accumulate within lysosomes. Severe deficiency results in the generalized glycogenosis of infancy, *Pompe disease* (Chapter 5). Milder deficiency can cause a progressive adult onset myopathy that preferentially involves the respiratory and truncal muscles. Enzyme replacement therapy is now being used to treat affected patients.

Mitochondrial Myopathies

Mitochondrial diseases are complex systemic conditions that can involve many organ systems, including skeletal muscle. The genetics of these disorders are varied and unusually complex (discussed later), but many of the causative mutations appear to impair the ability of mitochondria to generate ATP. As a result, these diseases tend to affect skeletal muscles and other tissues rich in cell types with high ATP requirements, particularly cardiac muscle cells and neurons.

Skeletal muscle involvement can manifest as weakness, elevations in serum creatine kinase levels, or rhabdomyolysis. Although the anatomic pattern of muscle weakness is variable, involvement of extraocular eye muscles is common and can be a clue to the diagnosis. Indeed, *chronic progressive external ophthalmoplegia* is a common feature of mitochondrial disorders, and may occur as an isolated phenomenon or a part of a multisystem syndrome. The reason that extraocular eye muscles are particularly sensitive to mitochondrial disease is uncertain, but it may be that these muscles have exceptionally high requirements for ATP. In line with this idea, extraocular eye muscles have the most mitochondria per mass of any of the body's muscles.

Mitochondrial proteins and tRNAs may be encoded by either the nuclear genome or the mitochondrial genome (mtDNA). While mutations in nuclear mitochondrial genes follow Mendelian inheritance patterns, mutations in mtDNA are maternally inherited, since all of the mitochondria in the embryo are contributed by the oocyte (Chapter 5). In addition, unlike nuclear DNA, which is present in only two copies and is evenly distributed from a mother cell to daughter cells during cell division, each cell contains thousands of mtDNA copies, which are distributed in a random fashion to daughter cells at the time of cell division. It is believed that disease results only when a certain threshold of mutated mtDNA copies is exceeded within a substantial fraction of "at-risk" cells (e.g., skeletal muscle cells) in a tissue.

MORPHOLOGY

The most consistent pathologic change in skeletal muscle is abnormal aggregates of mitochondria that are seen preferentially in the subsarcolemmal area of affected myofibers, producing an appearance that is referred to as "ragged red fibers" (Fig. 27-12). By electron microscopy, morphologically abnormal mitochondria are seen. Loss of particular mitochondrial enzyme activities characterizes some mitochondrial diseases and may be appreciated by histochemical staining for cytochrome oxidase. Some mitochondrial diseases lack morphologic changes and can only be diagnosed through enzymatic assays or genetic analyses.

Clinical Features. Due to the complexity of mitochondrial genetics, genotype/phenotype relationships in mitochondrial disorders are not straightforward. For example, a single point mutation in the mitochondrial leucine tRNA gene may produce isolated chronic progressive external ophthalmoplegia in one patient and a much more severe phenotype, *mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes*, in a second. Similarly, deletions in mtDNA may lead to either isolated ophthalmoplegia or to *Kearns-Sayre syndrome*, characterized by ophthalmoplegia, pigmentary degeneration of the retina, and complete heart block. *Myoclonic epilepsy with ragged red fibers* and *Leber hereditary optic neuropathy* are other examples of mitochondrial disease caused by point mutations in mtDNA. Many mitochondrial disorders, such as subacute necrotizing encephalopathy (*Leigh syndrome*), are remarkably heterogeneous genetically and may be caused by mutations in either mtDNA or the nuclear genome. In the case of Leigh syndrome, at last count causative mutations have been identified in more than 30 different genes, the common feature being that all of the affected genes encode proteins with essential roles in mitochondrial metabolism.

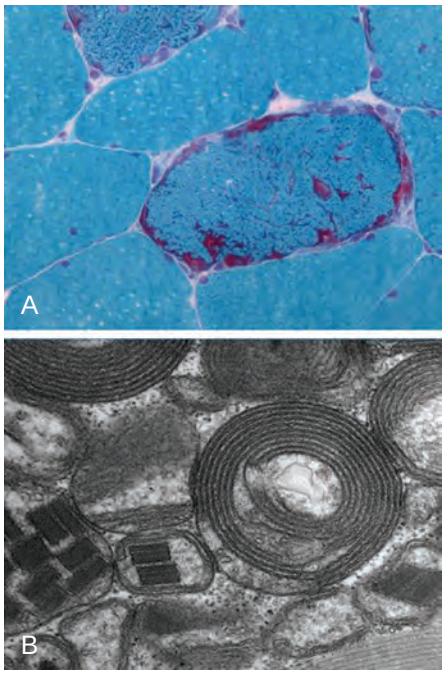

Figure 27-12 **A,** Ragged red fiber with increased reddish granular subsarcolemmal staining reflective of abnormal aggregation of mitochondria. **B,** Electron micrograph showing morphologically abnormal mitochondria with concentric membranous rings (so-called "phonograph records") and rhomboid paracrystalline inclusions (*lower left side*).

Spinal Muscular Atrophy and the Differential Diagnosis of a Hypotonic Infant

Spinal muscular atrophy is a neuropathic disorder in which loss of motor neurons leads to muscle weakness and atrophy. Infants with neurologic or neuromuscular disease may present with generalized hypotonia ("floppy infant"). The differential diagnosis of infantile hypotonia includes primary diseases of skeletal muscle (e.g., congenital myasthenic syndrome, congenital myotonia, congenital myopathies, and congenital muscular dystrophies),