12 Muscular Tissue

Objectives
In this chapter we will study
- the distinctions between muscular deconditioning and disuse atrophy;
- the neuromuscular disorders botulism, tetanus, and myasthenia gravis;
- the hereditary disease muscular dystrophy;
- the musculoskeletal disorder fibromyalgia; and
- the uses and risks of muscle relaxants.

Diagnosing Functional Disorders of the Muscular System
Chapter 11 described several muscle disorders that are primarily structural. This chapter focuses on the signs, symptoms, and treatment of muscle disorders that are more physiological in nature. It is important to note that the diagnostic techniques described in chapter 11 are equally useful in diagnosing the conditions discussed in this chapter.

Muscle Deconditioning and Disuse Atrophy
Lack of physical activity can cause a muscle to atrophy. Muscle deconditioning may become apparent within days to weeks of decreased physical activity. For example, we have all known individuals who were physically fit during their high school days and then became less active over time. The cessation of regular activity causes the muscles to decrease in size, but contrary to what some people say, the muscles themselves do not become “fat.” Rather, a continued high level of caloric intake, coupled with decreased activity, leads to increases in fat synthesis and storage by adipose tissue, which shows up most noticeably as subcutaneous fat in various body regions.

Disuse atrophy is a pathological condition in which muscle size is reduced as a result of prolonged inactivity such as bed rest, casting (immobilization of a limb in a cast), or damage to the nerves supplying a muscle (denervation atrophy). Individuals confined to bed have been known to lose up to 3% of their muscle strength per day, and long-term casting can result in the loss of up to 50% of muscle mass.

As a result of disuse, the size of the individual muscle fibers and the oxidative capacity of the mitochondria decline. Muscle fibers can enlarge again if use is restored (for example, when a cast is removed), but regrowth may be compromised if the muscle is not used for more than a year.

Treatments to prevent and/or minimize disuse atrophy focus on moving the immobilized limb, even if in a very limited way. Some of the more common physical therapy treatments are isometric muscle contractions and passive lengthening exercises. In addition, direct electrical stimulation of the immobilized muscles is sometimes used. In this procedure, small surface electrodes are placed on the skin, and a minimal electrical stimulus is applied to the muscle, causing slight contractions that help maintain the muscle.

Neuromuscular Disorders
Some muscular dysfunctions result from disorders of the motor neurons in the nervous system or disorders of the neuromuscular junction, the point where a nerve fiber contacts a skeletal muscle fiber. Motor neurons stimulate skeletal muscle fibers to contract by releasing acetylcholine (ACh). Muscle paralysis can result from several types of disorders: inhibition of ACh release (as in botulism); stimulation of excessive ACh release and overstimulation of the muscle (as in tetanus); reduction of the number of ACh receptors on the muscle fibers (as in myasthenia gravis); or blockage of the receptors so that ACh cannot bind to them (the mechanism involved in curare and some other muscle relaxants).

Botulism
Botulism is a form of poisoning caused by the bacterium Clostridium botulinum, which is often found in spoiled food but also introduced through skin
wounds. *Clostridium* releases the most potent bacterial toxin known—a neurotoxin that prevents motor neurons from releasing ACh. Because these neurons are unable to stimulate the skeletal muscles, the muscles exhibit **flaccid paralysis**—that is, they are limp and unable to contract.

The most common source of botulism in the United States is home-canned food, especially fruit, vegetables, and condiments. The botulism toxin is destroyed by ordinary cooking (boiling for 10 minutes), but the *C. botulinum* spores are highly resistant to heat and require a temperature of 120°C (as in a pressure cooker) to be destroyed. Symptoms of botulism can range from mild digestive upset to severe and fatal reactions. Symptoms typically begin 18 to 36 hours after ingestion; some patients die within 24 hours of exposure. Neuromuscular symptoms typically begin with double vision, difficulty swallowing, and other indications of cranial nerve damage, but then descend to the thoracic muscles where they may lead to paralysis and eventual respiratory arrest.

Patients must be hospitalized and monitored closely. They sometimes require **intubation** (insertion of a nasotracheal tube) or mechanical ventilation. The patient is given antitoxin to neutralize the toxin and antibiotics to eliminate the bacteria. Some patients continue to exhibit recurring symptoms such as weakness and autonomic nervous system dysfunction for as long as a year after exposure.

