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Information Resources
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Introduction

The first historical account of muscular dystrophy appeared in 1830, when Sir Charles Bell wrote an essay about an illness that caused progressive weakness in boys. Six years later, another scientist reported on two brothers who developed generalized weakness, muscle damage, and replacement of damaged muscle tissue with fat and connective tissue. At that time the symptoms were thought to be signs of tuberculosis.

In the 1850s, descriptions of boys who grew progressively weaker, lost the ability to walk, and died at an early age became more prominent in medical journals. In the following decade, French neurologist Guillaume Duchenne gave a comprehensive account of 13 boys with the most common and severe form of the disease (which now carries his name—Duchenne muscular dystrophy). It soon became evident that the disease had more than one form, and that these diseases affected people of either sex and of all ages.

What is muscular dystrophy?

Muscular dystrophy (MD) refers to a group of more than 30 genetic diseases that cause progressive weakness and degeneration of skeletal muscles used during voluntary movement. The word dystrophy is derived from the Greek dys, which means “difficult” or “faulty,” and troph, or “nourish.” These disorders vary in age of onset, severity, and pattern of affected muscles.
All forms of MD grow worse as muscles progressively degenerate and weaken. Many individuals eventually lose the ability to walk.

Some types of MD also affect the heart, gastrointestinal system, endocrine glands, spine, eyes, brain, and other organs. Respiratory and cardiac diseases may occur, and some people may develop a swallowing disorder. MD is not contagious and cannot be brought on by injury or activity.

**What causes MD?**

All of the muscular dystrophies are inherited and involve a mutation in one of the thousands of genes that program proteins critical to muscle integrity. The body’s cells don’t work properly when a protein is altered or produced in insufficient quantity (or sometimes missing completely). Many cases of MD occur from spontaneous mutations that are not found in the genes of either parent, and this defect can be passed to the next generation.

Genes are like blueprints: they contain coded messages that determine a person’s characteristics or traits. They are arranged along 23 rod-like pairs of chromosomes,* with one-half of each pair being inherited from each parent. Each half of a chromosome pair is similar to the other, except

* Terms in Italics are defined in the Glossary.
for one pair, which determines the sex of the individual. Muscular dystrophies can be inherited in three ways:

- **Autosomal dominant** inheritance occurs when a child receives a normal gene from one parent and a defective gene from the other parent. Autosomal means the genetic mutation can occur on any of the 22 non-sex chromosomes in each of the body’s cells. Dominant means only one parent needs to pass along the abnormal gene in order to produce the disorder. In families where one parent carries a defective gene, each child has a 50 percent chance of inheriting the gene and therefore the disorder. Males and females are equally at risk and the severity of the disorder can differ from person to person.

- **Autosomal recessive** inheritance means that both parents must carry and pass on the faulty gene. The parents each have one defective gene but are not affected by the disorder. Children in these families have a 25 percent chance of inheriting both copies of the defective gene and a 50 percent chance of inheriting one gene and therefore becoming a carrier, able to pass along the defect to their children. Children of either sex can be affected by this pattern of inheritance.

- **X-linked** (or sex-linked) recessive inheritance occurs when a mother carries the affected gene on one of her two X chromosomes and passes it to her son (males always inherit an X chromosome from their mother and a Y chromosome from their father, while daughters inherit an X chromosome from each parent).
Sons of carrier mothers have a 50 percent chance of inheriting the disorder. Daughters also have a 50 percent chance of inheriting the defective gene but usually are not affected, since the healthy X chromosome they receive from their father can offset the faulty one received from their mother. Affected fathers cannot pass an X-linked disorder to their sons but their daughters will be carriers of that disorder. Carrier females occasionally can exhibit milder symptoms of MD.

How many people have MD?

MD occurs worldwide, affecting all races. Its incidence varies, as some forms are more common than others. Its most common form in children, Duchenne muscular dystrophy, affects approximately 1 in every 3,500 to 6,000 male births each year in the United States. Some types of MD are more prevalent in certain countries and regions of the world. Many muscular dystrophies are familial, meaning there is some family history of the disease. Duchenne cases often have no prior family history. This is likely due to the large size of the dystrophin gene that is implicated in the disorder, making it a target for spontaneous mutations.

How does MD affect muscles?

Muscles are made up of thousands of muscle fibers. Each fiber is actually a number of individual cells that have joined together during development and

* Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities, July 17, 2013
Muscles are activated when an impulse, or signal, is sent from the brain through the spinal cord and peripheral nerves (nerves that connect the central nervous system to sensory organs and muscles) to the neuromuscular junction (the space between the nerve fiber and the muscle it activates). There, a release of the chemical acetylcholine triggers a series of events that cause the muscle to contract.

The muscle fiber membrane contains a group of proteins—called the dystrophin-glycoprotein complex—which prevents damage as muscle fibers contract and relax. When this protective membrane is damaged, muscle fibers begin to leak the protein creatine kinase (needed for the chemical reactions that produce energy for muscle contractions) and take on excess calcium, which causes further harm. Affected muscle fibers eventually die from this damage, leading to progressive muscle degeneration.

Although MD can affect several body tissues and organs, it most prominently affects the integrity of muscle fibers. The disease causes muscle degeneration, progressive weakness, fiber death, fiber branching and splitting, phagocytosis (in which muscle fiber material...
is broken down and destroyed by scavenger cells), and, in some cases, chronic or permanent shortening of tendons and muscles. Also, overall muscle strength and tendon reflexes are usually lessened or lost due to replacement of muscle by connective tissue and fat.

Are there other MD-like conditions?

