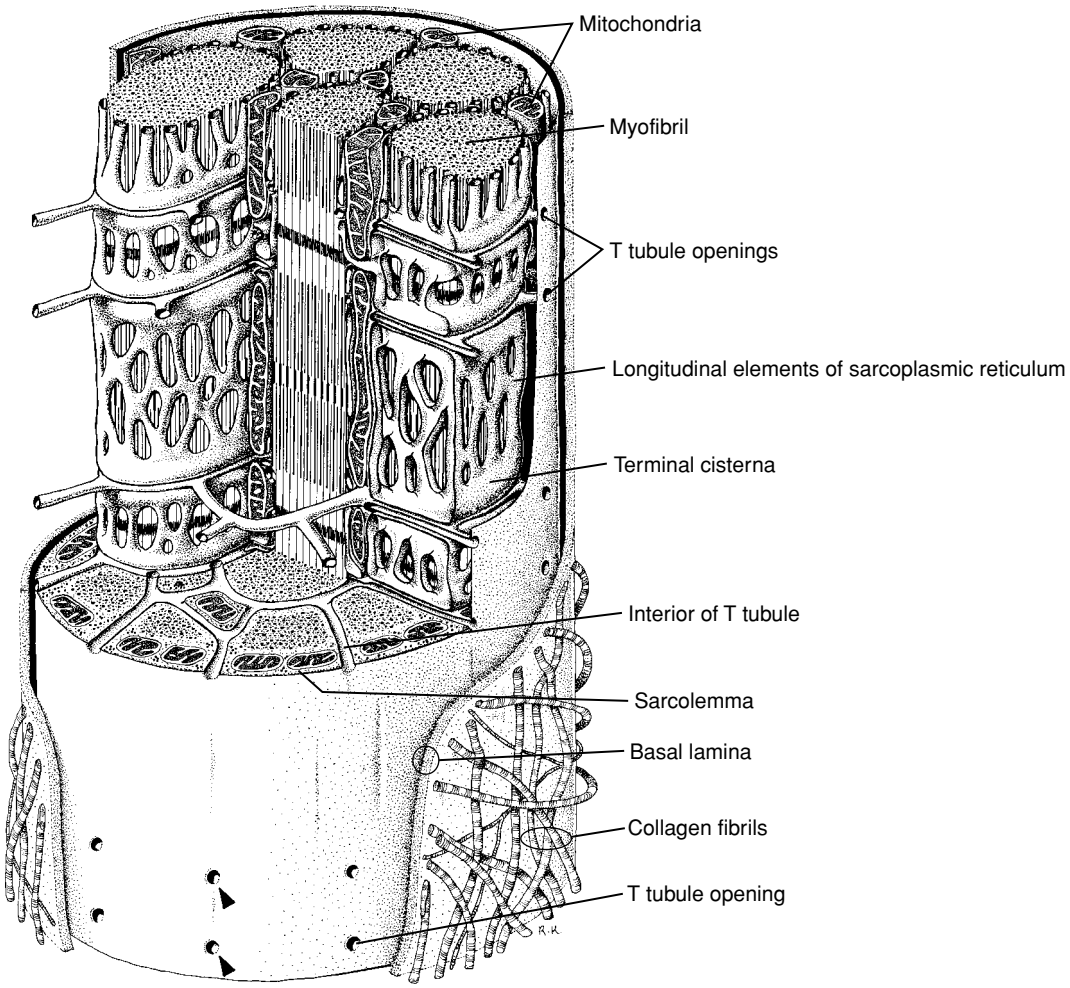

FIGURE 8.7 **The internal membrane system of skeletal muscle, responsible for communication between the surface membrane and contractile filaments.** This reconstruction is based on electron micrographs. (From Krstic RV. General Histology of the Mammal. New York: Springer-Verlag, 1984.)

CLINICAL FOCUS BOX 8.1

Muscular Dystrophy Research

The term ***muscular dystrophy*** (MD) encompasses a variety of degenerative muscle diseases. The most common of these diseases is **Duchenne's muscular dystrophy** (DMD) (also called pseudohypertrophic MD), which is an X-linked hereditary disease affecting mostly male children (1 of 3,500 live male births). DMD is manifested by progressive muscular weakness during the growing years, becoming apparent by age 4. A characteristic enlargement of the affected muscles, especially the calf muscles, is due to a gradual degeneration and necrosis of muscle fibers and their replacement by fibrous and fatty tissue. By age 12, most sufferers are no longer ambulatory, and death usually occurs by the late teens or early twenties. The most serious defects are in skeletal muscle, but smooth and cardiac muscle are affected as well, and many patients suffer from cardiomyopathy (see Chapter 10). A related (and rarer) disease**, Becker's muscular dystrophy** (BMD), has similar symptoms but is less severe; BMD patients often survive into adulthood. Some six other rarer forms of muscular dystrophy have their primary effect on particular muscle groups.

Using the genetic technique of chromosome mapping (using linkage analysis and positional cloning), researchers have localized the gene responsible for both DMD and BMD to the p21 region of the X chromosome, and the gene itself has been cloned. It is a large gene of some 2.5 million base pairs; apparently because of its great size, it has an unusually high mutation rate. About one third of DMD cases are due to new mutations and the other two thirds to sex-linked transmission of the defective gene. The BMD gene is a less severely damaged allele of the DMD gene.

The product of the DMD gene is dystrophin, a large protein that is absent in the muscles of DMD patients. Aberrant forms are present in BMD patients. The function of dystrophin in normal muscle appears to be that of a cytoskeletal component associated with the inside surface of the sarcolemma. Muscle also contains dystrophin-related proteins that may have similar functional roles. The most important of these is laminin 2, a protein associated with the basal lamina of muscle cells and concerned with mechanical connections between the exterior of muscle cells and the extracellular matrix. In several forms of muscular dystrophy, both laminin and dystrophin are lacking or defective.

