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CHAPTER 15

Skeletal Muscle[1]

Beth A. Valentine

Key Readings Index

Structure, 908
Function, 909
Dysfunction/Responses to Injury, 914
Portals of Entry/Pathways of Spread, 922
Defense Mechanisms/Barrier Systems, 923
Disorders of Domestic Animals, 923
Disorders of Horses, 932
Disorders of Cattle, 940
Disorders of Sheep and Goats, 944
Disorders of Pigs, 944
Disorders of Dogs, 946
Disorders of Cats, 952

Structure

Normal Skeletal Muscle

Understanding the normal structure and function of muscle, including gross, histologic, biochemical, physiologic, electrophysiologic, and ultrastructural features, is critical to understanding muscle disease.

Structure of Myofibers

Structural and physiologic features of skeletal muscle determine much of its response to injury. Although muscle cells are frequently called muscle *fibers* or *myofibers*, they are in fact multinucleated cells of considerable length, which in some animals may approach 1 m. Myonuclei are located peripherally in the cylindrical myofiber (Fig. 15-1) and direct the physiologic processes of the cellular constituents in their area through a process known as *nuclear domains*. This anatomic arrangement allows segments of the cell to react independently of other portions of the cell. Myonuclei are considered terminally differentiated, with little or no capacity for mitosis and thus for regeneration.

Associated with myofibers are the satellite cells, also known as *resting myoblasts* (E-Fig. 15-1). These cells are distributed along the length of the myofiber, between the plasma membrane (sarcolemma) and the basal lamina. Satellite cells in skeletal muscle are very different from cells of the same name found within the peripheral nervous system. Muscle satellite cells are fully capable of dividing, fusing, and reforming mature myofibers. Thus, under favorable conditions, muscle cells (myofibers) are able to fully restore themselves after damage. Recent studies have found that pluripotent cells derived from bone marrow can also contribute to skeletal muscle repair, albeit only to a very small degree.

Each myofiber is surrounded by a basal lamina and outside of this by the endomysium, a thin layer of connective tissue containing capillaries. Myofibers are organized into fascicles surrounded by the perimysium, a slightly more robust layer of connective tissue (E-Fig. 15-2). Entire muscles are encased in the epimysium, a protective fascia that merges with the muscle tendon. This connective tissue framework is not inert but in fact forms an integral part of the contractile function of muscle by storing and relaying force generated by myofiber contraction.

Ultrastructural examination reveals that skeletal muscle is a highly and rigidly organized tissue, with what are perhaps the most highly structured cells in the body. Each myofiber is composed of many closely packed myofibrils containing actin and myosin filaments. The striations visible with light microscopy (Fig. 15-2) represent the sarcomeric arrangement of muscle cells, in which actin and myosin filaments attached to transverse Z bands form the framework, and other organelles and intracytoplasmic materials are interspersed within this framework (Fig. 15-3). The endoplasmic reticulum of myofibers is called the *sarcoplasmic reticulum* and is modified to contain terminal cisternae that sequester the calcium ions necessary to initiate actin and myosin interaction and thus contraction. Sarcolemmal invaginations that traverse the cell, the T (for transverse) tubules, allow rapid dispersion of a sarcolemmal action potential to all portions of the myofiber. The terminal cisternae of two adjacent sarcomeres and the T tubule form what is called the *triad* (Fig. 15-3, A).

Neuromuscular junctions can only be visualized using electron microscopy or other specialized procedures (Fig. 15-4). Neuromuscular junctions occur only in specific zones within the muscle, usually forming an irregular circumferential "band" midway between myofiber origin and insertion.

Types of Myofibers

Mammalian muscles are composed of muscle fibers of different contractile properties. A common classification of these fibers is based on three major physiologic features: (1) rates of contraction (fast or slow), (2) rates of fatigue (fast or slow), and (3) types of metabolism (oxidative, glycolytic, or mixed). These physiologic differences form the basis of histochemical methods that demonstrate fiber types. There are several fiber-type classifications. Classification of fibers into type 1, type 2A, and type 2B (Table 15-1) has proved to have practical application in muscle pathology. It is the classification used in this text. Type 1 fibers are rich in mitochondria, rely heavily on oxidative metabolism, and are slow-contracting and slow-fatiguing.

[1]For a glossary of abbreviations and terms used in this chapter, see E-Glossary 15-1.

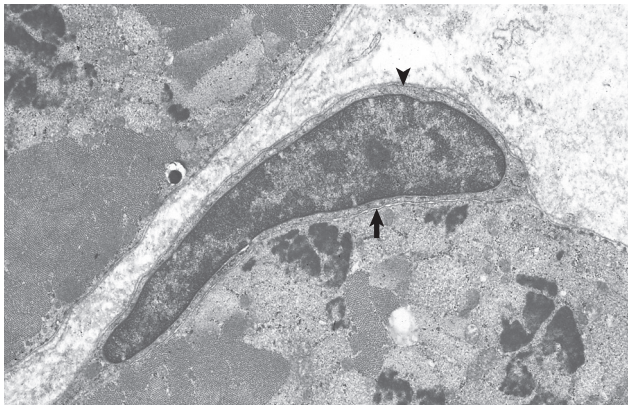
E-Glossary 15-1 Glossary of Abbreviations and Terms

Acetylcholine receptors–Postsynaptic receptors within the sarcolemma at the neuromuscular junctions. Binding of acetylcholine released from terminal axons causes sodium influx to generate a muscle action potential.
ALT–Alanine aminotransferase
ANA–Antinuclear antibody
AST–Aspartate aminotransferase
ATP–Adenosine triphosphate
ATPase–Adenosine triphosphatase; an enzyme that catalyzes the hydrolysis of ATP
Basal lamina–A layer of extracellular matrix encircling myofibers and peripheral nerve fibers
Cachexia–Generalized muscle atrophy due to disease or malnutrition
Chronic myopathic change–A variety of changes occurring in prolonged myopathic or neuropathic conditions, including cytoarchitectural changes, myofiber diameter changes, and infiltration by fat or connective tissue
CK–Creatine kinase
Compartment syndrome–Ischemic necrosis of muscle following swelling in a nonexpandable compartment
Congenital myopathy–Muscle disease present at birth
Degenerative myopathy–Muscle disease characterized by muscle necrosis
Denervating disease–Disease caused by motor neuron death or peripheral nerve axonal degeneration
Denervation atrophy–Muscle atrophy caused by motor neuron death or peripheral nerve axonal degeneration
Disuse atrophy–Muscle atrophy caused by lack of muscular activity
DNA–Deoxyribonucleic acid
Electrolyte-related myopathy–Muscle disease caused by electrolyte imbalance, most often hypokalemia
Electromyography–An electrodiagnostic method to evaluate skeletal muscle and peripheral structure and function
EMG–Electromyography
Endocrine myopathy–Muscle disease, typically atrophy of type 2 fibers, caused by hypothyroidism or hypercortisolism
Enzyme histochemistry–A panel of reactions for microscopic evaluation of skeletal muscle
EPSSM–Equine polysaccharide storage myopathy; also called PSSM and EPSM
Exertional rhabdomyolysis–Severe sudden skeletal muscle necrosis caused by overexertion
Fiber–A myofiber; a skeletal muscle cell
Fiber type–Physiologic characteristics of skeletal myofibers, ranging from oxidative and slow twitch (type 1) to glycolytic and fast twitch (type 2). Fiber type is primarily determined by the activity of the innervating motor neuron.
Fiber-type grouping–Alteration of the normal mosaic pattern of intermingled type 1 and type 2 fibers, resulting in groups of a single fiber type. Fiber-type grouping indicates prior denervation and reinnervation by a different type of neuron.
FIV–Feline immunodeficiency virus
GBE–Glycogen branching enzyme
GYS1–Glycogen synthase 1
H&E stain–Hematoxylin and eosin stain
HIV–Human immunodeficiency virus
HYPP–Hyperkalemic periodic paralysis
IgA–Immunoglobulin A
IL-1–Interleukin-1
IL-6–Interleukin-6
Inflammatory myopathy (myositis)–Muscle disease characterized by inflammation, caused by infection or immune-mediated disease
Ischemic myopathy–Muscle necrosis resulting from inadequate circulation
LD–Lethal dose
LDH–Lactic dehydrogenase
Lipomatosis–Adipose tissue infiltrating skeletal muscle; steatosis
Masticatory myositis–An immune-mediated inflammatory myopathy confined to masticatory muscles in dogs
Metabolic myopathy–Muscle disease caused by defects in muscle energy metabolism–for example, defective glycolysis, glycogenolysis, or mitochondrial enzymes
MH–Malignant hyperthermia
Monophasic muscle necrosis–Muscle necrosis caused by a single nonpersistent injury
Motor neuronopathy–Disease of motor neurons
Motor unit–All muscle fibers innervated by a single neuron
Muscular dystrophy–An inherited, progressive myopathy characterized by ongoing myofiber necrosis and regeneration
Myoblast–A mitotically active skeletal muscle precursor, derived from skeletal muscle satellite cells, capable of migration and fusion to form myotube during embryologic development and muscle regeneration
Myodegeneration–Muscle fiber necrosis
Myofiber–A muscle fiber; a muscle cell
Myoglobinuria–Passage of urine containing large amounts of myoglobin causing urine to be red. This occurs when there is severe sudden injury to a large amount of skeletal muscle.
Myopathy–Disease of skeletal muscle
Myostatin–A protein that limits the number of myofibers formed in embryologic development and also limits the diameter of mature myofibers
Myotonia–Prolonged contraction following stimulation; most often caused by ion channel dysfunction
Myotube–An immature myofiber, present during embryologic development and during muscle regeneration
Na-K ATPase–A sodium potassium exchanger on the muscle sarcolemma
NADH–Nicotinamide adenine dinucleotide, reduced form
Neuromuscular junction–A synaptic zone of the muscle membrane containing acetylcholine receptors
PAS–Periodic acid–Schiff
Peripheral neuropathy–Disease of peripheral nerves
Polymyositis–An immune-mediated inflammatory myopathy affecting multiple muscle groups
Polyphasic muscle necrosis–Muscle necrosis caused by repeated or continuous injury
Pseudohypertrophy–Muscle that is grossly enlarged by infiltrating fibrosis and/or fat
PTAH–Phosphotungstic acid hematoxylin
Rhabdomyolysis–Necrosis (lysis) of skeletal muscle; most often used for sudden, severe muscle necrosis such as that caused by overexertion
RNA–Ribonucleic acid
Sarcolemma–The skeletal muscle cell plasma membrane
Sarcolemmal tube–The basal lamina remaining following skeletal muscle cell necrosis that guides the regenerating myofiber
Sarcopenia–Age-related muscle atrophy and weakness
Sarcoplasmic reticulum–The skeletal muscle endoplasmic reticulum, modified to store calcium
Satellite cell–A resting myoblast, located between the sarcolemma and the basal lamina. Satellite cells undergo mitosis, migration, fusion, and eventual maturation resulting in skeletal muscle regeneration.
SDH–Succinate dehydrogenase