**Tetanus**

*Tetanus* has two meanings in neuromuscular physiology—a state of sustained muscle contraction that is normal and necessary to all muscular action and a pathological muscle paralysis caused by the bacterium *Clostridium tetani*. *C. tetani* often enters the body through animal bites, punctures, and other unclean skin wounds. It produces a toxin called *tetanospasmin* that causes overstimulation of the muscles. On average, symptoms begin to appear about 7 days after exposure. The muscles exhibit **spastic paralysis**, meaning that they are tense and unable to relax. Often the first effect to be noticed is spasm of the masseter muscles, thus giving tetanus its popular name, “lockjaw.” In severe cases, the patient may suffer violent and intensely painful muscle spasms. Since the thoracic muscles must be able to both contract and relax in order for a person to breathe, the most serious threat from tetanus is the same as in botulism—respiratory arrest.

*C. tetani* produces spores that can survive for years in soil and resist disinfectants and boiling. Worldwide, tetanus occurs predominantly in neonates and takes half a million infant lives per year, owing mainly to unsanitary care of the umbilical cord stump. In the United States, however, neonatal tetanus is rare, and the disease has its greatest incidence among elderly people and men whose occupations, such as farming and construction work, put them at risk of soil-contaminated skin wounds. Women are equally susceptible to tetanus, but less often exposed to the risk factors. All people working in the health-care professions have an increased risk of infection, necessitating a conscientious regimen of tetanus vaccination.

A patient with tetanus is kept in a quiet room in intensive care and sheltered from unnecessary stimulation such as noise and light, which can set off violent spasms. Because of the risk of laryngospasm and suffocation, it is important to keep the airway open. An antitoxin is given to bind and neutralize the tetanus toxin, and drugs are used to ease the muscle spasms by various mechanisms. Tetanus can be prevented with a vaccine consisting of an inactivated form of the tetanus toxin; this vaccine stimulates the body to produce antibodies against the toxin. If the toxin is later introduced into the body, these antibodies can incapacitate it before it does any neuromuscular harm. However, periodic booster vaccinations are needed to maintain this immunity.

**Myasthenia Gravis**

*Myasthenia gravis* (MG) is an autoimmune disorder of the skeletal muscles. Some further perspectives are added here.

Myasthenia gravis results in a loss of ACh receptors (AChR) from the neuromuscular junction. As a result, nerve fibers become less and less able to excite muscle fibers, leading to muscle weakness and paralysis. Between 70% and 80% of MG patients exhibit pathologies of the thymus, and 15% have thymic tumors. In addition, MG has been linked to other autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis (see chapter 10). Of children born to mothers with MG, 10% to 15% exhibit signs of the disease.

MG is divided into three types, depending on the muscles affected. *Generalized myasthenia* involves
muscles throughout the body. **Ocular myasthenia** involves the muscles of the eye. **Bulbar myasthenia** involves the muscles innervated by cranial nerves IX, X, XI, and XII. (These nerves are described in chapter 15) Of the three types of MG, bulbar myasthenia progresses most rapidly, and ocular myasthenia occurs most often in males. Generalized myasthenia follows a number of different courses—one characterized by periodic remissions, another that progresses slowly, and a third that progresses rapidly and is called “fulminating.”

MG progresses differently in all patients. It typically begins with increased fatigue after exercise and a history of recurring respiratory tract infections. The first muscles that are noticeably affected are those of the head and neck, especially facial and eye muscles. As it progresses to other muscles, the patient may exhibit a drooping or expressionless face, drooling, difficulty swallowing, an altered voice, difficulty holding the head erect, impaired breathing, and coughing. A **myasthenic crisis** occurs when the patient exhibits quardriparesis or quardriplegia—weakness or paralysis, respectively, of all four limbs. Respiratory paralysis may be not far behind.

In mild cases, spontaneous remission may occur. In others, the disease is characterized by periods of illness followed by intervals of weeks or months that are symptom-free. As MG progresses, the disease periods become longer in duration, and the intervals between them become shorter.