A disease as common and devastating as DMD has long been the focus of intensive research. The recent identification of three animals—dog, cat, and mouse—in which genetically similar conditions occur promises to offer significant new opportunities for study. The manifestation of the defect is different in each of the three animals (and also differs in some details from the human condition). The **mdx mouse**, although it lacks dystrophin, does not suffer the severe debilitation of the human form of the disease. Research is underway to identify dystrophin-related proteins that may help compensate for the major defect. Mice, because of their rapid growth, are ideal for studying the normal expression and function of dystrophin. Progress has been made in transplanting normal muscle cells into mdx mice, where they have expressed the dystrophin protein. Such an approach has been less successful in humans and in dogs, and the differences may hold important clues. A gene expressing a truncated form of dystrophin, called **utrophin**, has been inserted into mice using transgenic methods and has corrected the myopathy.

The **mdx dog**, which suffers a more severe and human-like form of the disease, offers an opportunity to test new therapeutic approaches, while the cat dystrophy model shows prominent muscle fiber hypertrophy, a poorly understood phenomenon in the human disease. Taking advantage of the differences among these models promises to shed light on many missing aspects of our understanding of a serious human disease.

References

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ternal membranes with several critical functions (see Fig. 8.7). A skeletal muscle fiber is surrounded on its outer surface by an electrically excitable cell membrane supported by an external meshwork of fine fibrous material. Together these layers form the cell's surface coat, the **sarcolemma**. In addition to the typical functions of any cell membrane, the sarcolemma generates and conducts action potentials much like those of nerve cells.

Contained wholly within a skeletal muscle cell is another set of membranes called the **sarcoplasmic reticulum** (SR), a specialization of the endoplasmic reticulum. The SR is specially adapted for the uptake, storage, and release of calcium ions, which are critical in controlling the processes of contraction and relaxation. Within each sarcomere, the SR consists of two distinct portions. The **longitudinal element** forms a system of hollow sheets and tubes that are closely associated with the myofibrils. The ends of the longitudinal elements terminate in a system of **terminal cisternae** (or lateral sacs). These contain a protein, calsequestrin, that weakly binds calcium, and most of the stored calcium is located in this region.

Closely associated with both the terminal cisternae and the sarcolemma are the **transverse tubules** (**T tubules**), inward extensions of the cell membrane whose interior is continuous with the extracellular space. Although they traverse the muscle fiber, T tubules do not open into its interior. In many types of muscles, T tubules extend into the muscle fiber at the level of the Z line, while in others they penetrate in the region of the junction between the A and I bands. The association of a T tubule and the two terminal cisternae at its sides is called a **triad**, a structure important in linking membrane action potentials to muscle contraction.

CLINICAL FOCUS BOX 8.2

Polymyositis

Polymyositis is a skeletal muscle disease known as an inflammatory myopathy. Children (about 20% of cases) and adults may both be affected. Patients with the condition complain of muscle weakness initially associated with the proximal muscles of the limbs, making it hard to get up from a chair or use the stairs. They may have difficulty combing their hair or placing objects on a high shelf. Many patients have difficulty eating (dysphagia) because of the involvement of the muscles of the pharynx and the upper esophagus. A small percentage (about one third) of patients with polymyositis experience muscle tenderness or aching pain; a similar proportion of patients have some involvement of the heart muscle. The disease is progressive during a course of weeks or months.

Primary idiopathic polymyositis cases comprise approximately one third of the inflammatory myopathies. Twice as many women as men are affected. Another one third of polymyositis cases are associated with a closely related condition called dermatomyositis, symptoms of which include a mild heliotrope (light purple) rash around the eyes and nose and other parts of the body, such as knees and elbows. Nail bed abnormalities may also be present. Still other cases (approximately 8%) are associated with cancer present in the lung, breast, ovary, or gastrointestinal tract. This association occurs mostly in older patients. Finally, about one fifth of polymyositis cases are associated with other connective tissue disorders, such as rheumatoid arthritis and lupus erythematosus. Polymyositis can also occur in AIDS, as a result of either the disease itself or to a reaction to azidothymidine (AZT) therapy.

Polymyositis is thought to be primarily an autoimmune disease. Muscle histology shows infiltration by inflammatory cells such as lymphocytes, macrophages, and neutrophils. Muscle tissue destruction, which is almost always present, occurs by phagocytosis. The route of infiltration often follows the vascular supply. There may be elevated serum levels of enzymes normally present in muscle, such as creatine kinase (CK). These enzymes are released as muscle breaks down, and in severe cases, myoglobin may be found in the urine. The electrical activity of the affected muscle, as measured by electromyography, may show a characteristic pattern of abnormalities. In some cases, the weakness felt by the patient is greater than that suggested by the microscopic appearance of the tissue, and evidence indicates that diffusible factors produced by immune cells may have a direct effect on muscle contractile function. While the condition is not directly inherited, there is a strong familial component in its incidence. The cases of polymyositis associated with cancer (a paraneoplastic syndrome) are thought to be due to the altered immune status or tumor antigens that cross-react with muscle.

Several other disorders may present symptoms similar to polymyositis; these include neurological or neuromuscular junction conditions that result in muscle weakness without actual muscle pathology (see Chapter 9). Early stages of muscular dystrophy may mimic polymyositis, although the overall courses of the diseases differ considerably; the decline in function is much more rapid in untreated polymyositis. The parasitic infection trichinosis can produce symptoms of the disease, depending on the severity of the infection. A large number of commonly used drugs may produce the typical symptoms of muscle pain and weakness, and a careful drug history may suggest a specific cause. In cases in which dermatomyositis is combined with the typical symptoms of polymyositis, the diagnosis is quite certain.

Treatment of the disease usually involves high doses of glucocorticoids such as prednisone. Careful follow-up (by direct muscle strength testing and measurement of serum CK levels) is necessary to determine the ongoing effectiveness of treatment. After a course of treatment, the disease may become inactive, but relapses can occur, and other treatment approaches, such as the use of cytotoxic drugs, may be necessary. Long-term physical therapy and assistive devices are required when drug therapy is not sufficiently effective.