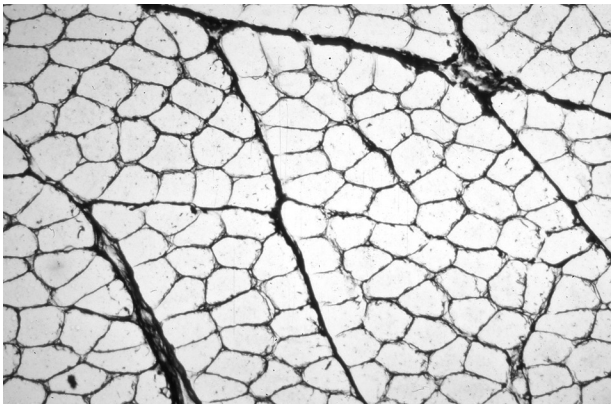
Continued

E-Glossary 15-1 Glossary of Abbreviations and Terms–cont'd

Segmental necrosis–Necrosis involving segments of the myofiber but not the entire cell
Steatosis–A condition in which myofibers are replaced by mature adipocytes
T tubule–Transverse tubule
TNF-α–Tumor necrosis factor-α
Type 1 fiber–Oxidative, slow twitch, fatigue-resistant myofibers. A high percentage of type 1 fibers are found in postural muscles.
Type 2 fiber–Glycolytic, fast twitch, fatigue-sensitive myofibers. Locomotory muscles contain many type 2 fibers. Type 2 fibers can be further divided into subgroups; for example, type 2A are mixed oxidative glycolytic and type 2B are purely glycolytic.



E-Figure 15-1 **Skeletal Muscle Myofibers, Transverse Section.** Note the satellite cell (resting myoblast) located between the sarcolemma *(arrow)* and the basal lamina *(arrowhead)*. TEM. Uranyl acetate and lead citrate stain. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)



E-Figure 15-2 **Skeletal Muscle, Transverse Section, Normal Mammalian Muscle.** Each myofiber is surrounded by an endomysium of fine collagenous connective tissue. Myofibers are organized into fascicles, which are surrounded by a slightly thicker perimysium. Frozen section, reticulin stain. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

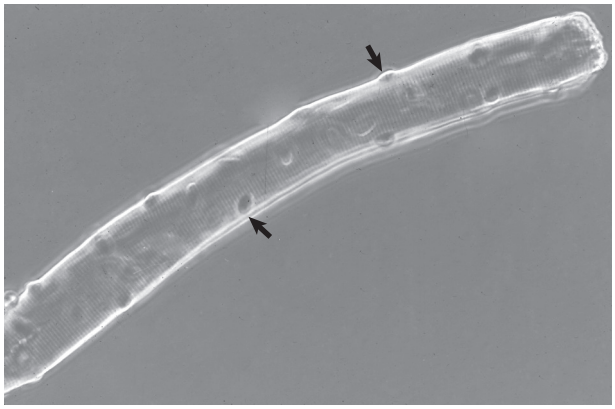


Figure 15-1 Skeletal Muscle, Isolated Intact Myofiber. Note the multiple peripherally located nuclei *(arrows)*. Phase contrast microscopy. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

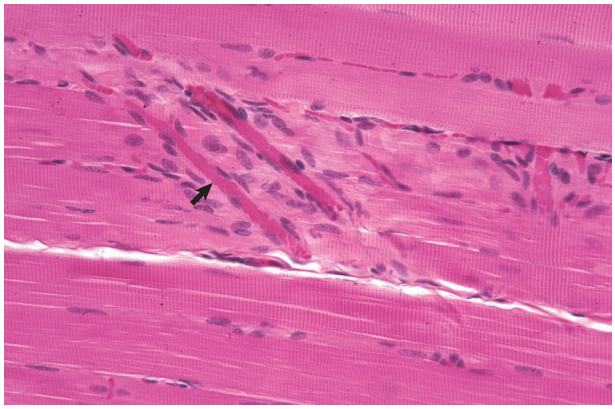


Figure 15-2 Skeletal Muscle, Longitudinal Section, Normal Mammalian Muscle, Cytoarchitectural Characteristics. Note the peripherally located myofiber nuclei and cross-striations on the muscle fibers. The cross-striations correspond to the A bands *(dark lines)* and I bands *(light lines)* in the transmission electron micrograph of Fig. 15-3, *B*. Myofibers are surrounded by an extensive capillary network *(arrow)*. H&E stain. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Type 2 fibers have fewer mitochondria and are glycolytic, fast-contracting, and more easily fatigable. In most species, type 2 fibers can be subdivided into type 2A and type 2B. Type 2B fibers are the fast-contracting, fast-fatiguing, glycolytic fibers that depend on glycogen for their energy supply. Type 2A fibers are mixed oxidative-glycolytic and therefore, although fast-contracting, are also slow-fatiguing. Thus type 2A fibers are "intermediate" in the concentration of mitochondria, fat, and glycogen between type 1 and type 2B.

Most muscles contain both type 1 and type 2 fibers, and these can be demonstrated by the myosin adenosine triphosphatase (ATPase) reaction (Fig. 15-5, *A*). Notice that the different fiber types are normally intermingled, forming what is called a mosaic pattern of fiber types. In most mature muscles, the staining pattern of the ATPase reaction reverses when sections are preincubated in an acid rather than an alkaline solution. There are examples of both patterns in the illustrations in this section. Acid preincubation can also be used to distinguish type 2A and type 2B fibers (Fig. 15-5, *B*). Regenerating fibers, classified as type 2C fibers, stain darkly in both acid and alkaline preparations, which is a distinguishing feature. In most species, oxidative enzyme reactions to demonstrate mitochondria also demonstrate fiber types to some degree (Fig. 15-6, *A*). Fiber typing can also be done by utilizing immunohistochemical procedures to identify specific myosin isoforms.

The percentage of each fiber type varies from muscle to muscle (Fig. 15-7). Type 1 fibers (slow-contracting, slow-fatiguing, and oxidative) are plentiful in those muscles in which the main function is slow, prolonged activity, such as those that maintain posture. Type 1 predominant postural muscles are most often located deep in the limb. Within the same muscle, the percentage of type 1 fibers often increases in the deeper portions. Muscles that contract quickly and for short periods of time, such as those designed for sprinting, contain more type 2B fibers. Only rarely are muscles composed of only one fiber type (e.g., the ovine vastus intermedius is type 1). Athletic training causes some type 2B fibers to be converted to 2A. There are also variations within breeds and differences in the same muscle in different species. For example, the dog has no type 2B purely glycolytic fibers; all canine fibers have strong oxidative capacity (see Fig. 15-6, *B*).