There are many other heritable diseases that affect the muscles, the nerves, or the neuromuscular junction. Such diseases as inflammatory myopathy, progressive muscle weakness, and cardiomyopathy may produce symptoms that are very similar to those found in some forms of MD, but they are caused by different genetic defects. The differential diagnosis for people with similar symptoms includes congenital myopathy, spinal muscular atrophy, and congenital myasthenic syndromes. The sharing of symptoms among multiple neuromuscular diseases, and the prevalence of sporadic cases in families not previously affected by MD, often makes it difficult for people with MD to obtain a quick diagnosis. Gene testing can provide a definitive diagnosis for many types of MD, but not all genes have been discovered that are responsible for some types of MD. Some individuals may have signs of MD, but carry none of the currently recognized genetic mutations. Studies of other related muscle diseases may, however, contribute to what we know about MD.
How do the muscular dystrophies differ?

There are nine major groups of the muscular dystrophies. The disorders are classified by the extent and distribution of muscle weakness, age of onset, rate of progression, severity of symptoms, and family history (including any pattern of inheritance). Although some forms of MD become apparent in infancy or childhood, others may not appear until middle age or later. Overall, incidence rates and severity vary, but each of the dystrophies causes progressive skeletal muscle deterioration, and some types affect cardiac muscle.

**Duchenne MD** is the most common childhood form of MD, as well as the most common of the muscular dystrophies overall, accounting for approximately 50 percent of all cases. Because inheritance is X-linked recessive (caused by a mutation on the X, or sex, chromosome), Duchenne MD primarily affects boys, although girls and women who carry the defective gene may show some symptoms. About one-third of the cases reflect new mutations and the rest run in families. Sisters of boys with Duchenne MD have a 50 percent chance of carrying the defective gene.

Duchenne MD usually becomes apparent during the toddler years, sometimes soon after an affected child begins to walk. Progressive weakness and *muscle wasting* (a decrease in muscle strength and size) caused by degenerating muscle fibers begins in the upper legs and pelvis before spreading into the upper arms. Other symptoms include loss of some reflexes, a waddling gait, frequent falls and clumsiness (especially when running), difficulty when rising from a sitting or lying position or when
climbing stairs, changes to overall posture, impaired breathing, lung weakness, and cardiomyopathy (heart muscle weakness that interferes with pumping ability). Many children are unable to run or jump. The wasting muscles, in particular the calf muscles (and, less commonly, muscles in the buttocks, shoulders, and arms), may be enlarged by an accumulation of fat and connective tissue, causing them to look larger and healthier than they actually are (called pseudohypertrophy). As the disease progresses, the muscles in the diaphragm that assist in breathing and coughing may weaken. Affected individuals may experience breathing difficulties, respiratory infections, and swallowing problems. Bone thinning and scoliosis (curving of the spine) are common. Some affected children have varying degrees of cognitive and behavioral impairments. Between ages 3 and 6, children may show brief periods of physical improvement followed later on by progressive muscle degeneration. Children with Duchenne MD typically lose the ability to walk by early adolescence. Without aggressive care, they usually die in their late teens or early twenties from progressive weakness of the heart muscle, respiratory complications, or infection. However, improvements in multidisciplinary care have extended the life expectancy and improved the quality of life significantly for

This classic illustration depicts Duchenne MD, the most common childhood form of the disorder, characterized by progressive weakness and muscle wasting. As the disease progresses patients may experience breathing difficulties, bone thinning, and scoliosis, or curving of the spine.
these children; numerous individuals with Duchenne muscular dystrophy now survive into their 30s, and some even into their 40s.

Duchenne MD results from an absence of the muscle protein dystrophin. Dystrophin is a protein found in muscle that helps muscles stay healthy and strong. Blood tests of children with Duchenne MD show an abnormally high level of creatine kinase; this finding is apparent from birth.

Becker MD is less severe than but closely related to Duchenne MD. People with Becker MD have partial but insufficient function of the protein dystrophin. There is greater variability in the clinical course of Becker MD compared to Duchenne MD. The disorder usually appears around age 11 but may occur as late as age 25, and affected individuals generally live into middle age or later. The rate of progressive, symmetric (on both sides of the body) muscle atrophy and weakness varies greatly among affected individuals. Many individuals are able to walk until they are in their mid-thirties or later, while others are unable to walk past their teens. Some affected individuals never need to use a wheelchair. As in Duchenne MD, muscle weakness in Becker MD is typically noticed first in the upper arms and shoulders, upper legs, and pelvis.

Early symptoms of Becker MD include walking on one’s toes, frequent falls, and difficulty rising from the floor. Calf muscles may appear large and healthy as deteriorating muscle fibers are replaced by fat, and muscle activity may cause cramps in some people. Cardiac complications are not as consistently present in Becker MD compared to Duchenne MD, but may be as severe in some cases. Cognitive and behavioral
impairments are not as common or severe as in Duchenne MD, but they do occur.

**Congenital MD** refers to a group of autosomal recessive muscular dystrophies that are either present at birth or become evident before age 2. They affect both boys and girls. The degree and progression of muscle weakness and degeneration vary with the type of disorder. Weakness may be first noted when children fail to meet landmarks in motor function and muscle control. Muscle degeneration may be mild or severe and is restricted primarily to skeletal muscle. The majority of individuals are unable to sit or stand without support, and some affected children may never learn to walk. There are three groups of congenital MD:

- **merosin-negative disorders**, where the protein *merosin* (found in the connective tissue that surrounds muscle fibers) is missing;
- **merosin-positive disorders**, in which merosin is present but other needed proteins are missing; and
- **neuronal migration disorders**, in which very early in the development of the fetal nervous system the migration of nerve cells (neurons) to their proper location is disrupted.

Defects in the protein merosin cause nearly half of all cases of congenital MD.

People with congenital MD may develop *contractures* (chronic shortening of muscles or tendons around joints, which prevents the joints from moving freely), scoliosis, respiratory and swallowing difficulties, and foot deformities. Some individuals have normal intellectual development while others become severely impaired. Weakness in diaphragm muscles
may lead to respiratory failure. Congenital MD may also affect the central nervous system, causing vision and speech problems, seizures, and structural changes in the brain. Some children with the disorders die in infancy while others may live into adulthood with only minimal disability.