Myasthenia gravis is treated with **cholinesterase inhibitors** and **immunosuppressants**. **Plasmapheresis** is used to remove some of the autoantibodies from the blood. This is a procedure in which blood is removed from the patient and then centrifuged to separate the red blood cells (RBCs) from the plasma. The RBCs are resuspended in physiological saline and returned to the patient’s body, while the plasma with the autoantibodies in it is discarded. Because the thymus stimulates the immune system, physicians treating MG may recommend its removal (thymectomy).

**Muscular Dystrophy**

**Muscular dystrophy** (MD) is a family of inherited diseases characterized by degeneration of skeletal muscles. Four common forms of MD are Duchenne, limb-girdle, facioscapulohumeral, and myotonic. Table 12.1 shows how these types differ in age at onset, rate of progression, inheritance pattern, and distribution of affected muscles.

The skeletal muscles of affected individuals have a genetic abnormality that is thought to interfere with normal muscle cell metabolism. Affected cells exhibit an increased number of nuclei, which are arranged in chains in the center of the muscle fiber. The muscle fibers undergo necrosis and fragmentation; their myofilaments dissolve. The muscle fibers may be swollen and show irregular striations. Affected muscles exhibit both hypertrophied and atrophied muscle fibers as well as fatty and fibrous infiltration.

MD is diagnosed by a number of methods, including observation of the patient’s gait and facial features. Some patients also exhibit tonic muscle spasms. Once a type of muscular dystrophy is suspected, the clinician often uses electromyography (EMG), muscle biopsy, and evaluation of serum enzymes to arrive at a final diagnosis. Analysis of the muscle fibers of patients with Duchenne muscular dystrophy reveals a decreased amount of dystrophin, a protein essential for normal cellular structure and function, and often shows an increased number of abnormal mitochondria. Blood tests show elevated amounts of serum enzymes associated with skeletal muscle.

Each type of muscular dystrophy has a specific treatment regimen. Duchenne muscular dystrophy has no known cure, so the primary goal is to maintain function in unaffected muscle groups and delay the time when the patient must be confined to a wheelchair. Treatment involves range-of-motion exercises, surgical correction of contractures, and special braces. Treatment of facioscapulohumeral and limb-girdle dystrophies includes physical therapy to minimize contractures and orthotic devices for the ankle and foot to help maintain ambulation.

**Fibromyalgia**

**Fibromyalgia** (myofascial pain syndrome) is a general name describing a group of musculoskeletal disorders characterized by pain, tenderness, and stiffness in muscles, tendon insertions, and adjacent soft tissues. There is no inflammation. The disease is seen most often in individuals aged 30–50 and in 10 times as many women as men.
Table 12.1 The Four Main Types of Muscular Dystrophy

<table>
<thead>
<tr>
<th>Type</th>
<th>Age at Onset</th>
<th>Inheritance Pattern</th>
<th>Distribution of Affected Muscles</th>
<th>Rate of Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne</td>
<td>Around 3 years of age</td>
<td>X-linked recessive</td>
<td>Hips, shoulders, quadriceps femoris, gastrocnemius</td>
<td>Rapid</td>
</tr>
<tr>
<td>Limb-girdle</td>
<td>Variable</td>
<td>Recessive (not yet established)</td>
<td>Pelvic and shoulder girdles</td>
<td>Variable</td>
</tr>
<tr>
<td>Facioscapulohumeral</td>
<td>Between 7 and 20 years of age</td>
<td>Autosomal dominant</td>
<td>Shoulder girdle, neck, face</td>
<td>Moderate</td>
</tr>
<tr>
<td>Myotonic</td>
<td>Birth to age 50</td>
<td>Autosomal dominant</td>
<td>Distal extensors, eyelids, face, neck, hands, pharynx</td>
<td>Fast with younger patients; slower with older patients</td>
</tr>
</tbody>
</table>

The exact cause of fibromyalgia is not known, but its etiology appears to be complex. It is often precipitated by another condition, such as chronic fatigue syndrome, Lyme disease, physical or emotional trauma, viral flu-like illness, or HIV infection. Recent studies have reported that altered muscle metabolism (decreased ATP and ADP and higher AMP) and changes in muscle capillary density may be the cellular cause of fibromyalgia. Other studies suggest that the disease is related to functional abnormalities within the central nervous system, since individuals with fibromyalgia may show decreased serotonin and endorphin production and decreased blood flow in the thalamus, one of the brain regions involved in pain perception.