Innervation and Motor Units

The axons of the peripheral nerve trunks contain terminal branches that innervate multiple myofibers. The terminal branches form synapses with the myofibers at the neuromuscular junction. The myofibers innervated by a single axon form a motor unit, all fibers of which will contract simultaneously after stimulation. Different muscles have different sized motor units that relate to their function. For example, extraocular muscle function does not call for forceful contraction but, rather, for many fine movements to smoothly move the globe. Therefore these muscles have very small motor units, with only a small number of myofibers (1 to 4) innervated by each axon. In contrast, the quadriceps muscle is not designed for fine movement but instead is designed for generation of force; therefore motor units are quite large, with many myofibers (100 to 150 or more) innervated by a single axon.

Function

Skeletal muscle has many functions in the body. Some obvious and major functions are maintaining posture and enabling movement, including locomotion. The rhythmic contraction of the respiratory muscles (the intercostal muscles and the diaphragm) is essential for life. In addition, muscles play a major role in whole body homeostasis and are involved in glucose metabolism and maintenance of body temperature. On a purely esthetic level, muscle contributes to pleasing body contours.

The function of skeletal muscle is intimately related to the function of the peripheral nervous system. The physiologic attributes of a muscle fiber—its rate of contraction and type of metabolism (oxidative, anaerobic, or mixed)—are determined not by the muscle cell itself but by the motor neuron responsible for its innervation (Fig. 15-8). This fact is significant in evaluating histologic changes in muscle fibers. It is possible to divide changes in muscle fibers into two major classes: neuropathic and myopathic. Neuropathic changes are those that are determined by the effect or the absence of the nerve supply (e.g., atrophy after denervation). The term *myopathy* should be reserved for those muscle diseases in which the primary change takes place in the muscle cell, not in the interstitial tissue and not secondary to effects from the nerve supply. The term *neuromuscular disease* encompasses disorders involving lower motor neurons, peripheral nerves, neuromuscular junctions, and muscles.

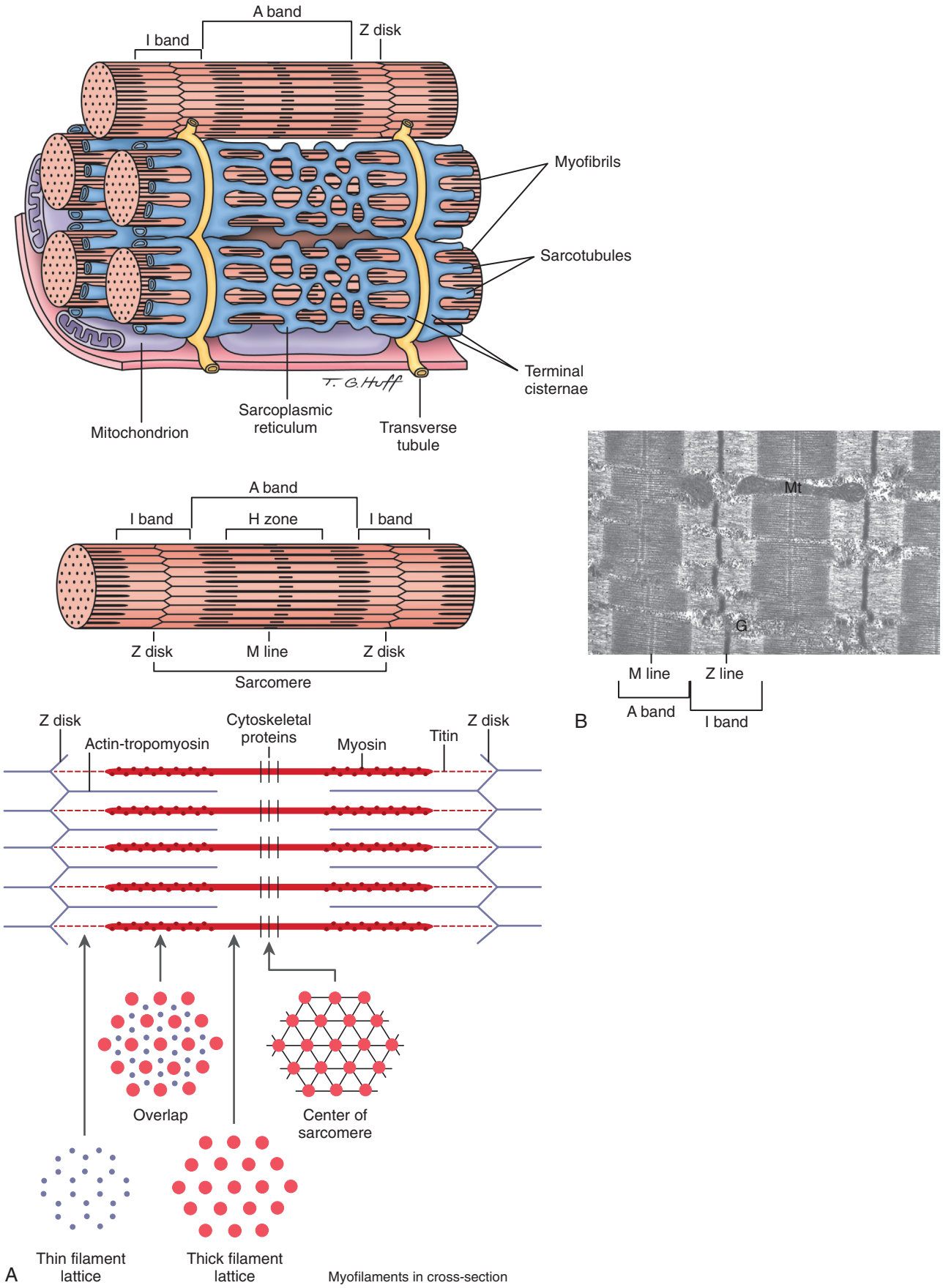


Figure 15-3 Myofiber Structure. A, Schematic diagram of skeletal muscle illustrating the sarcomeric arrangement of myofilaments that form myofibrils, cytoskeletal proteins, and interspersed organelles. **B,** Skeletal muscle, longitudinal section, mammalian skeletal muscle. Sarcomeres are defined by Z lines, thick myosin filaments form A bands, and thin actin filaments form I bands. Bisecting the A bands are dense M lines with adjacent clear H zones. Elongate mitochondria *(Mt)* and granular glycogen *(G)* are interspersed between the myofibrils. TEM. Uranyl acetate and lead citrate stain. (**B** courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

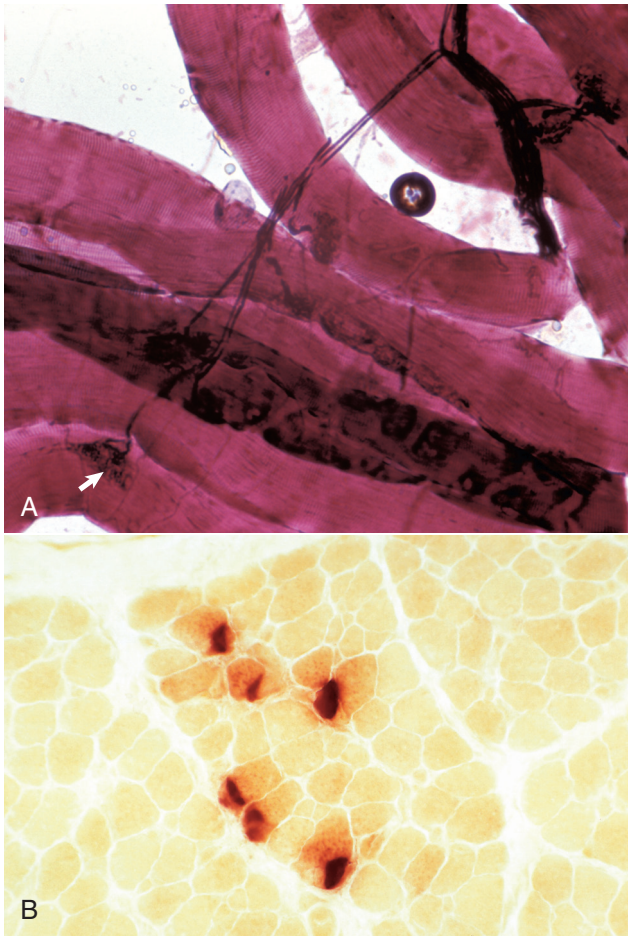


Figure 15-4 Neuromuscular Junctions. A, An intramuscular nerve *(top right)* has given off axons, which terminate on a myofiber at a neuromuscular junction *(arrow)*. Teased preparation, silver impregnation method. **B,** Neuromuscular junctions, transverse section through the center region of normal mammalian muscle. The neuromuscular junctions *(red-brown stain)* form a cluster. Nonspecific esterase stain, frozen section. (**A** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **B** courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

Table 15-1 Skeletal Muscle Fiber Types

Fiber Type	Physiologic Characteristics	Morphologic Characteristics
1	Slow twitch, oxidative, fatigue resistant, "red muscle," aerobic	High mitochondrial content, high fat content, low glycogen content
2A	Fast twitch, oxidative and glycolytic, fatigue resistant	Intermediate mitochondria, fat, and glycogen content
2B	Fast twitch, fatigue sensitive, glycolytic, "white muscle," anaerobic	Low mitochondrial and fat content, high glycogen content