The Sliding Filament Theory Explains Muscle Contraction

The structure of skeletal muscle provides important clues to the mechanism of contraction. The width of the A bands (thick-filament areas) in striated muscle remains constant, regardless of the length of the entire muscle fiber, while the width of the I bands (thin-filament areas) varies directly with the length of the fiber. At the edges of the A band are fainter bands whose width also varies. These represent material extending into the A band from the I bands. The spacing between Z lines also depends directly on the length of the fiber. The lengths of the thin and thick myofilaments remain constant despite changes in fiber length.

The **sliding filament theory** proposes that changes in overall fiber length are directly associated with changes in the overlap between the two sets of filaments; that is, the thin filaments telescope into the array of thick filaments. This interdigitation accounts for the change in the length of the muscle fiber. It is accomplished by the interaction of the globular heads of the myosin molecules (**crossbridges**, which project from the thick filaments) with binding sites on the actin filaments. The crossbridges are the sites where force and shortening are produced and where the chemical energy stored in the muscle is transformed into mechanical energy. The total shortening of each sarcomere is only about 1 μm, but a muscle contains many thousands of sarcomeres placed end to end (in series). This arrangement has the effect of multiplying all the small sarcomere length changes into a large overall shortening of the muscle (Fig. 8.8). Similarly, the amount of force exerted by a single sarcomere is small (a few hundred micronewtons), but, again, there are thousands of sarcomeres side by side (in parallel), resulting in the production of considerable force.

The effects of sarcomere length on force generation are summarized in Figure 8.9. When the muscle is stretched beyond its normal resting length, decreased filament overlap occurs (3.65 μm and 3.00 μm, Fig. 8.9). This limits the

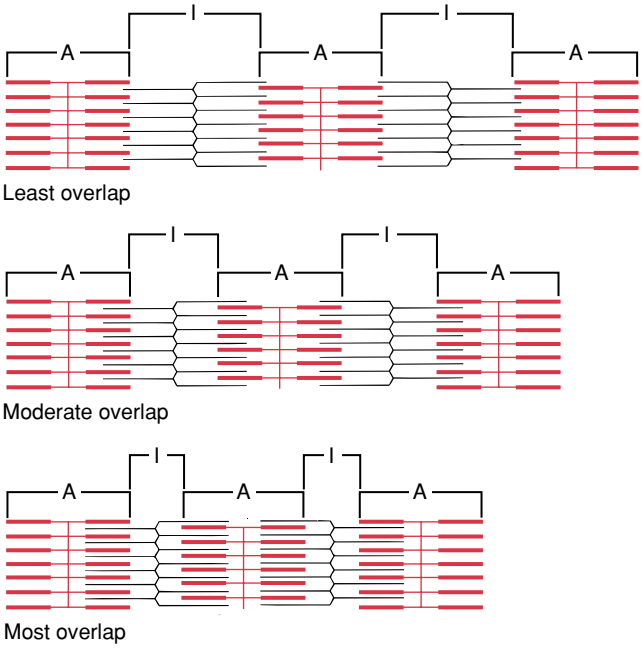

FIGURE 8.8 **The multiplying effect of sarcomeres placed in series.** The overall shortening is the sum of the shortening of the individual sarcomeres.

amount of force that can be produced, since a shorter length of thin filaments interdigitates with A band thick filaments and fewer crossbridges can be attached. Thus, over this region of lengths, force is directly proportional to the degree of overlap. At lengths near the normal **resting length** of the muscle (i.e., the length usually found in the body), the amount of force does not vary with the degree of overlap (2.25 μm and 1.95 μm, Fig. 8.10) because of the bare zone (the H zone) along the thick filaments at the center of the A band (where no myosin heads are present).

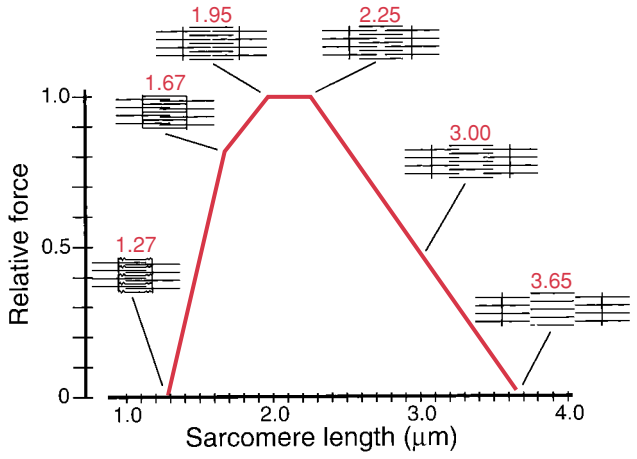

FIGURE 8.9 **Effect of filament overlap on force generation.** The force a muscle can produce depends on the amount of overlap between the thick and thin filaments because this determines how many crossbridges can interact effectively. (See text for details.)

Over this small region, further interdigitation does not lead to an increase in the number of attached crossbridges and the force remains constant.

At shorter lengths, additional geometric and physical factors play a role in myofilament interactions. Since muscle is a "telescoping" system, there is a physical limit to the amount of shortening. As thin myofilaments penetrate the A band from opposite sides, they begin to meet in the middle and interfere with each other (1.67 μm, Fig. 8.9). At the extreme, further shortening is limited by the thick filaments of the A band being forced against the structure of the Z lines (1.27 μm, Fig. 8.9).

The relationship between overlap and force at short lengths is more complex than that at longer lengths, since more factors are involved. It has also been shown that at very short lengths, the effectiveness of some of the steps in the excitation-contraction coupling process is reduced. These include reduced calcium binding to troponin and some loss of action potential conduction in the T tubule system. Some of the consequences for the muscle as a whole are apparent when the mechanical behavior of muscle is examined in more detail (see Chapter 9).

Events of the Crossbridge Cycle Drive Muscle Contraction

The process of contraction involves a cyclic interaction between the thick and thin filaments. The steps that comprise the **crossbridge cycle** are attachment of thick-filament crossbridges to sites along the thin filaments, production of a mechanical movement, crossbridge detachment from the thin filaments, and subsequent reattachment of the crossbridges at different sites along the thin filaments (Fig. 8.10). These mechanical changes are closely related to the biochemistry of the contractile proteins. In fact, the crossbridge association between actin and myosin actually functions as an enzyme, **actomyosin ATPase**, that catalyzes the breakdown of ATP and releases its stored chemical energy. Most of our knowledge of this process comes from studies on skeletal muscle, but the same basic steps are followed in all muscle types.

