supplanted by other related drugs with a similar mechanism of action.

KEY CONCEPTS

Diseases of the Neuromuscular Junction

- Disorders of neuromuscular junctions present with painless weakness.
- Myasthenia gravis and Lambert-Eaton myasthenic syndrome, the most common forms, are both immune mediated, being caused by antibodies to postsynaptic acetylcholine receptors and presynaptic calcium channels, respectively.
- **Myasthenia gravis** is often associated with thymic hyperplasia or thymoma, frequently involves ocular muscles, and is marked by fluctuating weakness that worsens with exertion.
- **Lambert-Eaton** myasthenic presents with weakness in the extremities that improves with repetitive stimulation and is often a paraneoplastic disorder associated with lung cancer.
- Genetic defects in neuromuscular junction proteins give rise to **congenital myasthenic syndromes.**
- **Bacterial toxins** such as Botox can block neuromuscular transmission by blocking the release of acetylcholine from presynaptic neurons.

Diseases of Skeletal Muscle

Skeletal muscle has unique structural, cellular, and molecular characteristics and accordingly unique patterns of injury and repair. During embryogenesis, skeletal muscle develops through the fusion of mononucleated precursor cells (myoblasts) into multinucleated myotubes. These subsequently mature into myofibers (muscle fibers) of varying length that contain thousands of nuclei. In adult tissues, these myofibers are arranged in fascicles, each associated with a small pool of tissue stem cells referred to as satellite cells, which can contribute to muscle regeneration following injury (outlined later). Myofibers are of two main types, type I and type II (Table 27-1), which are admixed in a checkerboard pattern in normal skeletal muscle. Fiber type is determined by signals received from innervating motor neurons and, as a result, all fibers that are part of a motor unit are of the same type.

Skeletal Muscle Atrophy

Skeletal muscle atrophy is a common feature of many disorders. Loss of innervation, disuse, cachexia, old age, and primary myopathies can all produce muscle atrophy and, if the atrophy is severe, loss of muscle mass. Certain patterns of atrophy are suggestive of specific underlying etiologies:

- Clusters or groups of atrophic fibers are seen in neurogenic disease (Fig. 27-7).
- Perifascicular atrophy is seen in dermatomyositis (see later).
- Type II fiber atrophy with sparing of type I fibers is seen with prolonged corticosteroid therapy or disuse.

Table 27-1 Muscle fiber types

	Type I	Type II
Action	Sustained force	Fast movement
Activity type	Aerobic exercise	Anaerobic exercise
Power produced	Low	High
Resistance to fatigue	High	Low
Lipid content	High	Low
Glycogen content	Low	High
Energy metabolism	Low glycolytic capacity, high oxidative capacity	High glycolytic capacity, low oxidative capacity
Mitochondrial density	High	Low
Enzyme activity	NADH-TR, dark staining ATPase at pH 4.3, dark staining ATPase at pH 9.4, light staining	NADH-TR, light staining ATPase at pH 4.3, light staining ATPase at pH 9.4, dark staining
Myosin heavy chain gene expressed	*MYH7*	*MYH2*, *MYH4*, *MYH1*
Color	Red (high myoglobin content)	Pale red / tan (low myoglobin content)
Prototype	Soleus (pigeon)	Pectoral (pigeon)

ATPase, Adenosine triphosphatase; NADH-TR, nicotinamide adenine dinucleotide, reduced form, tetrazolium reductase.

Neurogenic and Myopathic Changes in Skeletal Muscle

Disorders impacting skeletal muscle may do so by damaging myofibers directly (myopathic injury) or by disrupting muscle innervation (neurogenic injury). Neurogenic injuries lead to *fiber type grouping* and *grouped atrophy* (Fig. 27-7), both of which stem from the disruption of muscle innervation. The key to understanding these abnormalities is to recognize that muscle fiber type is determined by the innervating motor neuron and can switch if the innervating motor neuron changes from one type to the other. Following denervation, myofibers undergo atrophy, often assuming a flattened, angulated shape. Reinnervation restores fiber size and shape, but may make a denervated myofiber part of a different motor unit and that may lead to a switch in fiber type. In the face of ongoing axonal or neuronal damage and drop out, residual motor axons may innervate increasingly larger numbers of myofibers, leading to enlargement of motor units, each comprised of a single type of muscle fiber (fiber type grouping). These large motor units are also susceptible to grouped atrophy if the innervating axon is damaged.

In contrast, most primary myopathic processes are associated with a distinct set of morphologic changes that include the following:

- *Segmental myofiber degeneration and regeneration* is seen when only part of a myofiber undergoes necrosis. Degeneration is associated with release of cytoplasmic enzymes into the blood such as creatine kinase, making these useful markers of muscle damage. The sarcomeres and other components of the damaged myofiber segment are removed by macrophages in a process termed *myophagocytosis*. This sets the stage for