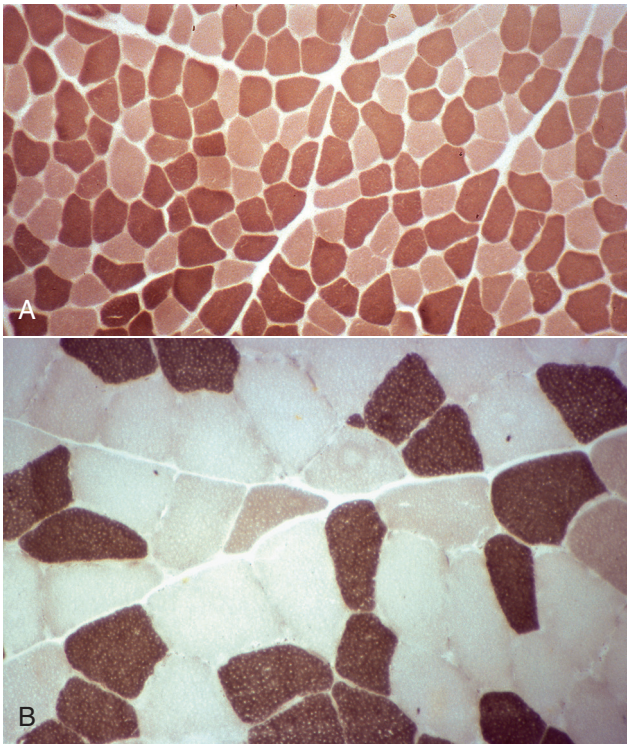


Figure 15-5 Muscle Fiber Typing, Myofibrillar Adenosine Triphosphatase (ATPase) Reaction, Normal Skeletal Muscle, Transverse Section. A, Dog. Type 1 *(light)* and type 2 *(dark)* fibers are arranged in a mosaic pattern. Frozen section, ATPase pH 10.0. **B,** Horse. Acid preincubation allows differentiation of three fiber types: type 1 *(dark)*, type 2A *(light)*, and type 2B *(intermediate = gray)*. Frozen section, ATPase 4.35. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

Metabolism and Ionic Homeostasis

Myofibers require a great deal of energy in the form of adenosine triphosphate (ATP) to generate force and movement. Type 1 oxidative and type 2A oxidative-glycolytic fibers use aerobic metabolism of glucose, stored in the muscle as glycogen, and fat. Type 2B glycolytic fibers rely primarily on anaerobic metabolism of glycogen for energy. Inherent or acquired metabolic defects that reduce skeletal muscle energy production can result in severe muscle dysfunction. A commonly encountered postmortem change, rigor mortis, illustrates the importance of ATP generation within skeletal muscle. The muscle contractile apparatus is still active immediately after death. ATP is necessary for the release of actin from myosin, the interaction that results in the sliding of myofilaments and contraction of muscle. After death, the absence of adequate ATP production causes the muscle fibers to undergo sustained contraction, which is known as *rigor mortis*. Rigor mortis eventually disappears because of muscle structural breakdown caused by autolysis or putrefaction (bacterial decomposition). The period of time for onset and release of rigor mortis varies, depending on physiologic (glycogen stores at the time of death) and environmental factors such as the environmental temperature (see Chapter 1).

Skeletal muscle is also excitable tissue, similar to that of the nervous system. Maintenance of proper ionic gradients across the sarcolemma is essential for initiation of the action potential. Internal ionic gradients, especially of calcium ions, are critical for initiation and termination of contraction. Alterations of ionic fluxes across the sarcolemma, or within the sarcoplasmic reticulum, can have a serious negative impact on myofiber function.

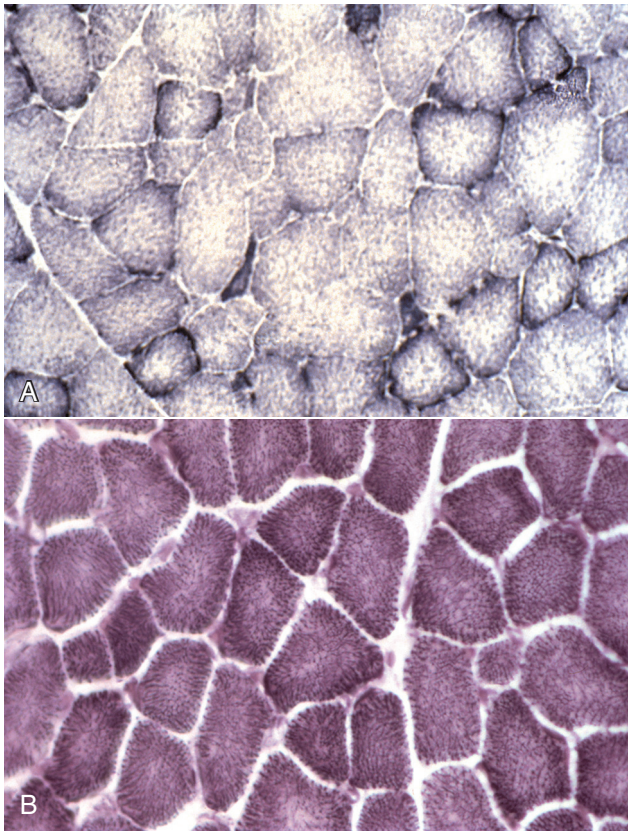


Figure 15-6 Mitochondria, NADH Reaction *(Blue Stained)*, Skeletal Myocytes, Normal Skeletal Muscle, Transverse Section. A, Horse. Type 1 fibers contain the most mitochondria, type 2B the least, and mitochondrial content of type 2A fibers is intermediate between type 1 and type 2B. Frozen section, NADH reaction. **B,** Dog. All fiber types have a similar mitochondrial content; therefore this reaction cannot be used to identify different types of myofibers in canine muscle. Frozen section, NADH reaction. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

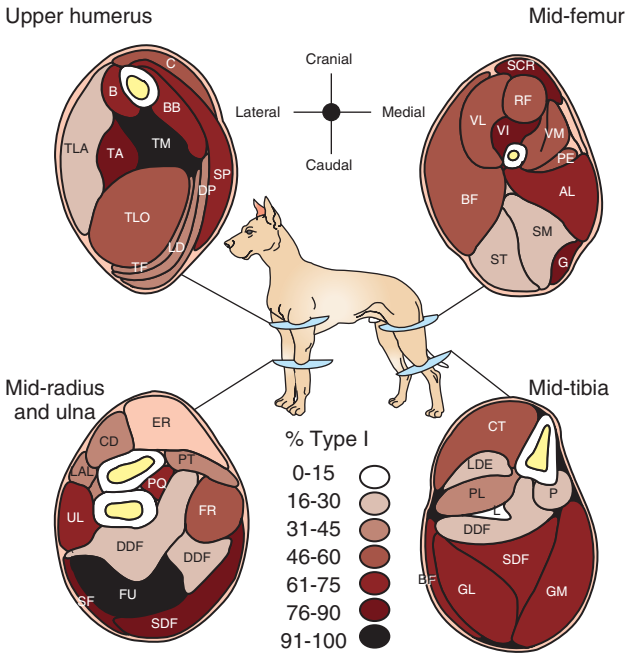


Figure 15-7 Percentage of Type 1 and Type 2 Myofibers in Limb Muscles in the Dog. There is a wide variation from muscle to muscle. Deeply located muscles have the most type 1 myofibers, indicative of their function in maintaining posture. (Redrawn from Armstrong RB, Sauber CW, Seeherman HJ, Taylor CR: *Am J Anat* 163:87-98, 1987.)

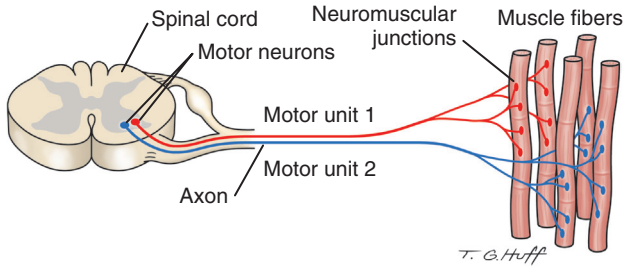


Figure 15-8 Motor Units of a Muscle. Motor neuron cell bodies within the ventral horn of the spinal cord give rise to axons that often travel long distances (meters) and eventually branch to innervate multiple skeletal muscle fibers at neuromuscular junctions.

Examination of Muscle: Clinical, Gross, and Microscopic

The decision to closely examine muscle, either by a biopsy or at necropsy, relies on recognition of indicators of neuromuscular dysfunction. A summary of clinical signs of muscle disease is provided in Box 15-1.

Clinical Findings

Information on this topic is available at www.expertconsult.com.

Clinicopathologic Findings

Information on this topic is available at www.expertconsult.com.

Electromyography

Information on this topic is available at www.expertconsult.com.

Methods of Gross and Microscopic Examination of Muscle

A variety of examination techniques are often necessary to best appreciate changes occurring in muscle.

