polymorphisms appear to have different allele frequencies in specific ethnic groups.

CELLULAR BASIS OF CARDIAC CONTRACTION

CARDIAC ULTRASTRUCTURE

About three-fourths of the ventricular mass is composed of cardiomyocytes, normally 60–140 μm in length and 17–25 μm in diameter (Fig. 265e-4*A*). Each cell contains multiple, rodlike cross-banded strands (myofibrils) that run the length of the cell and are composed of serially repeating structures, the sarcomeres. The cytoplasm between the myofibrils contains other cell constituents, including the single centrally located nucleus, numerous mitochondria, and the intracellular membrane system, the sarcoplasmic reticulum.

The *sarcomere*, the structural and functional unit of contraction, lies between adjacent Z lines, which are dark repeating bands that are apparent on transmission electron microscopy. The distance between Z lines varies with the degree of contraction or stretch of the muscle and ranges between 1.6 and 2.2 μm. Within the confines of the sarcomere are alternating light and dark bands, giving the myocardial fibers their striated appearance under the light microscope. At the center of the sarcomere is a dark band of constant length (1.5 μm), the A band, which is flanked by two lighter bands, the I bands, which are of variable length. The sarcomere of heart muscle, like that of skeletal muscle, consists of two sets of interdigitating myofilaments. Thicker filaments, composed principally of the protein myosin, traverse the A band; they are about 10 nm (100 Å) in diameter, with tapered ends. Thinner filaments, composed primarily of actin, course from the Z lines through the I band into the A band; they are approximately 5 nm (50 Å) in diameter and 1.0 μm in length. Thus, thick and thin filaments overlap only within the (dark) A band, whereas the (light) I band contains only thin filaments. On electron-microscopic examination, bridges may be seen to extend between the thick and thin filaments within the A band; these are myosin heads (see below) bound to actin filaments.