In resting skeletal muscle (Fig. 8.10, step 1), the interaction between actin and myosin (via the crossbridges) is weak, and the muscle can be extended with little effort. When the muscle is activated, the actin-myosin interaction becomes quite strong, and crossbridges become firmly attached (step 2). Initially, the crossbridges extend at right angles from each thick filament, but they rapidly undergo a change in angle of nearly 45 degrees. An ATP molecule bound to each crossbridge supplies the energy for this step. This ATP has been bound to the crossbridge in a partially broken-down form (ADP*P_i in step 1). The myosin head to which the ATP is bound is called "charged myosin" (M*ADP*P_i in step 1). When charged myosin interacts with actin, the association is represented as A*M*ADP*P_i (step 2).

The partial rotation of the angle of the crossbridge is associated with the final hydrolysis of the bound ATP and release of the hydrolysis products (step 3), an inorganic phosphate ion (P_i) and ADP. Since the myosin heads are temporarily attached to the actin filament, the partial rota-

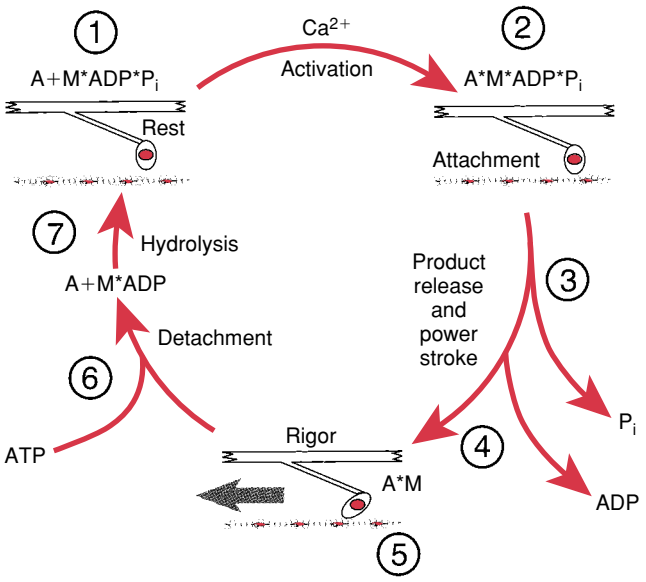

FIGURE 8.10 **The events of the crossbridge cycle in skeletal muscle.** ① At rest, ATP has been bound to the myosin head and hydrolyzed, but the energy of the reaction cannot be released until ② the myosin head can interact with actin. ③ The release of the hydrolysis products is associated with ④ the power stroke. ⑤ The rotated and still-attached crossbridge is now in the rigor state. ⑥ Detachment is possible when a new ATP molecule binds to the myosin head and is ⑦ subsequently hydrolyzed. These cyclic reactions can continue as long as the ATP supply remains and activation (via Ca^{2+}) is maintained. (See text for further details.) A, actin; M, myosin; *, chemical bond; +, a potential interaction.

tion pulls the actin filaments past the myosin filaments, a movement called the **power stroke** (step 4). Following this movement (which results in a relative filament displacement of around 10 nm), the actin-myosin binding is still strong and the crossbridge cannot detach; at this point in the cycle, it is termed a **rigor crossbridge** (A*M, step 5). For detachment to occur, a new molecule of ATP must bind to the myosin head (M*ATP, step 6) and undergo partial hydrolysis to M*ADP*P_i (step 7).

Once this new ATP binds, the newly recharged myosin head, momentarily not attached to the actin filament (step 1), can begin the cycle of attachment, rotation, and detachment again. This can go on as long as the muscle is activated, a sufficient supply of ATP is available, and the physiological limit to shortening has not been reached. If cellular energy stores are depleted, as happens after death, the crossbridges cannot detach because of the lack of ATP, and the cycle stops in an attached state (at step 5). This produces an overall stiffness of the muscle, which is observed as the **rigor mortis** that sets in shortly after death.

The crossbridge cycle obviously must be subject to control by the body to produce useful and coordinated muscular movements. This control involves several cellular processes that differ among the various types of muscle. Here, again, the case of skeletal muscle provides the basic description of the control process.

THE ACTIVATION AND INTERNAL CONTROL OF MUSCLE FUNCTION

Control of the contraction of skeletal muscle involves many steps between the arrival of the action potential in a motor nerve and the final mechanical activity. An important series of these steps, called **excitation-contraction coupling**, takes place deep within a muscle fiber. This is the subject of the remainder of this chapter; the very early events (communication between nerve and muscle) and the very late events (actual mechanical activity) are discussed in Chapter 9.

The Interaction Between Calcium and Specialized Proteins Is Central to Muscle Contraction

The most important chemical link in the control of muscle protein interactions is provided by calcium ions. The SR controls the internal concentration of these ions, and changes in the internal calcium ion concentration have profound effects on the actions of the contractile proteins of muscle.

Calcium and the Troponin-Tropomyosin Complex. The chemical processes of the crossbridge cycle in skeletal muscle are in a state of constant readiness, even while the muscle is relaxed. Undesired contraction is prevented by a specific inhibition of the interaction between actin and myosin. This inhibition is a function of the troponin-tropomyosin complex of the thin myofilaments. When a muscle is relaxed, calcium ions are at very low concentration in the region of the myofilaments. The long tropomyosin molecules, lying in the grooves of the entwined actin filaments, interfere with the myosin binding sites on the actin molecules. When calcium ion concentrations increase, the ions bind to the Tn-C subunit associated with each tropomyosin molecule. Through the action of Tn-I and Tn-T, calcium binding causes the tropomyosin molecule to change its position slightly, uncovering the myosin binding sites on the actin filaments. The myosin (already "charged" with ATP) is allowed to interact with actin, and the events of the crossbridge cycle take place until calcium ions are no longer bound to the Tn-C subunit.