Gross Examination of Muscle

Gross examination includes evaluation of changes in size (atrophied, hypertrophied, or normal), color, and texture. The gross pathologic appearance of skeletal muscle can be quite deceiving. What appear to be mild changes in muscle on gross examination often can be severe on microscopic examination, and what appear to be severe changes on gross examination can turn out to be artifact. Subjective evaluation of size can be highly unreliable unless control muscles (e.g., from normal animals or from the opposite sides) are available for weighing and measuring.

Color changes are common. The intensity of the red color of muscle varies, depending on the type of muscle, the age and species

Box 15-1 Clinical Signs of Muscle Disease

Muscle atrophy	Muscle spasm
Muscle hypertrophy	Abnormal gait
Muscle swelling	Esophageal dysfunction (dogs, cats, camelids)
Weakness	

Clinical signs of muscular disease are variable (see Box 15-1). The most common manifestations are alteration in muscle size, muscle weakness, and abnormal gait. Depending on the nature of the disorder, clinical signs can be localized, multifocal, or generalized.

Alteration in muscle size is readily detected with careful physical examination. Unilateral atrophy is best appreciated by comparing muscles on both sides of the body. In cases of generalized atrophy, it is important to bear in mind the normal muscling of the breed. For example, the muscling of dairy cattle is less prominent than that of beef cattle, and mild generalized muscle atrophy in a draft horse breed is more difficult to detect than in a light horse breed.

Weakness can be obvious, as in an animal that is unable to rise or prefers to remain recumbent, or can be manifested primarily as exercise intolerance. Special attention should be paid to gait analysis. The gait of an animal with generalized weakness caused by muscle or peripheral nerve dysfunction will have a short stride and often be stiff, and all four legs are often positioned well under the body for support while standing. The abnormal gait of an animal with neuromuscular disease must be distinguished from a similar gait that can occur because of musculoskeletal disease (which is a misnomer because these disorders affect bone and joint, not muscle). Muscle or peripheral nerve dysfunction in the horse, with this species' unique biomechanics of the pelvic limb, can result in mechanical lameness that can be mistaken for neurologic disease. Odd equine hind limb gaits designated with such terms as *shivers*, *stringhalt*, and *fibrotic myopathy* are caused by muscle or peripheral nerve disorders. A fibrotic myopathy-like condition also occurs less commonly in the dog and can involve the forelimb. Severe denervating or progressive myopathic conditions that begin in utero or at an early age can cause joint contractures and limb deviation (see Fig. 15-43).

Animals with myotonia often exhibit a stiff gait and develop episodic muscle spasms that can lead to collapse. Percussion of muscle groups can cause a persistent muscle contraction known as *dimpling*.

In dogs, horses, and ruminants, the esophagus contains a large percentage of skeletal muscle. In dogs and camelids, myopathic, neuropathic, and neuromuscular junction disorders can involve these muscles, causing esophageal dysfunction and megaesophagus. Denervation can also contribute to esophageal dysfunction in cattle with vagal indigestion.

As far as can be determined by clinical evaluation and extrapolation from similar conditions in other species, most neuromuscular disorders in animals are not associated with pain. Muscle cramps, caused by either primary myopathy or partial denervation, and muscle swelling are exceptions to this rule.

If the plasma membrane of the myofiber is damaged or a segment of the myofiber becomes necrotic, some of the contents of the muscle cell will "leak out" and be taken up into the blood. The concentrations of some of these components in serum are used as an index of the extent of myofiber damage. The most commonly used is creatine kinase (CK). Aspartate aminotransferase (AST) and lactic dehydrogenase (LDH) are also released but are not specific indicators of muscle damage because they are also present in other tissues. Because CK has a low renal threshold, it is quickly excreted in the urine. The half-life of circulating CK varies somewhat between species but is generally approximately 6 to 12 hours. The half-life of AST and LDH in the serum is much longer, and serum AST and LDH concentrations remain elevated for several days after muscle injury. Serum concentration of alanine aminotransferase (ALT) will also increase in all species from severe muscle cell necrosis. Other serum indicators of skeletal muscle injury include carbonic anhydrase III and fatty acid binding protein, but these latter proteins are not part of a routine serum chemistry panel. It has been speculated that the sarcolemma can become "leaky," leading to release of CK and other enzymes, without the affected segment becoming overtly necrotic. This possibility is very difficult to prove or disprove.

Although the laboratory testing for CK and AST is relatively standardized, laboratory normal ranges may vary considerably within and among laboratories. Determining the normal range of blood values for animals is a difficult task. Normal serum CK concentration in animals is generally less than 500 U/L. Normal serum concentrations of AST, ALT, and LDH vary greatly between species. Tests included in chemistry panels also vary in different laboratories. Some laboratories do not include CK in small animal chemistry panels, which can result in a misdiagnosis of hepatic disease in a dog or cat with a persistent increase in serum AST and ALT concentrations because of degenerative muscle disease. For the purposes of discussion in this chapter, a mild increase in CK or AST is considered to be up to 2 to 3 times normal, a moderate increase is 4 to 10 times normal, and a severe increase is 10 times normal or more.

It should be emphasized that myofibers can be dysfunctional without undergoing necrosis. Myopathic and neuropathic conditions resulting in atrophy, weakness, spasm, stiffness, or myotonia rarely result in significant increase in serum muscle enzyme concentrations. At this time, there is no biochemical parameter that will assess muscle fiber function; only morphologic or structural muscle fiber integrity can be assessed.

Electromyography (EMG) can be a valuable tool when evaluating patients with suspected neuromuscular disease. Concentric needle EMG studies search for abnormal spontaneous activity generated by myofibers. In contrast to other electrodiagnostic studies, a flat line generated by a noncontracting muscle indicates a healthy muscle. Abnormal spontaneous activity includes wave forms designated as positive sharp waves, fibrillations, and myotonic bursts. These abnormal spontaneous electrical events are associated with characteristic sounds emitted by the EMG machine. Abnormal spontaneous activity, typically dense and sustained fibrillations and sharp waves, is generated in denervated muscle because of alteration in sodium channel activity in the membrane of denervated fibers. Spontaneous activity in degenerative myopathies, usually scattered fibrillations, positive sharp waves, and myotonic bursts, is likely related to ionic disturbances associated with fiber degeneration and regeneration; functional denervation after segmental necrosis of the segment containing the neuromuscular junction is also possible. Myotonic conditions result in notably abnormal ionic fluxes leading to waxing and waning of spontaneous potentials with a characteristic "dive bomber" sound. Severe denervating and degenerative disorders and canine cushingoid myotonia can be accompanied by myotonic bursts that start and stop abruptly, characteristic of pseudomyotonia.

Nerve conduction velocity studies evaluate the integrity and function of the peripheral nervous system. Primary demyelinating disorders result in severe reduction of nerve conduction velocity, but axons are intact and muscles are still technically innervated; therefore spontaneous activity does not occur. Repetitive nerve stimulation tests the function of the neuromuscular junctions.