**Distal MD**, also called distal myopathy, describes a group of at least six specific muscle diseases that primarily affect distal muscles (those farthest away from the shoulders and hips) in the forearms, hands, lower legs, and feet. Distal dystrophies are typically less severe, progress more slowly, and involve fewer muscles than other forms of MD, although they can spread to other muscles, including the proximal ones later in the course of the disease. Distal MD can affect the heart and respiratory muscles, and individuals may eventually require the use of a ventilator. Affected individuals may not be able to perform fine hand movement and have difficulty extending the fingers. As leg muscles become affected, walking and climbing stairs become difficult and some people may be unable to hop or stand on their heels. Onset of distal MD, which affects both men and women, is typically between the ages of 40 and 60 years. In one form of distal MD, a muscle membrane protein complex called dysferlin is known to be lacking.

Although distal MD is primarily an autosomal dominant disorder, autosomal recessive forms have been reported in young adults. Symptoms are similar to those of Duchenne MD but with a different pattern of muscle damage. An infantile-onset form of autosomal recessive distal MD has also been reported. Slow but progressive weakness
is often first noticed around age 1, when the child begins to walk, and continues to progress very slowly throughout adult life.

**Emery-Dreifuss MD** primarily affects boys. The disorder has two forms: one is X-linked recessive and the other is autosomal dominant.

Onset of Emery-Dreifuss MD is usually apparent by age 10, but symptoms can appear as late as the mid-twenties. This disease causes slow but progressive wasting of the upper arm and lower leg muscles and symmetric weakness. Contractures in the spine, ankles, knees, elbows, and back of the neck usually precede significant muscle weakness, which is less severe than in Duchenne MD. Contractures may cause elbows to become locked in a flexed position. The entire spine may become rigid as the disease progresses. Other symptoms include shoulder deterioration, toe-walking, and mild facial weakness. Serum creatine kinase levels may be moderately elevated. Nearly all people with Emery-Dreifuss MD have some form of heart problem by age 30, often requiring a pacemaker or other assistive device. Female carriers of the disorder often have cardiac complications without muscle weakness. Affected individuals often die in mid-adulthood from progressive pulmonary or cardiac failure. In some cases, the cardiac symptoms may be the earliest and most significant symptom of the disease, and may appear years before muscle weakness does.

**Facioscapulohumeral MD** (FSHD) initially affects muscles of the face (facio), shoulders (scapulo), and upper arms (humera) with progressive weakness. Also known as Landouzy-Dejerine disease, this
third most common form of MD is an autosomal dominant disorder. Most individuals have a normal life span, but some individuals become severely disabled. Disease progression is typically very slow, with intermittent spurts of rapid muscle deterioration. Onset is usually in the teenage years but may occur as early as childhood or as late as age 40. One hallmark of FSHD is that it commonly causes asymmetric weakness. Muscles around the eyes and mouth are often affected first, followed by weakness around the shoulders, chest, and upper arms. A particular pattern of muscle wasting causes the shoulders to appear slanted and the shoulder blades to appear winged. Muscles in the lower extremities may also become weakened. Reflexes are diminished, typically in the same distribution as the weakness. Changes in facial appearance may include the development of a crooked smile, a pouting look, flattened facial features, or a mask-like appearance. Some individuals cannot pucker their lips or whistle and may have difficulty swallowing, chewing, or speaking. In some individuals, muscle weakness can spread to the diaphragm, causing respiratory problems. Other symptoms may include hearing loss (particularly at high frequencies) and lordosis, an abnormal swayback curve in the spine. Contractures are rare. Some people with FSHD feel
severe pain in the affected limb. Cardiac muscles are not usually affected, and significant weakness of the pelvic girdle is less common than in other forms of MD. An infant-onset form of FSHD can also cause retinal disease and some hearing loss.

Limb-girdle MD (LGMD) refers to more than 20 inherited conditions marked by progressive loss of muscle bulk and symmetrical weakening of voluntary muscles, primarily those in the shoulders and around the hips. At least five forms of autosomal dominant limb-girdle MD (known as type 1) and 17 forms of autosomal recessive limb-girdle MD (known as type 2) have been identified. Some autosomal recessive forms of the disorder are now known to be due to a deficiency of any of four dystrophin-glycoprotein complex proteins called the sarcoglycans. Deficiencies in dystroglycan, classically associated with congenital muscular dystrophies, may also cause LGMD.

The recessive LGMDs occur more frequently than the dominant forms, usually begin in childhood or the teenage years, and show dramatically increased levels of serum creatine kinase. The dominant LGMDs usually begin in adulthood. In general, the earlier the clinical signs appear, the more rapid the rate of disease progression. Limb-girdle MD affects both males and females. Some forms of the disease progress rapidly, resulting in serious muscle damage and loss of the ability to walk, while others advance very slowly over many years and cause minimal disability, allowing a normal life expectancy. In some cases, the disorder appears to halt temporarily, but progression then resumes.

The pattern of muscle weakness is similar to that of Duchenne MD and Becker MD. Weakness is typically
noticed first around the hips before spreading to the shoulders, legs, and neck. Individuals develop a waddling gait and have difficulty when rising from chairs, climbing stairs, or carrying heavy objects. They fall frequently and are unable to run. Contractures at the elbows and knees are rare but individuals may develop contractures in the back muscles, which gives them the appearance of a rigid spine. Proximal reflexes (closest to the center of the body) are often impaired. Some individuals also experience cardiomyopathy and respiratory complications, depending in part on the specific subtype. Intelligence remains normal in most cases, though exceptions do occur. Many individuals with limb-girdle MD become severely disabled within 20 years of disease onset.