Fibromyalgia is diagnosed when a patient complains of chronic diffuse pain with a gradual onset that is aggravated by straining and overuse of muscles. The pain is localized to one of nine pairs of tender points: the occiput, trapezius, supraspinatus, gluteal region, greater trochanter, knee, lateral epicondyle, second rib, and lower cervical spine. The pain is often accompanied by a number of other symptoms, such as fatigue, irritable bowel, insomnia, anxiety, headache, and cold sensitivity. In making a diagnosis, it is important to exclude other diseases, such as arthritis, polymyositis, polymyalgia, and connective tissue disorders. Fibromyalgia patients show normal results in EMG, muscle biopsy, and blood chemistry testing.

Once diagnosed, fibromyalgia is treated with a combination of techniques that includes stretching exercises, therapeutic massage, local applications of heat, and aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). However, it is important to note that a single treatment regimen able to relieve symptoms in all patients has not been established. Milder cases of fibromyalgia have been observed to remit spontaneously if stress is decreased, but they can also become chronic and recur at more frequent intervals if stress increases or remains unchanged. Education and reassurance are believed to be extremely important in treating fibromyalgia.

The Clinical Use of Muscle Relaxants

Muscle relaxants are drugs used to inhibit skeletal muscle contraction. They are employed for such purposes as treating spastic muscle contraction and relaxing the abdominal muscles for surgery. They allow a lighter level of general anesthesia, since muscle relaxation is no longer dependent on the anesthetic. Lighter anesthesia reduces the risk of cardiovascular and respiratory depression.

Curare is a naturally occurring muscle relaxant derived from vines of the genus *Strychnos* and other tropical plants. It was first used clinically in 1932 to treat the muscle spasms of tetanus and other
neuromuscular disorders. It was first used in surgery in 1942. Curare acts by blocking ACh receptors, but most muscle relaxants used now act at the level of the central nervous system—for example, by enhancing the activity of neurotransmitters that inhibit motor neurons.

Muscle relaxants must be used with great care, because overdoses can cause side effects ranging from unpleasant (vomiting, double vision, and hallucinations) to life-threatening (cardiac arrhythmia, seizures, and hypotension). They are usually administered by anesthesiologists or others specially trained in their use, and only in clinical settings where cardiovascular and respiratory resuscitation equipment is close at hand if needed.

Case Study 12  The Professor with Double Vision

Max, a 55-year-old college professor, visits his physician for a routine physical. Like most people his age, he has had his share of colds, sprained ankles, scrapes, cuts, and bruises, but no previous serious injury or illness. Max has always been physically active and prides himself on being in good shape for his age. Lately, however, he becomes fatigued more easily than before. He also reports some difficulty chewing and swallowing, and says, “Sometimes I start seeing double when I’m watching the late news on TV.”

While taking Max’s history, the physician notes that he speaks in a somewhat slurred, high-pitched monotone. The doctor asks Max to blink his eyes five times at 2-second intervals. He notices that Max takes longer to reopen his eyes each time, and after the third blink, he keeps his eyes closed for about 15 seconds, almost as if he has fallen asleep. From Max’s medical record, the doctor notes that Max’s mother suffered from rheumatoid arthritis and his father had a thyroid disorder. Results of Max’s physical examination are shown here.

Mental status: Alert
Weight: 172 lb; has lost 10 lb since routine physical 12 months ago
Oral temperature: 98.6°F (37.0°C)
Heart rate: 68 beats/min
Respiratory rate: 11 breaths/min
Blood pressure: 140/85 mmHg
Sensory function: Cannot sustain straight gaze; left eye wanders after 10–15 seconds, and patient reports seeing double.

Movement and reflexes: Voluntary movement somewhat sluggish; some weakness noted in arms; patellar tendon reflex normal.