The Switching Action of Calcium. An effective switching function requires the transition between the "off" and "on" states to be rapid and to respond to relatively small changes in the controlling element. The calcium switch in skeletal muscle satisfies these requirements well (Fig. 8.11). The curve describing the relationship between the relative force developed and the calcium concentration in the region of the myofilaments is very steep. At a calcium concentration of 1×10^{-8} M, the interaction between actin and myosin is negligible, while an increase in the calcium concentration to 1×10^{-5} M produces essentially full force development. This process is saturable, so that further increases in calcium concentration lead to little increase in force. In skeletal muscle, an excess of calcium ions is usually present during activation, and the contractile system is normally fully saturated. In cardiac and smooth muscle, however, only partial saturation occurs under normal conditions, and the

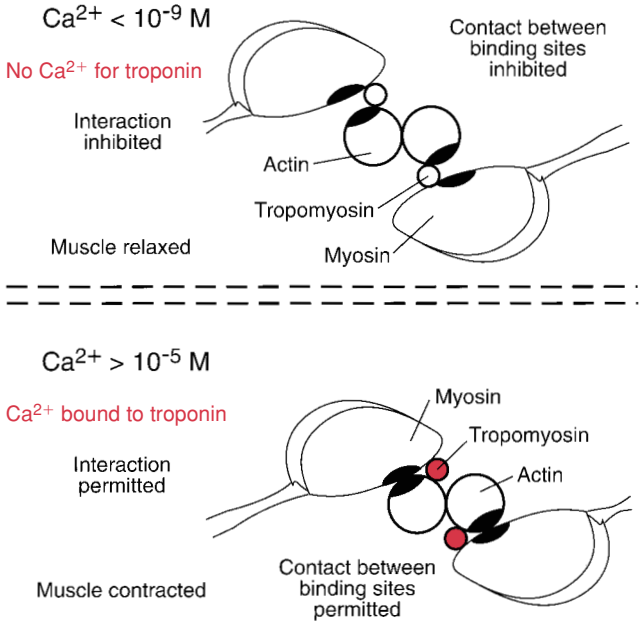

FIGURE 8.11 **The calcium switch for controlling skeletal muscle contraction.** Calcium ions, via the troponin-tropomyosin complex, control the unblocking of the interaction between the myosin heads (the crossbridges) and the active site on the thin filaments. The geometry of each tropomyosin molecule allows it to exert control over seven actin monomers.

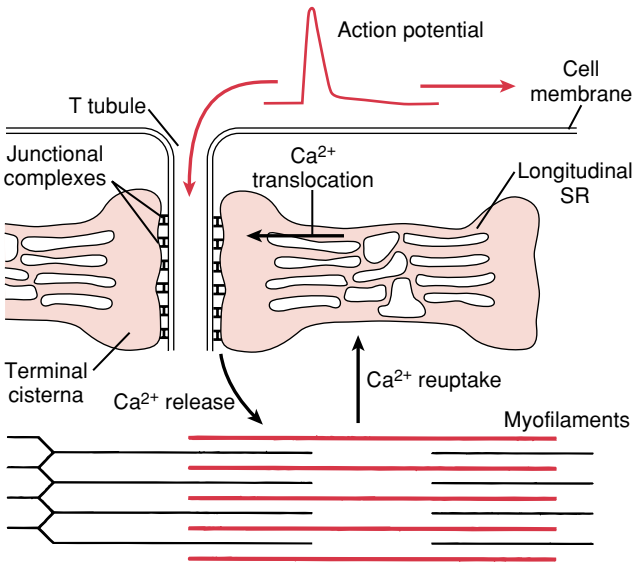

FIGURE 8.12 **Excitation-contraction coupling and the cyclic movement of calcium.** (See text for details of the process.)

degree of muscle activation can be adjusted by controlling the calcium concentration.

The switching action of the calcium-troponin-tropomyosin complex in skeletal and cardiac muscle is extended by the structure of the thin filaments, which allows one troponin molecule, via its tropomyosin connection, to control seven actin monomers. Since the calcium control in striated muscle is exercised through the thin filaments, it is termed **actin-linked regulation**. While the cellular control of smooth muscle contraction is also exercised by changes in calcium concentration, its effect is exerted on the thick (myosin) filaments. This is termed **myosin-linked regulation** and is described in Chapter 9.

Excitation-Contraction Coupling Links Electrical and Mechanical Events

When a nerve impulse arrives at the neuromuscular junction and its signal is transmitted to the muscle cell membrane, a rapid train of events carries the signal to the interior of the cell, where the contractile machinery is located. The large diameter of skeletal muscle cells places interior myofilaments out of range of the immediate influence of events at the cell surface, but the T tubules, SR, and their associated structures act as a specialized internal communication system that allows the signal to penetrate to interior parts of the cell. The end result of electrical stimulation of the cell is the liberation of calcium ions into regions of the sarcoplasm near the myofilaments, initiating the crossbridge cycle.

The process of excitation-contraction coupling, as outlined in Figure 8.12, begins in skeletal muscle with the electrical excitation of the surface membrane. An action potential sweeps rapidly down the length of the fiber. Its propagation is similar to that in nonmyelinated nerve fibers, in which successive areas of membrane are stimulated by local ionic currents flowing from adjacent areas of excited membrane. The lack of specialized conduction adaptations (e.g., myelination) makes this propagation slow compared with that in the motor nerve, but its speed is still sufficient to ensure the practically simultaneous activation of the entire fiber. When the action potential encounters the openings of T tubules, it propagates down the T tubule membrane. This propagation is also regenerative, resulting in numerous action potentials, one in each T tubule, traveling toward the center of the fiber. In the T tubules, the velocity of the action potentials is rather low, but the total distance to be traveled is quite short.