**Myotonic dystrophy (DM1)**, also known as Steinert’s disease and dystrophia myotonica, is another common form of MD. **Myotonia**, or an inability to relax muscles following a sudden contraction, is found only in this form of MD, but is also found in other non-dystrophic muscle diseases. People with DM1 can live a long life, with variable but slowly progressive disability. Typical disease onset is between ages 20 and 30, but childhood onset and congenital
onset are well-documented. Muscles in the face and the front of the neck are usually first to show weakness and may produce a haggard, “hatchet” face and a thin, swan-like neck. Wasting and weakness noticeably affect forearm muscles. DM1 affects the central nervous system and other body systems, including the heart, adrenal glands and thyroid, eyes, and gastrointestinal tract. Other symptoms include cardiac complications, difficulty swallowing, droopy eyelids (called ptosis), cataracts, poor vision, early frontal baldness, weight loss, impotence, testicular atrophy, mild mental impairment, and increased sweating. Individuals may also feel drowsy and have an excess need to sleep. There is a second form of the disease that is similar to the classic form, but usually affects proximal muscles more significantly. This form is known as myotonic dystrophy type 2 (DM2).

This autosomal dominant disease affects both men and women. Females may have irregular menstrual periods and are sometimes infertile. The disease may occur earlier and be more severe in successive generations. A childhood-onset form of myotonic MD may become apparent between ages 5 and 10. Symptoms include general muscle weakness (particularly in the face and distal muscles), lack of muscle tone, and mental impairment.

A woman with DM1 can give birth to an infant with a rare congenital form of the disorder. Symptoms at birth may include difficulty swallowing or sucking, impaired breathing, absence of reflexes, skeletal deformities and contractures (such as club feet), and muscle weakness, especially in the face. Children
with congenital myotonic MD may also experience mental impairment and delayed motor development. This severe infantile form of myotonic MD occurs almost exclusively in children who have inherited the defective gene from their mother, whose symptoms may be so mild that she is sometimes not aware that she has the disease until she has an affected child.

The inherited gene defect that causes DM1 is an abnormally long repetition of a three-letter “word” in the genetic code. In unaffected people, the word is repeated a number of times, but in people with DM1, it is repeated many more times. This triplet repeat gets longer with each successive generation. The triplet repeat mechanism has now been implicated in at least 15 other disorders, including Huntington’s disease and the spinocerebellar ataxias.

Oculopharyngeal MD (OPMD) generally begins in a person’s forties or fifties and affects both men and women. In the United States, the disease is most common in families of French-Canadian descent and among Hispanic residents of northern New Mexico. People first report drooping eyelids, followed by weakness in the facial muscles and pharyngeal muscles in the throat, causing difficulty swallowing. The tongue may atrophy and changes to the voice may occur. Eyelids may droop so dramatically that some individuals compensate by tilting back their heads. Affected individuals may have double vision and problems with upper gaze, and others may have retinitis pigmentosa (progressive degeneration of the retina that affects night vision and peripheral vision) and cardiac irregularities. Muscle weakness
and wasting in the neck and shoulder region is common. Limb muscles may also be affected. Persons with OPMD may find it difficult to walk, climb stairs, kneel, or bend. Those persons most severely affected will eventually lose the ability to walk.

How are the muscular dystrophies diagnosed?

Both the individual’s medical history and a complete family history should be thoroughly reviewed to determine if the muscle disease is secondary to a disease affecting other tissues or organs or is an inherited condition. It is also important to rule out any muscle weakness resulting from prior surgery, exposure to toxins, or current medications that may affect the person’s functional status or rule out many acquired muscle diseases. Thorough clinical and neurological exams can rule out disorders of the central and/or peripheral nervous systems, identify any patterns of muscle weakness and atrophy, test reflex responses and coordination, and look for contractions.

Various laboratory tests may be used to confirm the diagnosis of MD.

Blood and urine tests can detect defective genes and help identify specific neuromuscular disorders. For example:

- Creatine kinase is an enzyme that leaks out of damaged muscle. Elevated creatine kinase levels
may indicate muscle damage, including some forms of MD, before physical symptoms become apparent. Levels are significantly increased in the early stages of Duchenne and Becker MD. Testing can also determine if a young woman is a carrier of the disorder.

- The level of serum aldolase, an enzyme involved in the breakdown of glucose, is measured to confirm a diagnosis of skeletal muscle disease. High levels of the enzyme, which is present in most body tissues, are noted in people with MD and some forms of myopathy.

- Myoglobin is measured when injury or disease in skeletal muscle is suspected. Myoglobin is an oxygen-binding protein found in cardiac and skeletal muscle cells. High blood levels of myoglobin are found in people with MD.

- Polymerase chain reaction (PCR) can detect some mutations in the dystrophin gene. Also known as molecular diagnosis or genetic testing, PCR is a method for generating and analyzing multiple copies of a fragment of DNA.

- Serum electrophoresis is a test to determine quantities of various proteins in a person’s DNA. A blood sample is placed on specially treated paper and exposed to an electric current. The charge forces the different proteins to form bands that indicate the relative proportion of each protein fragment.

**Exercise tests** can detect elevated rates of certain chemicals following exercise and are used to determine the nature of the MD or other muscle disorder. Some exercise tests can be performed bedside while others are done at clinics or other sites using sophisticated
equipment. These tests also assess muscle strength. They are performed when the person is relaxed and in the proper position to allow technicians to measure muscle function against gravity and detect even slight muscle weakness. If weakness in respiratory muscles is suspected, respiratory capacity may be measured by having the person take a deep breath and count slowly while exhaling.

**Genetic testing** looks for genes known to either cause or be associated with inherited muscle disease. DNA analysis and enzyme assays can confirm the diagnosis of certain neuromuscular diseases, including MD. Genetic linkage studies can identify whether a specific genetic marker on a chromosome and a disease are inherited together. They are particularly useful in studying families with members in different generations who are affected. An exact molecular diagnosis is necessary for some of the treatment strategies that are currently being developed. Advances in genetic testing include whole exome and whole genome sequencing, which will enable people to have all of their genes screened at once for disease-causing mutations, rather than have just one gene or several genes tested at a time. Exome sequencing looks at the part of the individual’s genetic material, or genome, that “code for” (or translate) into proteins.

