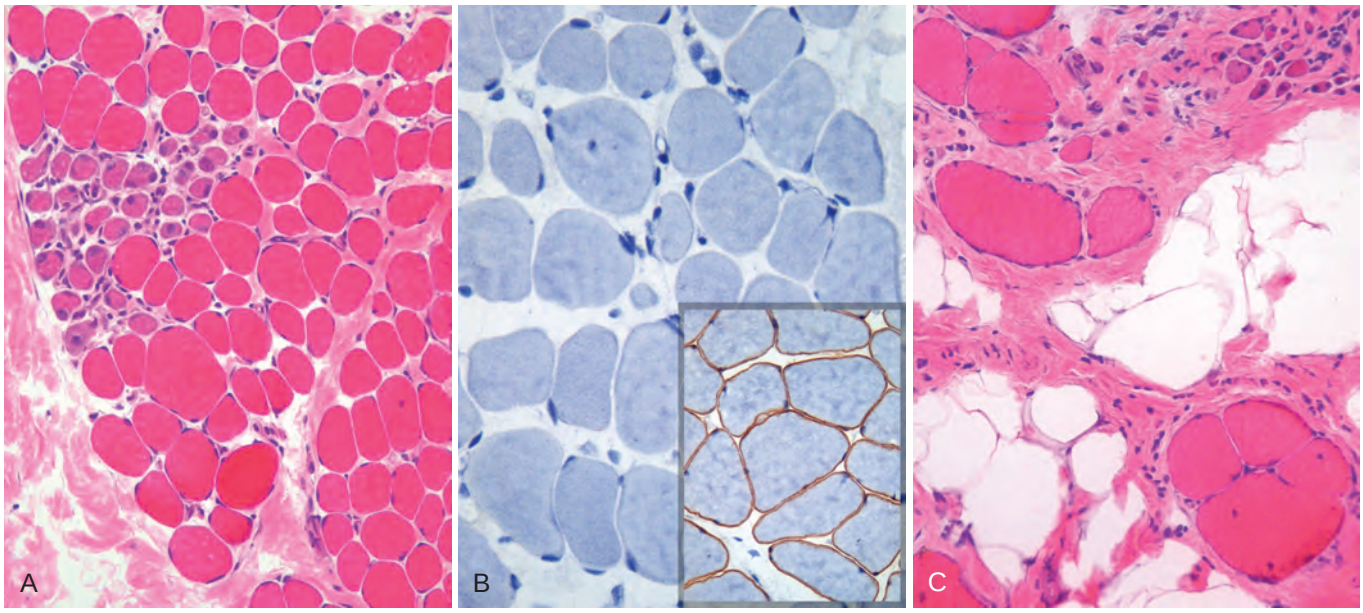

Figure 27-11 Duchenne muscular dystrophy. Histologic images of muscle biopsy specimens from two brothers. **A** and **B,** Specimens from a 3-year-old boy. **C,** Specimen from his 9-year old brother. As seen in **A,** at a younger age fascicular muscle architecture is maintained, but myofibers show variation in size. Additionally, there is a cluster of basophilic regenerating myofibers (*left side*) and slight endomysial fibrosis, seen as focal pink-staining connective tissue between myofibers. In **B,** immunohistochemical staining shows complete absence of membrane-associated dystrophin, seen as a brown stain in normal muscle (*inset*). In **C,** the biopsy from the older brother illustrates disease progression, which is marked by extensive variation in myofiber size, fatty replacement, and endomysial fibrosis.

and there is usually no inflammation except for the presence of myophagocytosis. As the disease progresses, muscle tissue is replaced by collagen and fat cells (**"fatty replacement"** or "fatty infiltration"). The remaining myofibers at this point in the course show prominent variation in size, from small atrophic fibers to large hypertrophied fibers. This remodeling distorts the fascicular architecture of the muscle, which becomes markedly abnormal over time. **Immunohistochemical studies for dystrophin show absence of the normal sarcolemmal staining pattern in Duchenne muscular dystrophin and reduced staining in Becker muscular dystrophy.**

Clinical Features. Boys with Duchenne muscular dystrophy are normal at birth. Very early motor milestones are met, but walking is often delayed. The first indications of muscle weakness are clumsiness and inability to keep up with peers. Weakness begins in the pelvic girdle muscles and then extends to the shoulder girdle. Enlargement of the muscles of the lower leg associated with weakness, termed *pseudohypertrophy*, is often present. The mean age of wheel chair dependence is around 9.5 years. Patients develop joint contractures, scoliosis, worsening respiratory reserve, and sleep hypoventilation.

Dystrophin is also expressed in the heart and the central nervous system, hence both are affected. Dystrophin deficiency in cardiac muscle often leads to the development of cardiomyopathy and arrhythmias, particulary in older patients. Cognitive impairment, presumably due to a functional role for dystrophin in the brain, is also common and sometimes produces frank mental retardation. Despite supportive care, the mean age of death for patients with Duchenne muscular dystrophy is 25 to 30 years of age, with most patients succumbing to respiratory insufficiency, pulmonary infection, or heart failure. In contrast, Becker muscular dystrophy presents in later childhood, adolescence or adult life. Its course is more slowly progressive often with a near normal life expectancy.

The diagnosis is based on the history, physical exam, and laboratory studies. Serum creatine kinase is markedly elevated during the first decade of life due to ongoing muscle damage, and then falls as the disease progresses and muscle mass is lost. The presence of a dystrophin mutation can be confirmed by genetic studies.

Treatment of patients with dystrophinopathies is challenging. Current treatment consists primarily of supportive care. Definitive therapy requires restoration of dystrophin levels in skeletal and cardiac muscle fibers. Work in this area is emboldened by the recognition that expression of some dystrophin protein (as in patients with Becker muscular dystrophy) is sufficient to substantially ameliorate the disease phenotype. One approach involves the expression of antisense RNAs that alter RNA splicing so as to cause "skipping" of exons containing deleterious mutations, thus permitting the expression of a truncated, but partially functional, dystrophin protein. A second strategy is exploring the use of drugs that promote ribosomal "read-through" of stop codons, another ploy that may enable the expression of some dystrophin protein. Both of these approaches are mutation-specific and thus need to be tailored to individual patients. Gene therapy (introduction of a normal dystrophin gene) is being investigated, but gene delivery to skeletal muscle cells remains a daunting hurdle.

Myotonic Dystrophy

Myotonic dystrophy is an autosomal dominant multisystem disorder associated with skeletal muscle weakness,