A blood test reveals the presence of serum antibodies against the ACh receptor, leading to a diagnosis of early myasthenia gravis. The physician then refers Max for a clinical test with a drug called edrophonium. Edrophonium is a cholinesterase inhibitor. When given intravenously, it produces a brief (< 5 min) improvement in muscular function. It must be given in a clinical setting under careful observation, because in conditions other than MG, edrophonium can cause a dangerous depression in cardiopulmonary function.

The physician tells Max that there is no cure for MG, but that the symptoms are treatable. He says MG is a difficult disease to manage, so he refers Max to a specialist who prescribes neostigmine. This is an oral cholinesterase inhibitor that prolongs the action of ACh at the neuromuscular junction by slowing its breakdown by AChE. In order to reduce the autoimmune attack on Max’s neuromuscular junctions, the specialist recommends three measures: (1) thymectomy; (2) plasmapheresis; and (3) prednisone, an immunosuppressive corticosteroid.

The specialist tells Max that he may experience periods of remission, but his symptoms will increase in severity over time. Possible complications include extreme muscle weakness and respiratory difficulties, most likely accompanied by respiratory infections.

Based on this case study and other information in this chapter, answer the following questions.

1. Why do you think Max’s voice is altered by his condition?
2. Many myasthenia gravis patients have difficulty holding their heads erect. Explain.
3. Why do you think Max takes longer and longer to reopen his eyes each time he blinks? In a related vein, why do you think he notices double vision especially when watching the late-night news, rather than at other times of day?

4. Max’s doctor remembers a previous myasthenia gravis patient who said she often woke up in the middle of the night choking on her saliva. Explain why that would occur.

5. A thymectomy will not be done, of course, without Max’s informed consent. The specialist advises Max that, although the benefits of thymectomy outweigh the risks in cases like his, it does carry a risk of increased susceptibility to infectious diseases such as pneumonia. Explain why this would be true.

6. Curare has been known for centuries to the natives of South America, who extract it from a vine and apply it to the tips of the blowgun darts they use for shooting down monkeys and parrots from the high jungle canopy. Explain why curare would be useful for this purpose.

7. Susan, a 16-year-old high school distance runner, is training with her team when she steps in a hole in the ground and feels a “pop” in her left foot. She tries to continue running, but it hurts too much. Suspecting that she has sprained her ankle, her coach refers her to the team doctor, who orders an X ray. To her surprise, Susan learns that she has fractured the third metatarsal bone and will have to wear a cast on her foot for 6 weeks. When the cast is removed, Susan notices that her left calf is markedly smaller than her right. Why did this occur, and how could the size difference have been minimized?

8. Jason, a 3-year-old, explores under the kitchen sink at his grandparents’ house and ingests some ant poison. The warning label on the package says that the active ingredient in the poison is a cholinesterase inhibitor. At the hospital, Jason’s treatment is similar in some ways to the way a tetanus patient would be treated. Predict how the two treatments would be similar and explain why.

9. Carla, a 60-year-old public health nurse, is herself under treatment for myasthenia gravis. Her profession calls for periodic tetanus boosters. Explain why the effectiveness of these booster shots may be compromised by her treatment regimen for MG.

10. Rhonda, who has experienced fatigue and muscle pain for 6 years, has finally been diagnosed with fibromyalgia. She complains to her friend about how long it took to diagnose her condition and accuses the doctors of not knowing what they’re doing. If you were to take the doctors’ side, what would you give as some reasons that fibromyalgia is so hard to diagnose?

**Selected Clinical Terms**

- **Cholinesterase inhibitor**: A chemical that inhibits the action of acetylcholinesterase, thus slowing the rate of acetylcholine (ACh) breakdown and prolonging or intensifying the action of ACh at a synapse.

- **Disuse atrophy**: A loss of muscular mass and strength as a result of the immobilization of a body region or damage to the nerve that innervates a muscle.

- **Flaccid paralysis**: A state in which a muscle is relaxed (flaccid) and unable to contract.

- **Immunosuppressant**: A drug that inhibits the immune system; used for such purposes as treating autoimmune diseases or preventing the immune rejection of a transplanted organ.

- **Intubation**: Insertion of a tube in order to maintain an open (patent) passage such as the airway.

- **Muscle deconditioning**: A loss of muscular mass and strength as a result of reduced exercise.

- **Spastic paralysis**: A state in which a muscle is contracted and unable to relax.