**Genetic counseling** can help parents who have a family history of MD determine if they are carrying one of the mutated genes that cause the disorder. Two tests can be used to help expectant parents find out if their child is affected.

- **Amniocentesis**, done usually at 14-16 weeks of pregnancy, tests a sample of the amniotic fluid in
the womb for genetic defects (the fluid and the fetus have the same DNA). Under local anesthesia, a thin needle is inserted through the woman’s abdomen and into the womb. About 20 milliliters of fluid (roughly 4 teaspoons) is withdrawn and sent to a lab for evaluation. Test results often take 1-2 weeks.

• Chorionic villus sampling, or CVS, involves the removal and testing of a very small sample of the placenta during early pregnancy. The sample, which contains the same DNA as the fetus, is removed by catheter or a fine needle inserted through the cervix or by a fine needle inserted through the abdomen. The tissue is tested for genetic changes identified in an affected family member. Results are usually available within 2 weeks.

Diagnostic imaging can help determine the specific nature of a disease or condition. One such type of imaging, called magnetic resonance imaging (MRI), is used to examine muscle quality, any atrophy or abnormalities in size, and fatty replacement of muscle tissue, as well as to monitor disease progression. MRI scanning equipment creates a strong magnetic field around the body. Radio waves are then passed through the body to trigger a resonance signal that can be detected at different angles within the body. A computer processes this resonance into either a three-dimensional picture or a two-dimensional “slice” of the tissue being scanned. MRI is a noninvasive, painless procedure. Other forms of diagnostic imaging for MD include phosphorus magnetic resonance spectroscopy, which measures cellular response to exercise and the amount of energy available to
muscle fiber, and ultrasound imaging (also known as sonography), which uses high-frequency sound waves to obtain images inside the body. The sound wave echoes are recorded and displayed on a computer screen as a real-time visual image. Ultrasound may be used to measure muscle bulk. MRI scans of the brain may be useful in diagnosing certain forms of congenital muscular dystrophy where structural brain abnormalities are typically present.

**Muscle biopsies** are used for diagnostic purposes, and in research settings, to monitor the course of disease and treatment effectiveness. Using local or general anesthesia, a physician or surgeon can remove a small sample of muscle for analysis. The sample may be gathered either surgically, through a slit made in the skin, or by needle biopsy, in which a thin hollow needle is inserted through the skin and into the muscle. A small piece of muscle remains in the hollow needle when it is removed from the body. The muscle specimen is stained and examined to determine whether the person has muscle disease, nerve disease (*neuropathy*), inflammation, or another myopathy. Muscle biopsies can sometimes also assist in carrier testing. With the advent of accurate molecular techniques, muscle biopsy is less frequently needed to diagnose muscular dystrophies. Muscle biopsy is still necessary to make the diagnosis in most of the acquired muscle diseases.

**Immunofluorescence** testing can detect specific proteins such as dystrophin within muscle fibers. Following biopsy, fluorescent markers are used to stain the sample that has the protein of interest.
Electron microscopy can identify changes in subcellular components of muscle fibers. Electron microscopy can also identify changes that characterize cell death, mutations in muscle cell mitochondria, and an increase in connective tissue seen in muscle diseases such as MD. Changes in muscle fibers that are evident in a rare form of distal MD can be seen using an electron microscope.

Neurophysiology studies can identify physical and/or chemical changes in the nervous system.

- Nerve conduction velocity studies measure the speed and strength with which an electrical signal travels along a nerve. A small surface electrode stimulates a nerve, and a recording electrode detects the resulting electrical signal either elsewhere on the same nerve or on a muscle controlled by that nerve. The response can be assessed to determine whether nerve damage is present.

- Repetitive stimulation studies involve electrically stimulating a motor nerve several times in a row to assess the function of the neuromuscular junction. The recording electrode is placed on a muscle controlled by the stimulated nerve, as is done for a routine motor nerve conduction study.
Electromyography (EMG) can record muscle fiber and motor unit activity. A tiny needle containing an electrode is inserted through the skin into the muscle. The electrical activity detected in the muscle can be displayed on a monitor, and can also be heard when played through a speaker. Results may reveal electrical activity characteristic of MD or other neuromuscular disorders.

How are the muscular dystrophies treated?

There is no specific treatment that can stop or reverse the progression of any form of MD. All forms of MD are genetic and cannot be prevented at this time, aside from the use of prenatal screening interventions. However, available treatments are aimed at keeping the person independent for as long as possible and prevent complications that result from weakness, reduced mobility, and cardiac and respiratory difficulties. Treatment may involve a combination of approaches, including physical therapy, drug therapy, and surgery. The available treatments are sometimes quite effective and can have a significant impact on life expectancy and quality of life.

Assisted ventilation is often needed to treat respiratory muscle weakness that accompanies many forms of MD, especially in the later stages. Air that includes supplemental oxygen is fed through a flexible mask (or, in some cases, a tube inserted through the esophagus and into the lungs) to help the lungs
inflate fully. Since respiratory difficulty may be most extreme at night, some individuals may need overnight ventilation. Many people prefer non-invasive ventilation, in which a mask worn over the face is connected by a tube to a machine that generates intermittent bursts of forced air that may include supplemental oxygen. Some people with Duchenne MD, especially those who are overweight, may develop obstructive sleep apnea and require nighttime ventilation. Individuals on a ventilator may also require the use of a gastric feeding tube.