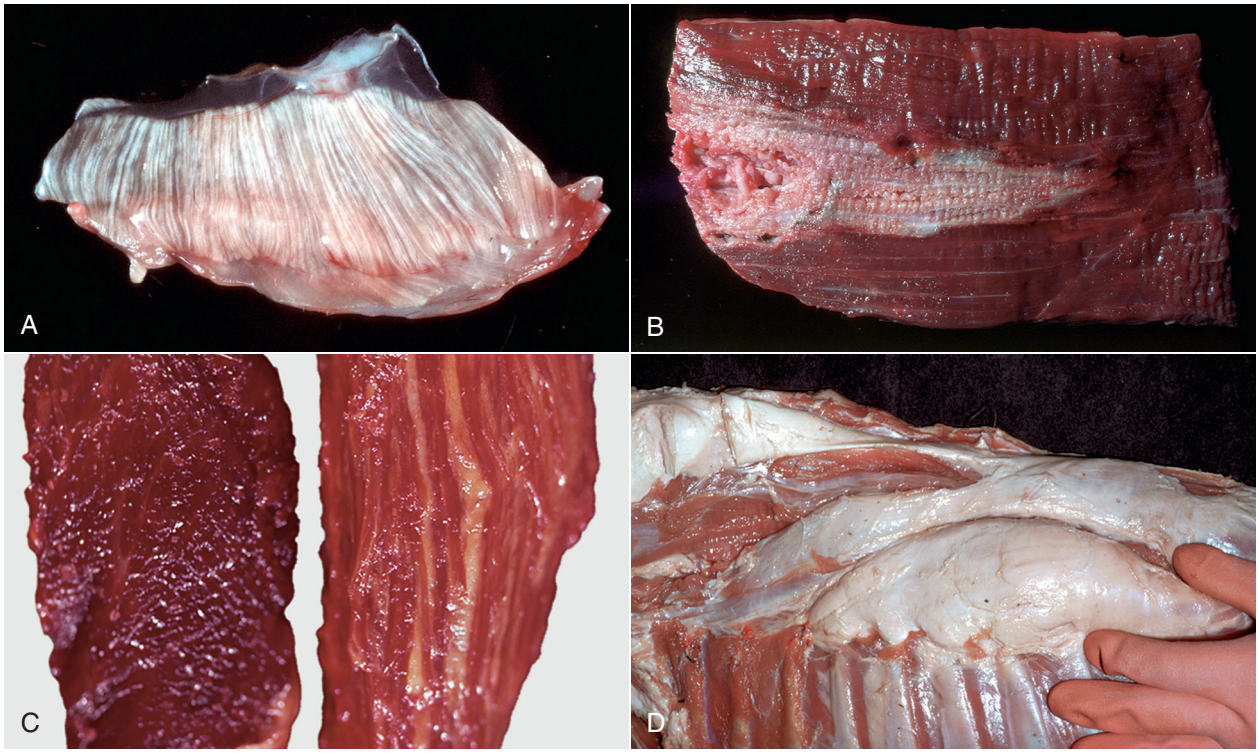


Figure 15-9 Pathologic Changes Resulting in Pale Skeletal Muscle. A, Pale streaks, necrosis and mineralization, degenerative myopathy, canine X-linked muscular dystrophy, diaphragm *(left side)*, dog. **B,** Localized pallor, necrosis, injection site of an irritant substance, semitendinosus muscle, cow. The irritant was injected just under the perimysium and caused necrosis and disruption of the myofibers. Some irritant seeped down between the fascicles to cause necrosis, but the fascicles of myofibers are still in place. **C,** Overall pale muscle with pale streaks from collagen and fat infiltration, denervation atrophy, equine motor neuron disease, horse. Equine motor neuron disease muscle *(right)* compared with normal muscle *(left)*. **D,** Enlargement and pallor, steatosis, longissimus muscles, neonatal calf. The majority of the muscles have been replaced by fat. (**A** courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University. **B** and **D** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **C** courtesy Dr. A. de Lahunta, College of Veterinary Medicine, Cornell University.)

of animal, and the extent of blood perfusion. Pale muscle can indicate necrosis (Fig. 15-9, *A* and *B*; see Figs. 15-25; 15-33, *A*; 15-35, *A*; and 15-39) or denervation (Fig. 15-9, *C*; see Fig. 15-36) but is also common in young animals and anemic animals. Pale streaking of muscle most often reflects myofiber necrosis and mineralization (see Fig. 15-9, *A* and *B*) or infiltration by collagen or fat (see Fig. 15-9, *C* and *D*), and it is one of the more reliable indicators of gross pathologic changes. Muscle parasites can be grossly visible as discrete, round to oval, pale and slightly firm zones (see Figs. 15-40 and 15-41, *A*). Dark red mottling of skeletal muscle can indicate congestion, hemorrhage, hemorrhagic necrosis (see Figs. 15-31, *A*, and 15-37), inflammation, or myoglobin staining after massive muscle damage (see Fig. 15-35, *A*) or can simply reflect vascular stasis (hypostatic congestion) after death. Hemorrhagic streaks within the diaphragm often accompany death caused by acute exsanguination. A green discoloration can indicate either eosinophilic inflammation (Fig. 15-10) or severe putrefaction. Lipofuscin accumulation in old animals, especially cattle, can cause a tan-brown discoloration of muscle. Black discoloration of the fascia occurs in calves with melanosis as an incidental finding and in older gray horses with metastasis of dermal melanoma to muscle fascia.

Evaluation of texture is also important. Severely thickened and often calcified fascia occurs in cats with fibrodysplasia ossificans progressiva. Fat infiltration or necrosis can result in abnormally soft muscle. Decreased or increased muscle tone can be caused by denervation. Decreased tone can also occur as a result of a lack of muscle conditioning or postmortem autolysis.

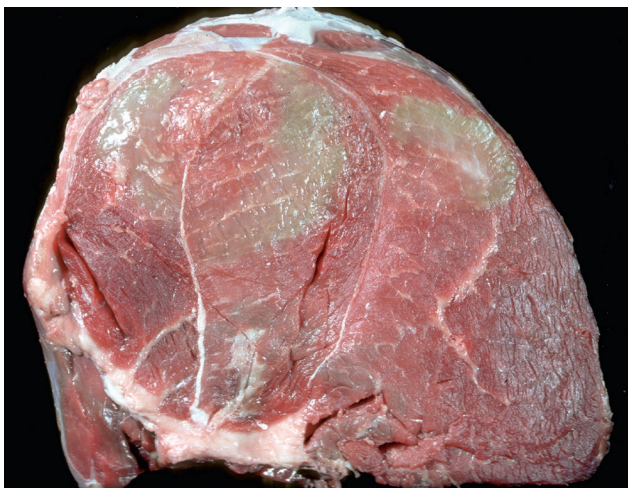


Figure 15-10 Bovine Eosinophilic Myositis, Gluteal Muscles, Cow. Green discoloration of the muscle is due to inflammation that has abundant eosinophils. The inflammation is attributed to degenerating *Sarcocystis* spp. For histopathologic findings, see Fig. 15-38. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Careful microscopic examination of multiple muscles is often required to detect lesions. In cases of suspected neuromuscular disease, multiple muscle samples should include active muscle (tongue, diaphragm, intercostals, and masticatory muscles), proximal muscle (lateral triceps, biceps femoris, semimembranosus, semitendinosus, and gluteal), and distal muscle (extensor carpi radialis and cranial tibial). For purposes of a biopsy, certain muscles (e.g., lateral triceps, biceps femoris, cranial tibial, semimembranosus, and semitendinosus) are easier to sample because of their parallel myofiber orientation. The ideal samples will also vary, depending on the suspected disorder, such as a type 1 predominant postural muscle for diagnosis of equine motor neuron disease, a type 2 predominant locomotory muscle for diagnosis of equine polysaccharide storage myopathy (EPSSM), and temporal or masseter muscle for diagnosis of masticatory myositis in dogs and masseter myopathy in horses. Short fibers, such as those in the intercostal muscle, are preferred for physiologic studies in which intact muscle fibers are necessary and for studies of neuromuscular junction zones.

Sampling of Muscle for Examination

Information on this topic is available at www.expertconsult.com.

Microscopic Examination

Information on this topic is available at www.expertconsult.com.

Enzyme Histochemistry and Immunohistochemistry

Information on this topic is available at www.expertconsult.com.

Electron Microscopy

Information on this topic is available at www.expertconsult.com.

Other Methods of Evaluation

Information on this topic is available at www.expertconsult.com.

Dysfunction/Responses to Injury

It is often said that the range of response of muscle to injury is limited, consisting primarily of necrosis and regeneration. Actually, muscle is a remarkably adaptive tissue, with a wide range of response to physiologic and pathologic conditions. Myofibers can add or delete sarcomeres to cause elongation or shortening of the entire muscle. In addition to necrosis and regeneration, myofibers can atrophy and hypertrophy, they can split, they can undergo a variety of cytoarchitectural alterations, and they can completely alter their physiologic functions when undergoing fiber-type conversion. To describe muscle response to injury as stereotypical does not do justice to this inherent plasticity. What is true, though, is that it is frequently not possible to determine the cause of muscle injury based on gross or histologic lesions alone. Supplementary tests and clinical histories are often essential.

Necrosis and Regeneration

Myofiber necrosis can accompany a variety of disorders. Because of their multinucleate nature, myofibers often undergo segmental necrosis, with involvement of only one or several contiguous segments within the cell. Global necrosis of the entire length of the myofiber occurs only under severe duress, such as extreme pressure to the entire muscle causing crush injury, or widespread ischemia because of pressure on, or thromboembolism of, a large artery.

Necrotic portions of myofibers have several different histologic appearances. The earliest change is often segmental hypercontraction, resulting in segments of slightly larger diameter that are slightly darker staining ("large dark fibers") that are best seen on transverse sections (Fig. 15-11, *A*). On longitudinal sections, "twisting" or "curling" of affected fibers is often seen. But similar changes occur as an artifactual change in improperly handled samples. The cytoplasm of fully necrotic portions of the fiber is often homogeneously eosinophilic and pale (hyaline degeneration), with loss of the normal cytoplasmic striations and the adjacent muscle nucleus. The affected cytoplasm then becomes floccular or granular as that portion of the myofiber starts to fragment (Fig. 15-11, *B*; see Fig. 15-14, *B*).