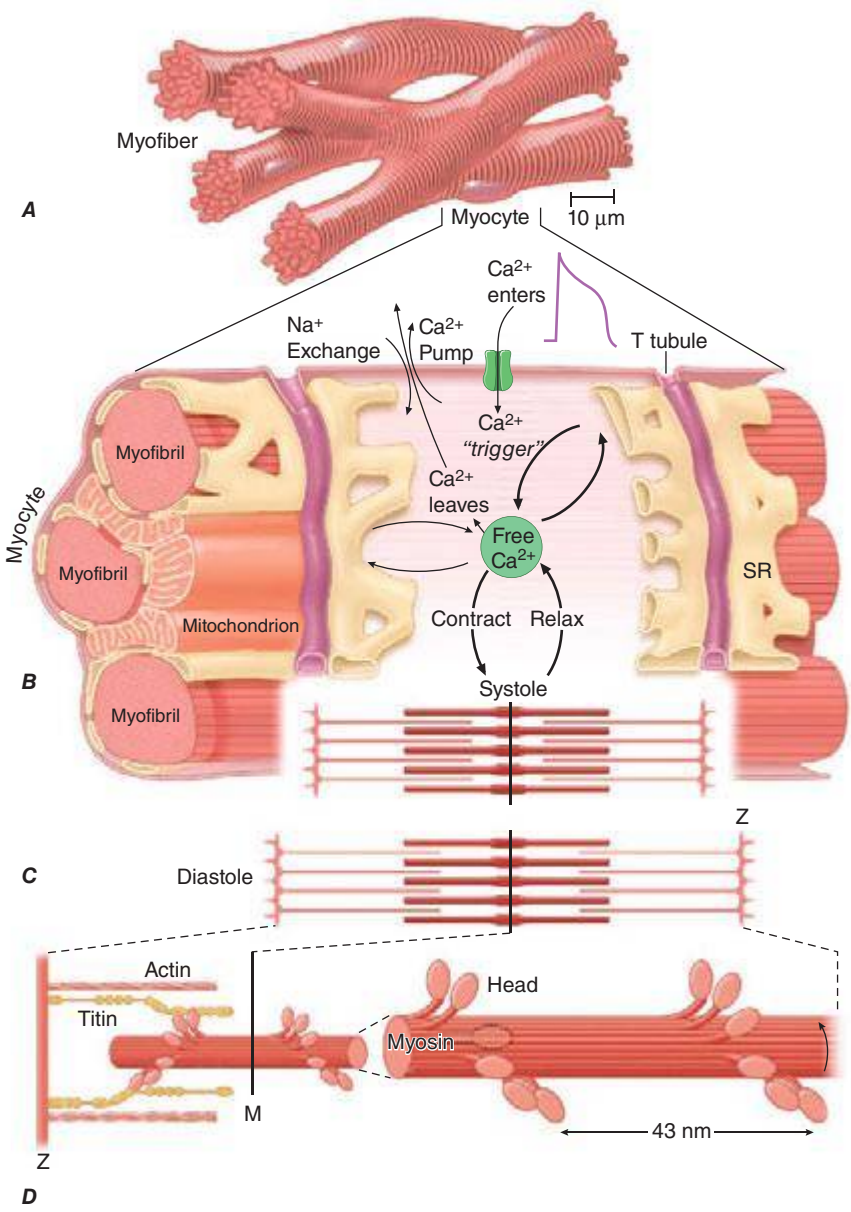

FIGURE 265e-4 ***A*** shows the branching myocytes making up the cardiac myofibers. ***B*** illustrates the critical role played by the changing [Ca^{2+}] in the myocardial cytosol. Ca^{2+} ions are schematically shown as entering through the calcium channel that opens in response to the wave of depolarization that travels along the sarcolemma. These Ca^{2+} ions "trigger" the release of more calcium from the sarcoplasmic reticulum (SR) and thereby initiate a contraction-relaxation cycle. Eventually the small quantity of Ca^{2+} that has entered the cell leaves predominantly through an Na^+/Ca^{2+} exchanger, with a lesser role for the sarcolemmal Ca^{2+} pump. The varying actin-myosin overlap is shown for (***B***) systole, when [Ca^{2+}] is maximal, and (***C***) diastole, when [Ca^{2+}] is minimal. ***D.*** The myosin heads, attached to the thick filaments, interact with the thin actin filaments. *(From LH Opie: Heart Physiology: From Cell to Circulation, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2004. Reprinted with permission. Copyright LH Opie, 2004.)*

THE CONTRACTILE PROCESS

The sliding filament model for muscle contraction rests on the fundamental observation that both the thick and the thin filaments are constant in overall length during both contraction and relaxation. With activation, the actin filaments are propelled farther into the A band. In the process, the A band remains constant in length, whereas the I band shortens and the Z lines move toward one another.

The *myosin* molecule is a complex, asymmetric fibrous protein with a molecular mass of about 500,000 Da; it has a rodlike portion that is about 150 nm (1500 Å) in length with a globular portion (head) at its end. These globular portions of myosin form the bridges between the myosin and actin molecules and are the site of ATPase activity. In forming the thick myofilament, which is composed of ~300 longitudinally stacked myosin molecules, the rodlike segments of the myosin molecules are laid down in an orderly, polarized manner, leaving the globular portions projecting outward so that they can interact with actin to generate force and shortening (Fig. 265e-4*B*).

Actin has a molecular mass of about 47,000 Da. The thin filament consists of a double helix of two chains of actin molecules wound about each other on a larger molecule, tropomyosin. A group of regulatory proteins—troponins C, I, and T—are spaced at regular intervals on this filament (Fig. 265e-5). In contrast to myosin, actin lacks intrinsic enzymatic activity but does combine reversibly with myosin in the presence of ATP and Ca^{2+}. The calcium ion activates the myosin ATPase, which in turn breaks down ATP, the energy source for contraction (Fig. 265e-5). The activity of myosin ATPase determines the rate of forming and breaking of the actomyosin cross-bridges and ultimately the velocity of muscle contraction. In relaxed muscle, tropomyosin inhibits this interaction. *Titin* (Fig. 265e-4*D*) is a large, flexible, myofibrillar protein that connects myosin to the Z line; its stretching contributes to the elasticity of the heart.