**Drug therapy** may be prescribed to delay muscle degeneration. Corticosteroids such as prednisone can slow the rate of muscle deterioration in Duchenne MD and help children retain strength and prolong independent walking by as much as several years. However, these medicines have side effects such as weight gain, facial changes, loss of linear (height) growth, and bone fragility that can be especially troubling in children. Immunosuppressive drugs such as cyclosporine and azathioprine can delay some damage to dying muscle cells. Drugs that may provide short-term relief from myotonia (muscle spasms and weakness) include mexiletine; phenytoin; baclofen, which blocks signals sent from the spinal cord to contract the muscles; dantrolene, which interferes with the process of muscle contraction; and quinine. (Drugs for myotonia may not be effective in myotonic MD but work well for myotonia congenita, a genetic neuromuscular disorder characterized by the slow relaxation of the muscles.) Respiratory infections may be treated with antibiotics.
Physical therapy can help prevent deformities, improve movement, and keep muscles as flexible and strong as possible. Options include passive stretching, postural correction, and exercise. A program is developed to meet the individual’s needs. Therapy should begin as soon as possible following diagnosis, before there is joint or muscle tightness.

- Passive stretching can increase joint flexibility and prevent contractures that restrict movement and cause loss of function. When done correctly, passive stretching is not painful. The therapist or other trained health professional slowly moves the joint as far as possible and maintains the position for about 30 seconds. The movement is repeated several times during the session. Passive stretching on children may be easier following a warm bath or shower.

- Regular, moderate exercise can help people with MD maintain range of motion and muscle strength, prevent muscle atrophy, and delay the development of contractures. Individuals with a weakened diaphragm can learn coughing and deep breathing exercises that are designed to keep the lungs fully expanded.
• Postural correction is used to counter the muscle weakness, contractures, and spinal irregularities that force individuals with MD into uncomfortable positions. When possible, individuals should sit upright, with feet at a 90-degree angle to the floor. Pillows and foam wedges can help keep the person upright, distribute weight evenly, and cause the legs to straighten. Armrests should be at the proper height to provide support and prevent leaning.

• Support aids such as wheelchairs, splints and braces, other orthopedic appliances, and overhead bed bars (trapezes) can help maintain mobility. Braces are used to help stretch muscles and provide support while keeping the person ambulatory. Spinal supports can help delay scoliosis. Night splints, when used in conjunction with passive stretching, can delay contractures. Orthotic devices such as standing frames and swivel walkers help people remain standing or walking for as long as possible, which promotes better circulation and improves calcium retention in bones.

• Repeated low-frequency bursts of electrical stimulation to the thigh muscles may produce a slight increase in strength in some boys with Duchenne MD, though this therapy has not been proven to be effective.

**Occupational therapy** may help some people deal with progressive weakness and loss of mobility. Some individuals may need to learn new job skills or new ways to perform tasks while other persons may need to change jobs. Assistive technology may include modifications to home and workplace settings and the use of motorized wheelchairs, wheelchair accessories, and adaptive utensils.
Speech therapy may help individuals whose facial and throat muscles have weakened. Individuals can learn to use special communication devices, such as a computer with voice synthesizer.

Dietary changes have not been shown to slow the progression of MD. Proper nutrition is essential, however, for overall health. Limited mobility or inactivity resulting from muscle weakness can contribute to obesity, dehydration, and constipation. A high-fiber, high-protein, low-calorie diet combined with recommended fluid intake may help. Feeding techniques can help people with MD who have a swallowing disorder and find it difficult to pass from or liquid from the mouth to the stomach.

Corrective surgery is often performed to ease complications from MD.

- Tendon or muscle-release surgery is recommended when a contracture becomes severe enough to lock a joint or greatly impair movement. The procedure, which involves lengthening a tendon or muscle to free movement, is usually performed under general anesthesia. Rehabilitation includes the use of braces and physical therapy to strengthen muscles and maintain the restored range of motion. A period of immobility is often needed after these orthopedic procedures, thus the benefits of the procedure should be weighed against the risk of this period of immobility, as the latter may lead to a setback.

- Individuals with either Emery-Dreifuss or myotonic dystrophy may require a pacemaker at some point to treat cardiac problems.
• Surgery to reduce the pain and postural imbalance caused by scoliosis may help some individuals. Scoliosis occurs when the muscles that support the spine begin to weaken and can no longer keep the spine straight. The spinal curve, if too great, can interfere with breathing and posture, causing pain. One or more metal rods may need to be attached to the spine to increase strength and improve posture. Another option is spinal fusion, in which bone is inserted between the vertebrae in the spine and allowed to grow, fusing the vertebrae together to increase spinal stability.

• People with myotonic dystrophy often develop cataracts, a clouding of the lens of the eye that blocks light. Cataract surgery involves removing the cloudy lens to improve the person’s ability to see.

What is the prognosis?

The prognosis varies according to the type of MD and the speed of progression. Some types are mild and progress very slowly, allowing normal life expectancy, while others are more severe and result in functional disability and loss of ambulation. Life expectancy often depends on the degree of muscle weakness, as well as the presence and severity of respiratory and/or cardiac complications.
What research is being done?

The National Institute of Neurological Disorders and Stroke (NINDS), a part of the National Institutes of Health (NIH), supports a broad program of research on MD. The goals of these studies are to increase understanding of MD and its causes, develop better therapies, and, ultimately, find ways to treat it. The NINDS and its sister institutes, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI), lead the MD research efforts conducted at the NIH and at grantee institutions throughout the country.

The NIH supports a broad range of basic, translational, and clinical research in the MDs. Advances in basic research are essential to the basic understanding of each type of MD. While many genes that cause muscular dystrophy still remain to be identified, advances in gene sequencing has aided the identification of genes that may be involved for most types of muscular dystrophy. In turn, new knowledge of specific disease mechanisms is identifying potential targets for therapy development. In recent years, research into the underlying disease mechanisms has created new opportunities for therapy development in nearly all types of MD. For example, advances in targeted therapy have led to promising efforts in myotonic dystrophy and facioscapulohumeral muscular dystrophy.
Federal funding, through the NIH and other agencies, as well as the venture philanthropy programs supported by patient advocacy groups, have attracted biotechnology and pharmaceutical firm investments into therapies for the MDs.