Increased intracellular calcium is a common trigger of necrosis in all cells, and myofibers contain a high level of calcium ions stored in the sarcoplasmic reticulum. Therefore myofibers may be particularly sensitive to calcium-induced necrosis, either as a result of damage to the sarcolemma, causing influx of extracellular calcium, or from damage to the sarcoplasmic reticulum, releasing intracellular stores of calcium. Small wonder then that necrotic myofibers are often prone to overt mineralization. Overtly mineralized myofibers appear as chalky white streaks on gross examination (see Fig. 15-9, *A*) and as basophilic granular to crystalline material within myofibers on histologic examination. Large deposits of mineral can induce a foreign body granulomatous response. Although the presence or absence of myofiber mineralization has sometimes been used as a diagnostic aid, the circumstances under which a necrotic myofiber segment can become mineralized are so diverse that myofiber

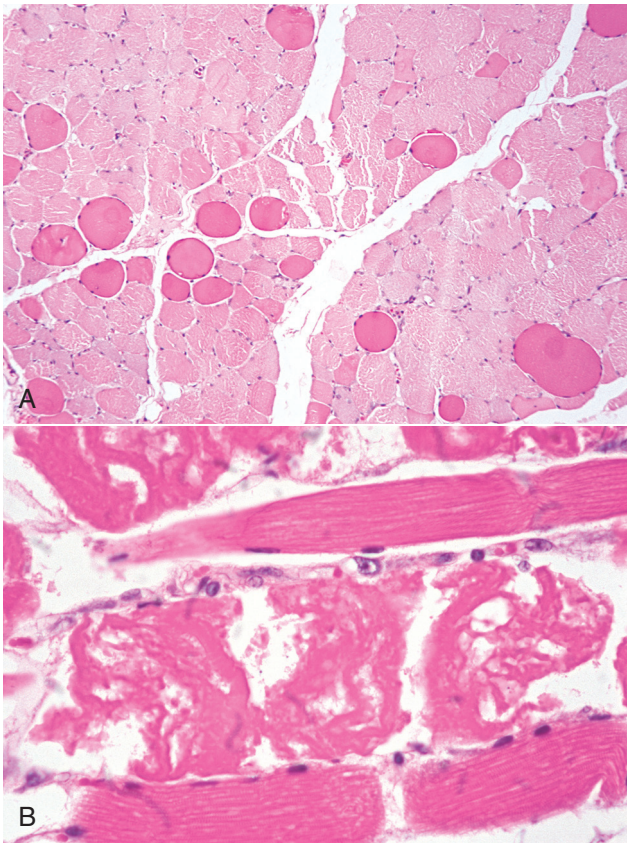
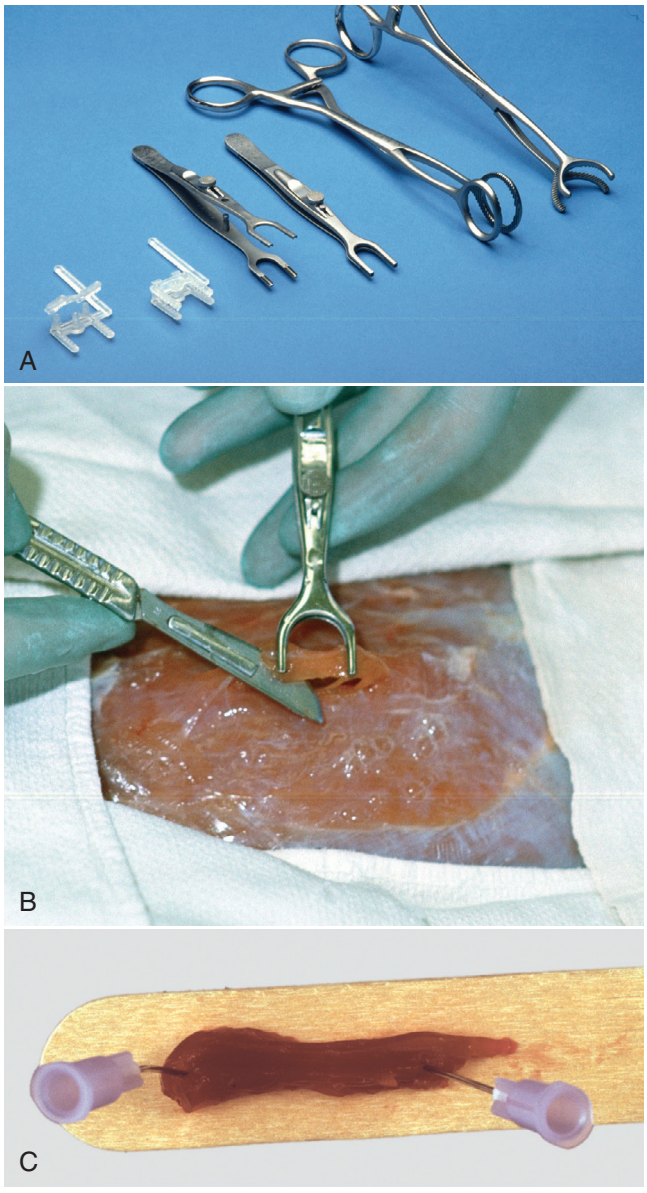


Figure 15-11 Myofiber Necrosis, Skeletal Muscle. A, Hypercontraction, transverse section. Large, deeply stained fibers (*large dark red fibers*) are hypercontracted segments of a myofiber, the initial stage of necrosis. Note the rounded outline of these myofibers compared with the polygonal outlines of normal myofibers. Formalin fixation, H&E stain. **B,** Segmental necrosis, monensin toxicosis, longitudinal section, horse. Segments of the myofibers have undergone hypercontraction *(center of figure)*, and the remaining cytoplasm is fragmented. Formalin fixation, H&E stain. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

To ensure proper fixation and orientation of sections prepared from fixed specimens, the sample should be a strip of muscle no more than 1 cm in diameter, with myofibers running lengthwise. Muscle maintains the ability to contract for some time after death, with the time varying, depending on the physiologic state.

Contraction of muscle after contact with fixative is the most common cause of an artifact called *contraction band artifact*. Contraction can be prevented or at least minimized by use of a specially designed muscle clamp (E-Fig. 15-3, *A*) or by placing the sample on a rigid surface, such as a portion of a tongue depressor, and fixing the ends with sutures, staples, or clamps before submersion in the fixative (E-Fig. 15-3, *B*).

Frequently, lesions in muscles can be detected and evaluated only by microscopic examination. Proper microscopic examination requires evaluation of both transverse and longitudinal sections. Myofiber diameters, cytoarchitectural changes, and the percentage of abnormal myofibers are most reliably evaluated in transverse sections. Longitudinal sections reveal the length of changes such as segmental necrosis or regeneration or deposition of storage material. Improperly oriented samples, which result in sections that have obliquely oriented myofibers and thus neither longitudinal nor transverse myofibers, are difficult to evaluate. Use of a magnifying glass or dissecting microscope can aid in determining the orientation of myofibers during trimming of muscle before sectioning. Routine stains, such as hematoxylin and eosin (H&E), run the risk of offering the pathologist a "vast pink wasteland" for evaluation and are often inadequate for detecting subtle myopathic changes, lesions within intramuscular nerves, or the presence of abnormal stored material. Various special stains, including reticulin, Masson trichrome, von Kossa, lipid (performed on frozen sections of fixed samples), and periodic acid–Schiff (PAS) for glycogen, are often invaluable in the evaluation of routinely processed skeletal muscle (E-Table 15-1). Examples of many of these disorders can be found in this chapter. Other valuable stains and reactions can only be performed on frozen sections of unfixed muscle samples (see E-Table 15-1).



E-Figure 15-3 Techniques for Collection of Muscle Samples for Histologic Examination. Clamps are used to prevent contraction of a fresh muscle specimen when it is immersed in 10% neutral-buffered formalin or EM fixative. **A**, Types of muscle clamps (*from left to right)*: disposable plastic clamps (open and closed), stainless steel clamps (open and closed), a gallbladder clamp (unmodified), and a modified gallbladder clamp. The stainless steel clamps are autoclavable, the best but expensive. A suitable and economical clamp (not shown) can be made by welding a bar approximately 1 cm long, 3 to 5 mm wide, and 3 mm thick between the lower jaws of two small hemostats. **B**, Final excision stage. Initially two longitudinal incisions, approximately 5 mm apart and 15 mm long, are made into the muscle in the direction of the myofibers. A horizontal cut is made 3 to 4 mm below the surface to undermine a piece of muscle. One jaw of the clamp is inserted under the muscle until its tip just exits on the other side. The clamp is lifted several millimeters above the surface of the muscle to ensure that the muscle fibers are tense and then the jaws are clamped. The clamped piece of muscle is excised by cutting at each end adjacent to the clamp as shown above. The muscle sample, still in the clamps, is placed in the fixative, usually 10% BNF, for histopathologic examination and fixed overnight. For fixation for electron microscopic examination, the muscle in the clamp is placed into EM fixative for 1 to 2 hours. For histopathologic examination, the muscle is trimmed by freeing the strip of muscle between the clamps by cutting immediately adjacent to the clamp jaws. Then a transverse section is cut from one end of this sample, avoiding any crushed area, and the remainder of the sample is cut longitudinally in the direction of the myofibers. Both samples are desirable for histopathologic examination. For electron microscopy, after fixation for 1 to 2 hours, slivers 0.5 to 1 mm thick are shaved from the outside of the sample. These are cut into pieces 0.2 mm in diameter and 0.5 mm long, with the longer dimension being in the direction of the myofibers. This long sample facilitates embedment so that the fibers are oriented either in cross section or longitudinally. Both sections are required for electron microscopy. **C**, Pinning strips of muscle onto a rigid surface, such as a piece of tongue depressor before immersion in 10% neutral-buffered formalin, will also minimize fixation artifacts but is not as effective as the clamps shown above. (**A** and **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **C** courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