At some point along the T tubule, the action potential reaches the region of a triad. Here the presence of the action potential is communicated to the terminal cisternae of the SR. While the precise nature of this communication is not yet fully understood, it appears that the T tubule action potential affects specific protein molecules called **dihydropyridine receptors** (DHPRs). These molecules, which are embedded in the T tubule membrane in clusters of four, serve as **voltage sensors** that respond to the T tubule action potential. They are located in the region of the triad where the T tubule and SR membranes are the closest together, and each group of four is located in close proximity to a specific channel protein called a **ryanodine receptor** (**RyR**), which is embedded in the SR membrane. The RyR serves as a controllable channel (termed a **calcium-release channel**) through which calcium ions can move readily when it is in the open state. DHPR and RyR form a functional unit called a **junctional complex** (Fig. 8.12).

When the muscle is at rest, the RyR is closed; when T tubule depolarization reaches the DHPR, some sort of linkage—most likely a mechanical connection—causes the

RyR to open and release calcium from the SR. In skeletal muscle, every other RyR is associated with a DHPR cluster; the RyRs without this connection open in response to calcium ions in a few milliseconds. This leads to rapid release of calcium ions from the terminal cisternae into the intracellular space surrounding the myofilaments. The calcium ions can now bind to the Tn-C molecules on the thin filaments. This allows the crossbridge cycle reactions to begin, and contraction occurs.

Even during calcium release from the terminal cisternae, the active transport processes in the membranes of the longitudinal elements of the SR pump free calcium ions from the myofilament space into the interior of the SR. The rapid release process stops very soon; there is only one burst of calcium ion release for each action potential, and the continuous **calcium pump** in the SR membrane reduces calcium in the region of the myofilaments to a low level (1×10^{-8} M). Because calcium ions are no longer available to bind to troponin, the contractile activity ceases and relaxation begins. The resequestered calcium ions are moved along the longitudinal elements to storage sites in the terminal cisternae, and the system is ready to be activated again. This entire process takes place in a few tens of milliseconds and may be repeated many times each second.

ENERGY SOURCES FOR MUSCLE CONTRACTION

Because contracting muscles perform work, cellular processes must supply biochemical energy to the contractile mechanism. Additional energy is required to pump the calcium ions involved in the control of contraction and for other cellular functions. In muscle cells, as in other cells, this energy ultimately comes from the universal high-energy compound, ATP.

Muscle Cells Obtain ATP From Several Sources

Although **ATP** is the immediate fuel for the contraction process, its concentration in the muscle cell is never high enough to sustain a long series of contractions. Most of the immediate energy supply is held in an "energy pool" of the compound **creatine phosphate** or **phosphocreatine** (**PCr**), which is in chemical equilibrium with ATP. After a molecule of ATP has been split and yielded its energy, the resulting ADP molecule is readily rephosphorylated to ATP by the high-energy phosphate group from a creatine phosphate molecule. The creatine phosphate pool is restored by ATP from the various cellular metabolic pathways. These reactions (of which the last two are the reverse of each other) can be summarized as follows:

$$\text{ATP} \rightarrow \text{ADP} + \text{P}_\text{i}\ (\text{Energy for contraction}) \quad (1)$$

$$\text{ADP} + \text{PCr} \rightarrow \text{ATP} + \text{Cr}\ (\text{Rephosphorylation of ATP}) \quad (2)$$

$$\text{ATP} + \text{Cr} \rightarrow \text{ADP} + \text{PCr}\ (\text{Restoration of PCr}) \quad (3)$$

Because of the chemical equilibria involved, the concentration of PCr can fall to very low levels before the ATP concentration shows a significant decline. It has been shown experimentally that when 90% of PCr has been used, the ATP concentration has fallen by only 10%. This situation results in a steady source of ATP for contraction that is maintained despite variations in energy supply and demand. Creatine phosphate is the most important storage form of high-energy phosphate; together with some other smaller sources, this energy reserve is sometimes called the **creatine phosphate pool**.

Two major metabolic pathways supply ATP to energy-requiring reactions in the cell and to the mechanisms that replenish the creatine phosphate pool. Their relative contributions depend on the muscle type and conditions of contraction. A simplified diagram of the energy relationships of muscle is shown in Figure 8.13. The first of the supply pathways is the **glycolytic pathway** or **glycolysis.** This is an **anaerobic** pathway; glucose is broken down without the use of oxygen to regenerate two molecules of ATP for every molecule of glucose consumed. Glucose for the glycolytic pathway may be derived from circulating blood glucose or from its storage form in muscle cells, the polymer **glycogen.** This reaction extracts only a small fraction of the energy contained in the glucose molecule.

The end product of anaerobic glycolysis is **lactic acid** or **lactate**. Under conditions of sufficient oxygen, this is converted to **pyruvic acid** or **pyruvate,** which enters another cellular (mitochondrial) pathway called the **Krebs cycle.** As a result of Krebs cycle reactions, substrates are made available for **oxidative phosphorylation.** The Krebs cycle and oxidative phosphorylation are **aerobic** processes that require a continuous supply of oxygen. In this pathway, an additional 36 molecules of ATP are regenerated from the energy in the original glucose molecule; the final products are carbon dioxide and water. While the oxidative phosphorylation pathway provides the greatest amount of energy, it cannot be used if the oxygen supply is insufficient; in this case, glycolytic metabolism predominates.

Glucose as an Energy Source. **Glucose** is the preferred fuel for skeletal muscle contraction at higher levels of exercise. At maximal work levels, almost all the energy used is derived from glucose produced by glycogen breakdown in muscle tissue and from bloodborne glucose from dietary sources. Glycogen breakdown increases rapidly during the first tens of seconds of vigorous exercise. This breakdown, and the subsequent entry of glucose into the glycolytic pathway, is catalyzed by the enzyme **phosphorylase a.** This enzyme is transformed from its inactive **phosphorylase b** form by a "cascade" of protein kinase reactions whose action is, in turn, stimulated by the increased Ca^{2+} concentration and metabolite (especially AMP) levels associated with muscle contraction. Increased levels of circulating epinephrine (associated with exercise), acting through cAMP, also increase glycogen breakdown. Sustained exercise can lead to substantial depletion of glycogen stores, which can restrict further muscle activity.