Currently, a variety of strategies are employed in developing new drug and biologic therapies for the range of MDs. Strategies being explored are either specific to a particular type of MD or may address disease progression that may apply to multiple types of MD.

**Gene replacement therapy**

Gene therapy has the potential for directly addressing the primary cause of MD by providing for the production of the missing protein. Hurdles to be overcome include determining the timing of the therapy (to possibly overcome the genetic defect), avoiding or easing potential immune responses to the replacement gene, and, in the case of Duchenne MD, the large size of the gene to be replaced. For those MDs with central nervous system consequences (congenital muscular dystrophy and myotonic dystrophy), researchers are developing and fine-tuning gene therapy vectors (a way to deliver genetic materials to cells) that can cross the protective blood-brain barrier.

Recent progress in delivery of replacement genes in MD includes considerable refinement of the viral vector types that improve the targeting to skeletal muscle and vascular approaches to deliver replacement gene to most or all skeletal muscles.
Approaches that work for skeletal muscles may or may not work for cardiac muscle; this is a challenge that must be met since many MDs cause cardiomyopathy. The strategies for assessing potential immune responses to the proteins encoded by replacement genes and for managing those responses also have received considerable attention in in animal model studies and in human clinical trials. Finally, for some MDs, early detection of the disease causing mutations, through newborn screening, may be necessary for gene replacement therapy to be used early enough to mitigate progression of the disease.

Clinical testing of gene therapy strategies in MD has been underway for Duchenne and limb girdle muscular dystrophy. Injections of gene therapy vectors into single muscles of participants were done as a first step to establish safety of the approach. With the support of extensive studies in animal models, clinical trials are now moving toward testing of gene therapy of all muscles of entire limbs, using an isolated vascular delivery approach. If isolated limb delivery approaches prove safe and effective, research will move to systemic delivery of gene therapy vectors so all muscles can be treated simultaneously.

Utrophin is a protein that is closely related to dystrophin and is not affected in the gene mutations that cause Duchenne MD. Targeting increased expression of utrophin may prove a useful approach in treating Duchenne MD. NIH supports both gene therapy and small molecule drug development programs to increase the muscle production of utrophin.
Finally, modifier genes—genes with activities that act to reduce the severity of MD—have been discovered by NIH-funded teams. These genes, including latent TGF binding protein 4 and osteopontin, represent new therapeutic targets to potentially reduce the severity of several types of muscular dystrophy.

Genetic modification therapy to bypass inherited mutations

Most individuals with Duchenne MD have mutations in the dystrophin gene that cause it to function improperly and stop producing the dystrophin protein. By manipulating the protein synthesis process, production of a gene that either “reads through” or “skips” the genetic mutation can result in at least partial functional dystrophin.

Two strategies are currently under study to bypass dystrophin mutations, one of which is drugs that cause the protein synthesis machinery to ignore the premature stop signal and produce functional dystrophin. This strategy, which is potentially useful in about 15 percent of individuals with Duchenne MD, is currently in clinical trials. Second, a more recent
approach uses antisense oligonucleotides (short strands of nucleic acid designed to block the transfer of some genetic information into protein production) to alter splicing and produce nearly a full-length dystrophin gene, potentially converting an individual with Duchenne to a much milder Becker MD. Two biotechnology companies are currently testing oligonucleotide drugs in advanced clinical trials for people who require skipping of exon 51 of dystrophin. (An exon is a coding sequence in a gene for a protein or amino acids). NINDS and NIAMS are supporting preclinical work on oligonucleotide drugs for individuals with Duchenne MD who require skipping of exon 45. While the exon skipping approach requires “personalized medicines” for subsets of people having Duchenne MD who need skipping of specific exons, as many as 80 percent of affected individuals could benefit from this new technology.

Antisense oligonucleotide technology is also being evaluated for use in myotonic dystrophy, but by a different mechanism than in Duchenne MD. In myotonic dystrophy, long duplications of repetitive DNA sequences lead to production of a toxic RNA that isolates a splicing regulator, Muscleblind, causing mis-splicing of many genes in muscle and brain. DNA, or deoxyribonucleic acid, stores and transfers genetic material; RNA, or ribonucleic acid, is involved in protein production. An NINDS and NIAMS-supported project is advancing an oligonucleotide therapeutic designed to degrade the toxic RNA and mitigate the splicing defects. This approach, in partnership with academic investigators and biotechnology and pharmaceutical companies, has the potential to address all people having myotonic dystrophy and is planned to be in clinical trials within the next few years.
Drug-based therapy to delay muscle wasting by promoting muscle growth or mitigating damage due to inflammation

Progressive loss of muscle mass is primarily responsible for reduced quality and length of life in MD. Drug treatment strategies designed to slow this muscle degeneration can have substantial impact on quality of life. Similarly, skeletal muscle has the ability to repair itself, but its regeneration and repair mechanisms are progressively depleted during the course of several types of MD. Understanding the repair mechanisms may provide new therapies to slow, and possibly stabilize, muscle degeneration.

Corticosteroids are known to extend the ability of people with Duchenne MD to walk by up to 2 years, but steroids have substantial side effects and their mechanism of action is unknown. Since several corticosteroid protocols are used, an NINDS-funded study is evaluating drugs and their efficacy and tolerability at different doses in order to determine optimal clinical practice for their use in Duchenne MD. In addition, a biotechnology company supported by the NIH’s National Center for Advancing Translational Sciences is developing a modified steroid to increase its efficacy in Duchenne MD while reducing the side effects that often limit individuals from using corticosteroid therapy.
Preclinical drug development efforts supported by NINDS and NIAMS are developing a peptide therapeutic that has, in animal models, dual activity in mitigating muscle damage due to inflammation and also enhancing muscle regeneration. Efforts to preserve muscle mass through inhibition of a negative regulator of muscle growth, myostatin, have encountered some roadblocks, including failed clinical trials, but are still under study.