Other Important Energy Sources. At lower exercise levels (i.e., below 50% of maximal capacity) fats may provide 50 to 60% of the energy for muscle contraction. Fat, the major energy store in the body, is mobilized from adipose tissue to provide metabolic fuel in the form of **free fatty acids.** This process is slower than the liberation of glucose

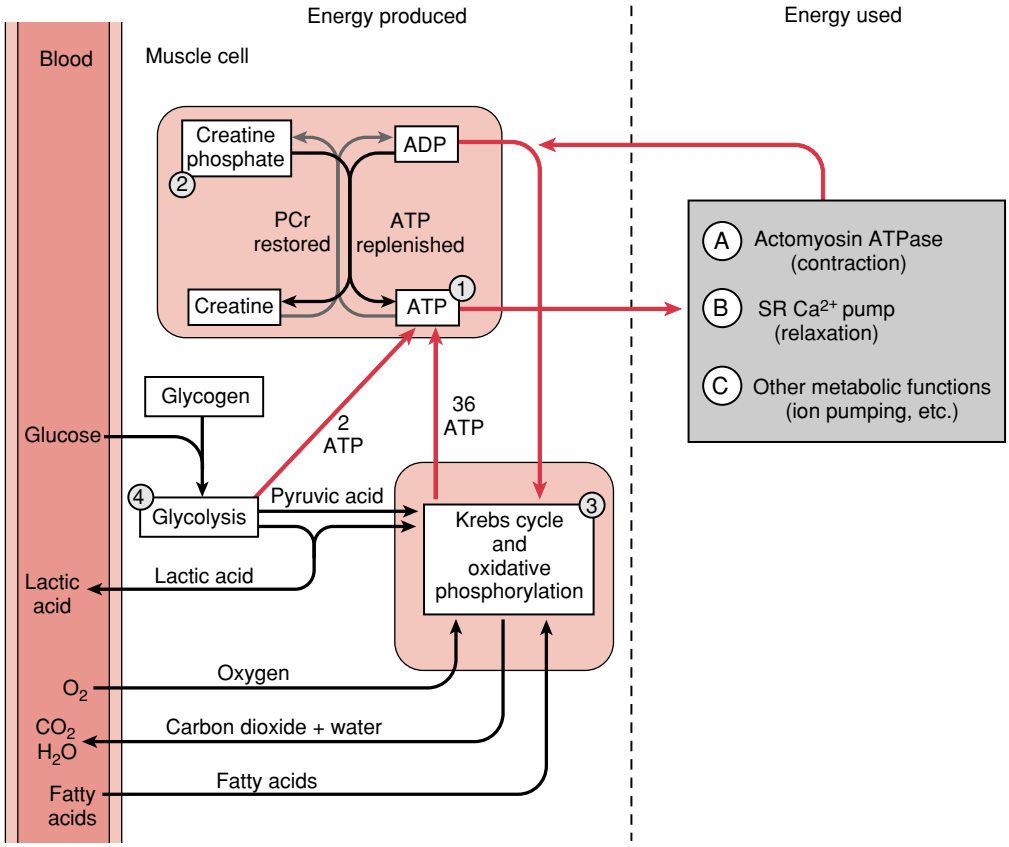

FIGURE 8.13 The major metabolic processes of skeletal muscle. These processes center on the supply of ATP for the actomyosin ATPase of the crossbridges. Energy sources are numbered in order of their proximity to the actual reactions of the crossbridge cycle. Energy is used by the cell in an *A*, *B*, and *C* order. The scheme shown here is typical for all types of muscle, although there are specific quantitative and qualitative variations.

from glycogen and cannot keep pace with the high demands of heavy exercise. Moderate activity, with brief rest periods, favors the consumption of fat as muscle fuel. Fatty acids enter the Krebs cycle at the acetyl-CoA-citrate step. Complete combustion of fat yields less ATP per mole of oxygen consumed than for glucose, but its high energy storage capacity (the equivalent of 138 moles of ATP per mole of a typical fatty acid) makes it an ideal energy store. The depletion of body fat reserves is almost never a limiting factor in muscle activity.

In the absence of other fuels, **protein** can serve as an energy source for contraction. However, protein is used by muscles for fuel mainly during dieting and starvation or during heavy exercise. Under such conditions, proteins are broken down into amino acids that provide energy for contraction and that can be resynthesized into glucose to meet other needs.

Many of the metabolic reactions and processes supplying energy for contraction and the recycling of metabolites (e.g., lactate, glucose) take place outside the muscle, particularly in the liver, and the products are transported to the muscle by the bloodstream. In addition to its oxygen- and carbon dioxide-carrying functions, the enhanced blood supply to exercising muscle provides for a rapid exchange of essential metabolic materials and the removal of heat.

Metabolic Adaptations Allow Contraction to Continue With an Inadequate Oxygen Supply

Glycolytic (anaerobic) metabolism can provide energy for sudden, rapid, and forceful contractions of some muscles. In such cases, the ready availability of glycolytic ATP compensates for the relatively low yield of this pathway, although a later adjustment must be made. In most muscles, especially under conditions of rest or moderate exercise, the supply of oxygen is adequate for aerobic metabolism (fed by fatty acids and by the end products of glycolysis) to supply the energy needs of the contractile system. As the level of exercise increases, several physiological mechanisms come into play to increase the blood supply (and, thus, the oxygen) to the working muscle. At some point, however, even these mechanisms fail to supply sufficient oxygen, and the end products of glycolysis begin to accumulate. The glycolytic pathway can continue to operate because the excess pyruvic acid that is produced is converted to **lactic acid,** which serves as a temporary storage medium. The formation of lactic acid, by preventing a buildup of pyruvic acid, also allows for the restoration of the enzyme cofactor NAD^+, needed for a critical step in the glycolytic pathway, so that the breakdown of glycogen can

continue. Thus, ATP can continue to be produced under anaerobic conditions.

The accumulation of lactic acid is the largest contributor (more than 60%) to **oxygen deficit,** which allows short-term anaerobic metabolism to take place despite a relative lack of oxygen. Other depleted muscle oxygen stores have a smaller capacity but can still participate in oxygen deficit. The largest of these is the creatine phosphate pool (approximately 25%). Tissue fluids (including venous blood) account for another 7%, and the protein myoglobin can hold about 2.5%.

Eventually the lactic acid must be oxidized in the Krebs cycle and oxidative phosphorylation reactions, and the other energy stores (as listed above) must be replenished. This "repayment" of the oxygen deficit occurs over several minutes during recovery from heavy exercise, when the oxygen consumption and respiration rate remain high and depleted ATP is restored from the glucose breakdown products temporarily stored as lactic acid. As the cellular ATP levels return to normal, the energy stored in the creatine phosphate energy pool is also replenished.

Those muscles adapted for mostly aerobic metabolism contain significant amounts of the protein **myoglobin.** This iron-containing molecule, essentially a monomeric form of the blood protein hemoglobin (see Chapter 11), gives aerobic muscles their characteristic red color. The total oxygen storage capacity of myoglobin is quite low, and it does not make a significant direct contribution to the cellular stores; all the myoglobin-bound oxygen could support aerobic exercise for less than 1 second. However, because of its high affinity for oxygen even at low concentrations, myoglobin plays a major role in facilitating the diffusion of oxygen through exercising muscle tissue by binding and releasing oxygen molecules as they move down their concentration gradient.

Muscles of different types have varying capacities for sustaining an oxygen deficit; some skeletal muscles can sustain a considerable deficit, while cardiac muscle has an almost exclusively aerobic metabolism. Chapters 9 and 10 discuss metabolic adaptations that are specific to skeletal, smooth, and cardiac muscles.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. Skeletal, smooth, and cardiac muscle all have which of the following in common?
   (A) Their cellular structure is based on repeating sarcomeres
   (B) The contractile cells are large relative to the size of the organ they comprise.
   (C) The contractile system is based on an enzymatic interaction of actin and myosin.
   (D) Initiation of contraction requires the binding of calcium ions to actin filaments
2. During the shortening of skeletal muscle,
   (A) The distance between Z lines stays the same
   (B) The width of the I band changes
   (C) The width of the A band changes
   (D) All internal spacings between repeating structures change proportionately
3. The compound ATP provides the energy for muscle contraction during the crossbridge cycle. A second important function for ATP in the cycle is to
   (A) Provide the energy for relaxation
   (B) Allow the thick and thin filaments to detach from each other during the crossbridge cycle
   (C) Maintain the separation of thick and thin filaments when the muscle is at rest
   (D) Promote the binding of calcium ions to the regulatory proteins
4. Calcium ions are required for the normal activation of all muscle types. Which statement below most closely describes the role of calcium ions in the control of skeletal muscle contraction?
   (A) The binding of calcium ions to regulatory proteins on the thin filaments removes the inhibition of actin-myosin interaction
   (B) The binding of calcium ions to the thick filament regulatory proteins activates the enzymatic activity of the myosin molecules
   (C) Calcium ions serve as an inhibitor of the interaction of thick and thin filaments
   (D) A high concentration of calcium ions in the myofilament space is required to maintain muscle in a relaxed state.
5. The normal process of relaxation in skeletal muscle depends on
   (A) A sudden reduction in the amount of ATP available for the crossbridge interactions
   (B) Metabolically supported pumping of calcium out of the cells when the membrane potential repolarizes
   (C) A rapid reuptake of calcium into the sarcoplasmic reticulum
   (D) An external force to separate the interacting myofilaments
6. When an isolated skeletal muscle is stretched beyond its optimal length (but not to the point where damage occurs), the reduction in contractile force is due to
   (A) Lengthening of the myofilaments so that crossbridges become spaced farther apart and can interact less readily
   (B) Decreased overlap between thick and thin filaments, which reduces the number of crossbridges that interact
   (C) The thinning of the muscle, which reduces its cross-sectional area and, hence, the force that it can produce
   (D) A proportional reduction in the amount of calcium released from the sarcoplasmic reticulum
7. The major immediate source of calcium for the initiation of skeletal muscle contraction is
   (A) Calcium entry through the sarcolemma during the passage of an action potential
   (B) A rapid release of calcium from its storage sites in the T tubules
   (C) A rapid release of calcium from the terminal cisternae of the sarcoplasmic reticulum
   (D) A release of calcium that is bound to cytoplasmic proteins in the region of the myofilaments
8. The relaxation of skeletal muscle is associated with a reduction in free intracellular calcium ion concentration. The effect of this reduction is
   (A) A reestablishment of the inhibition of the actin-myosin interaction
   (B) Deactivation of the enzymatic activity of the individual actin molecules

(continued)

(C) A change in the chemical nature of the myosin molecules, reducing their enzymatic activity
(D) Reduced contractile interaction by the binding of calcium to the active sites of the myosin molecules

9. The chemical energy source that most directly supports muscle contraction is
(A) Creatine phosphate
(B) Glucose
(C) ATP
(D) Free fatty acids

10. In the absence of an adequate supply of ATP for skeletal muscle contraction,
(A) Myofilament interaction ceases, and the muscle relaxes
(B) Actin and myosin filaments cannot separate, and the muscle stiffens
(C) Creatine phosphate can directly support myofilament interaction, although less efficiently
(D) The lower energy form, ADP, can support contraction at a reduced rate

11. In the face of insufficient oxygen to meet its current metabolic requirements, skeletal muscle
(A) Quickly loses its ability to contract and relaxes until oxygen is again available
(B) Maintains contraction by using metabolic pathways that do not require oxygen consumption
(C) Maintains contraction by using a large internal store of ATP that is kept in reserve
(D) Contracts more slowly at a given force, resulting in a saving of energy

12. If the calcium pumping ability of the sarcoplasmic reticulum were impaired (but not abolished),
(A) Muscles would relax more quickly because less calcium would be pumped
(B) Contraction would be slowed, but the muscle would relax normally
(C) The muscle would continue to develop force, but its relaxation would be slowed
(D) Activation of the muscle would no longer be possible

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