**Cell-based therapy**

The muscle cells of people with MD often lack a critical protein, such as dystrophin in Duchenne MD or sarcoglycan in some of the limb-girdle MDs. Scientists are exploring the possibility that the missing protein can be replaced by introducing muscle stem cells capable of making the missing protein in new muscle cells. Such new cells would be protected from the progressive degeneration characteristic of MD and potentially restore muscle function in affected persons.

The natural regenerative capacity of muscle provides possibilities for treatment of MD. Researchers have shown that stem cells can be used to deliver a functional dystrophin gene to skeletal muscles of dystrophic mice and dogs. The focus of research has been on identifying the cell types with the highest potential for engraftment and growth of muscle and on strategies to deliver these muscle precursor cells to human skeletal muscles. Overall, cell-based therapeutic approaches are under consideration for multiple types of MD.
Moving forward with research in MD

Until recently, most therapy development programs in MD were focused on Duchenne. With the dramatic advances in understanding disease mechanisms, significant therapy development efforts are now being launched in many types of MD. NINDS funding supports teams working on the disease mechanisms in facioscapulohumeral muscular dystrophy, central nervous system involvement in myotonic dystrophy, and on the role of fibrosis in Duchenne MD. Similarly, NIAMS-supported projects are identifying novel therapy development targets that are attracting interest from biotechnology and pharmaceutical companies and will help move toward therapy development programs for all types of MD.

Importantly, parallel efforts need to be made in clinical trial readiness, so that clinical trials are feasible when a candidate therapeutic reaches that stage. Patient registries, natural history studies, biomarker identification, development of clinical trial endpoint measures, and emergence of standards of care are all essential in supporting clinical trials and are being advanced in several types of muscular dystrophy with the support of both public and private sector partners. The NIH has recently undertaken several new initiatives in training, career development, and research that are targeted toward MD. These advances, along with the NINDS focus on translational and clinical research, will lead to the growth of clinical trials and promising treatment strategies.
The MD CARE Act and the federal commitment to muscular dystrophy

In December 2001, President George W. Bush signed into law the Muscular Dystrophy Community Assistance, Research, and Education Amendments Act of 2001 (the MD CARE Act, Public Law 107-84). The MD-CARE act was reauthorized in 2008.

In response to the MD CARE Act, the NIH formed the Muscular Dystrophy Coordinating Committee to help guide research on MD. The MD Coordinating Committee is made up of physicians, scientists, NIH professional staff, and representatives of other federal agencies and voluntary health organizations with a focus on MD. The purpose of the group is to help NIH add new capabilities to the national effort to understand and treat MD, without duplicating existing programs. The MD Coordinating Committee has developed a broad Action Plan for the Muscular Dystrophies and continues to refine the plan to improve basic, translational, and clinical research in MD, with the goal of improving the quality of life for people with MD. Information about the committee and plan is available at http://www.ninds.nih.gov/find_people/groups/mdcc/.

The NIH is expanding and intensifying its research efforts on the muscular dystrophies and has established the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers of Excellence to promote basic and clinical research on these disorders. Six Wellstone Centers are currently funded by NINDS, NIAMS, NICHD, and NHLBI. The Act also authorized the Centers for Disease Control and Prevention to award grants for epidemiologic studies, data collection, and
development of standards of care for several types of MD. Other federal agencies contribute to this research initiative.

Research has led to the discovery of disease mechanisms and improved treatment for many forms of MD. Current research promises to generate further improvements. In the coming years, physicians and affected individuals can look forward to new forms of therapy developed through an understanding of the unique traits of MD.
**Glossary**

*atrophy* — a decrease in size or wasting away of a body part or tissue.

*autosomal dominant* — a pattern of inheritance in which a child acquires a disease by receiving a normal gene from one parent and a defective gene from the other parent.

*autosomal recessive* — a pattern of inheritance in which both parents carry and pass on a defective gene to their child.

*biopsy* — a procedure in which tissue or other material is removed from the body and studied for signs of disease.

*carrier* — an individual who doesn’t have a disease but has one normal gene and one gene for a genetic disorder and is therefore capable of passing this disease to her or his children.

*chromosomes* — genetic structures that contain DNA.

*contracture* — chronic shortening of a muscle or tendon that limits movement of a bony joint, such as the elbow.

*creatine kinase* — a protein needed for the chemical reactions that produce energy for muscle contractions; high levels in the blood indicate muscle damage.

*dystrophin* — a protein that helps maintain the shape and structure of muscle fibers.

*electromyography* — a recording and study of the electrical properties of skeletal muscle.

*glycoprotein* — a molecule that has a protein and a carbohydrate component.
**linkage studies** — tests conducted among family members to determine how a genetic trait is passed on through generations.

**lordosis** — an abnormal forward curving of the spine.

**merosin** — a protein found in the connective tissue that surrounds muscle fibers.

**muscle wasting** — a decrease in muscle strength and size.

**myoglobin** — an oxygen-binding protein in muscle cells that generates energy by turning glucose into carbon dioxide and water.

**myopathy** — any disorder of muscle tissue or muscles.

**myotonia** — an inability to relax muscles following a sudden contraction.

**neuropathy** — nervous system disease or dysfunction that may cause symptoms including muscle weakness, loss of muscle bulk, muscle cramps and spasms, and pain.

**pseudohypertrophy** — a condition in which muscles may be enlarged by an accumulation of fat and connective tissue, causing them to look larger and healthier than they actually are.

**scoliosis** — an abnormal lateral, or sideways, curving of the spine.

**X-linked recessive** — a pattern of disease inheritance in which the mother carries the affected gene on the chromosome that determines the child’s sex and passes it to her son.
Credits

Muscular Dystrophy Association—cover, pages 23, 26, 29
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