E-Table 15-1 Useful Special Stains and Enzyme Reactions

Stain	Use
ROUTINE SECTIONS	
Masson trichrome	Differentiates collagen (blue) from other tissues, such as muscle and myelin (red)
Reticulin	Stains reticular fibers of the muscle interstitium including endomysium, therefore outlines individual myofibers
PTAH	Stains cross-striations in longitudinal sections of muscle
von Kossa	Stains carbonates and phosphates linked with calcium in mineralized fibers
Alizarin red S	Stains calcium in necrotic and mineralized fibers
PAS	Identifies glycogen and proteoglycans; also stains protozoal cysts
PAS with amylase (diastase)	Differentiates proteoglycans (amylase resistant) from glycogen (amylase sensitive)
FROZEN SECTIONS	
Modified Gomori's trichrome	Stains mitochondria (red), nemaline rods (red), collagen (green); differentiates myelin (red) from collagen (green) in nerves
NADH, SDH, cytochrome oxidase	Stains these mitochondrial enzymes
ATPase	Differentiates myofiber types
Acid phosphatase	Stains macrophages and denervated fibers
Nonspecific esterase	Stains macrophages and denervated fibers; identifies neuromuscular junctions
Oil red O; Sudan black	Stains lipid (only in frozen sections)
von Kossa, alizarin red S, PAS, PAS with amylase (diastase) digestion	Same as in routine stains (above)

ATPase, Adenosine triphosphatase; NADH, nicotinamide adenine dinucleotide dehydrogenase; PAS, periodic acid–Schiff; PTAH, phosphotungstic acid hematoxylin; SDH, succinate dehydrogenase.

For many decades, myofiber typing could be done only on frozen sections using the myosin ATPase reaction. Recently, immunohistochemical staining of myosin has been developed for demonstration of myofiber types in formalin-fixed muscle. This is a major advantage because fiber-type staining is often essential for the complete evaluation of muscle. It is most useful in demonstrating preferential involvement of a fiber type and alteration of the fiber-type pattern, the result of denervation and reinnervation.

There is no question that frozen section histochemistry of unfixed muscle samples is the "gold standard" of muscle pathology. Skeletal muscle may be the one tissue in which the morphology of cells and cellular components is best appreciated in frozen sections. Routine frozen section histochemistry on muscle includes a battery of stains applied to serial sections. Examples of many of these stains are illustrated in this chapter. Stains used include H&E, modified Gomori's trichrome, ATPase for fiber typing, nicotinamide adenine dinucleotide dehydrogenase (NADH), succinate dehydrogenase (SDH), cytochrome oxidase, and other mitochondrial enzyme stains, PAS for glycogen, alizarin red S for calcium, alkaline phosphatase and nonspecific esterase for macrophages and denervated fibers, and lipid stains. When indicated, frozen sections also allow for immunostaining for cytoskeletal proteins, such as dystrophin (see Fig. 15-45) and the dystrophin-associated proteins. Certain abnormal structures, such as nemaline rods formed by expansion of Z bands, as seen in nemaline rod myopathy, are not visible in routine sections but are readily identified in frozen sections stained with modified Gomori's trichrome.

The major disadvantage of frozen section histochemistry is that unless a neuromuscular disease laboratory is readily available to immediately process unfixed muscle samples, careful preparation for overnight shipping, on ice, in a moist but not overly wet environment, is necessary. Any delay in shipment or overwetting or overheating of the sample results in nondiagnostic samples. In addition, preparation of frozen sections is time- and labor-intensive, and in most cases only a single transverse section approximately 1 cm in diameter is examined. This can create a significant sampling error when evaluating a small sample of a large muscle in which lesions may not be evenly distributed.

Complete evaluation, which includes morphometric examination and calculation of the percentage and mean diameter of each fiber type, detects changes in the percentage of each fiber type and fiber atrophy or hypertrophy. But at this time, morphometric analysis is not routinely performed on samples submitted for diagnostic purposes.

Frozen section histochemistry is always a powerful tool for evaluation of muscle disease. But in many disorders, it is possible to obtain diagnostic sections from routinely processed muscle samples when appropriate sample selection, handling, and processing are performed, and sections are examined by a pathologist familiar with muscle pathology.

Although much of what used to be determined by electron microscopy has been supplanted by newer immunohistochemical procedures, electron microscopic evaluation of muscle is still important. Various structural alterations, such as abnormalities of neuromuscular junctions, mitochondria, sarcomeric disarray, sarcotubular dilation, Z-line streaming, and cytoplasmic inclusions, may be best visualized, and in some cases only visualized, by this method. Sampling and handling methods to minimize contraction and other artifacts and to allow for precise transverse and longitudinal sections are imperative.

Physiologic testing of isolated intact myofibers in vitro forms the basis for diagnosis of malignant hyperthermia (MH). Short fibers, such as from samples of intercostal muscle, are preferred. While maintained in a physiologic solution, myofiber bundles are exposed to various agents, such as caffeine and halothane, to detect abnormal contractural sensitivity. Biochemical and molecular biologic analysis of muscle samples can evaluate levels of muscle enzymes and other proteins, and genetic analysis can be performed to detect specific gene defects. These latter tests require fresh muscle samples snap-frozen in liquid nitrogen and maintained at −70° C until analysis.

mineralization must be considered a nonspecific response, indicative only of myofiber necrosis. Myofiber mineralization can be confirmed with histochemical stains, such as alizarin red S and von Kossa. Histochemical staining for calcium in frozen sections also detects increased intracytoplasmic calcium in damaged myofibers that are not overtly necrotic or mineralized (Fig. 15-12, A).

Provided there is still an adequate blood supply, macrophages derived from transformation of blood monocytes rapidly infiltrate areas of myofiber necrosis (Fig. 15-12, B). Macrophages are able to traverse the basal lamina and rapidly clear cytoplasmic debris (Fig. 15-13, A). Other leukocytes, including neutrophils, eosinophils, and lymphocytes, can also be recruited to sites of extensive myonecrosis, presumably because of various cytokines released from damaged muscle. The infiltration of macrophages and other cells into areas of damaged muscle to clear away necrotic myofibers does not in any way constitute a form of myositis.

Because myonuclei are unable to divide, regeneration of muscle relies on satellite cell activation. Muscle satellite cells are resistant to many of the insults that result in myofiber necrosis, and activation of satellite cells is triggered by necrosis of adjacent segments of that myofiber. Therefore, as macrophages are clearing cytoplasmic debris, satellite cells are becoming activated and begin to divide in preparation for regeneration of the affected myofiber segment. If the myofiber basal lamina is still intact, it will leave an empty cylindrical space known as a *sarcolemmal tube*. This name is clearly a misnomer, dating from the days when the term *sarcolemma* was applied to the

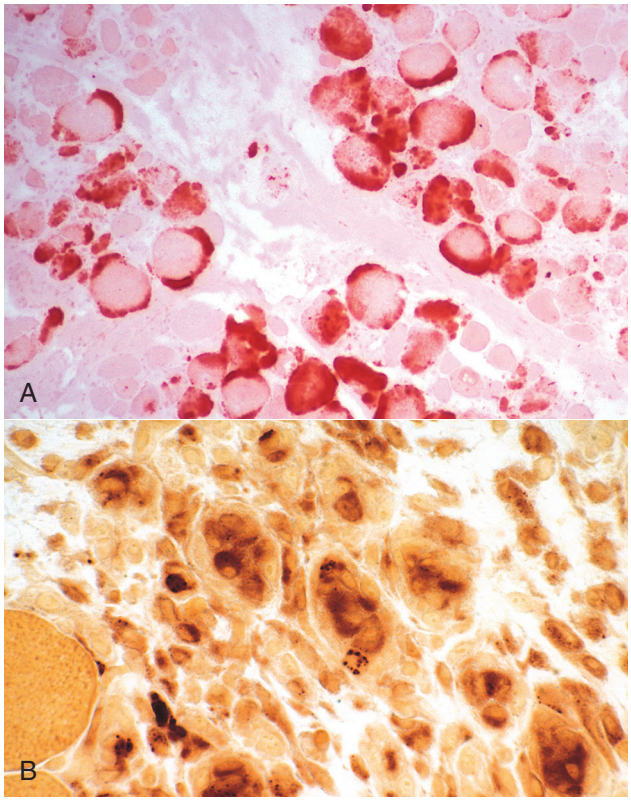


Figure 15-12 Myofiber Necrosis, Skeletal Muscle, Transverse Section. A, There has been a massive influx of calcium *(stained red-orange)* into acutely necrotic fibers. Frozen section, alizarin red S stain. **B,** Macrophages with red-brown staining cytoplasm invading necrotic myofibers. Portions of intact fibers are in the lower left. Frozen section, nonspecific esterase stain. (**A** courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University. **B** courtesy Dr. B.J. Cooper, College of Veterinary Medicine, Oregon State University.)

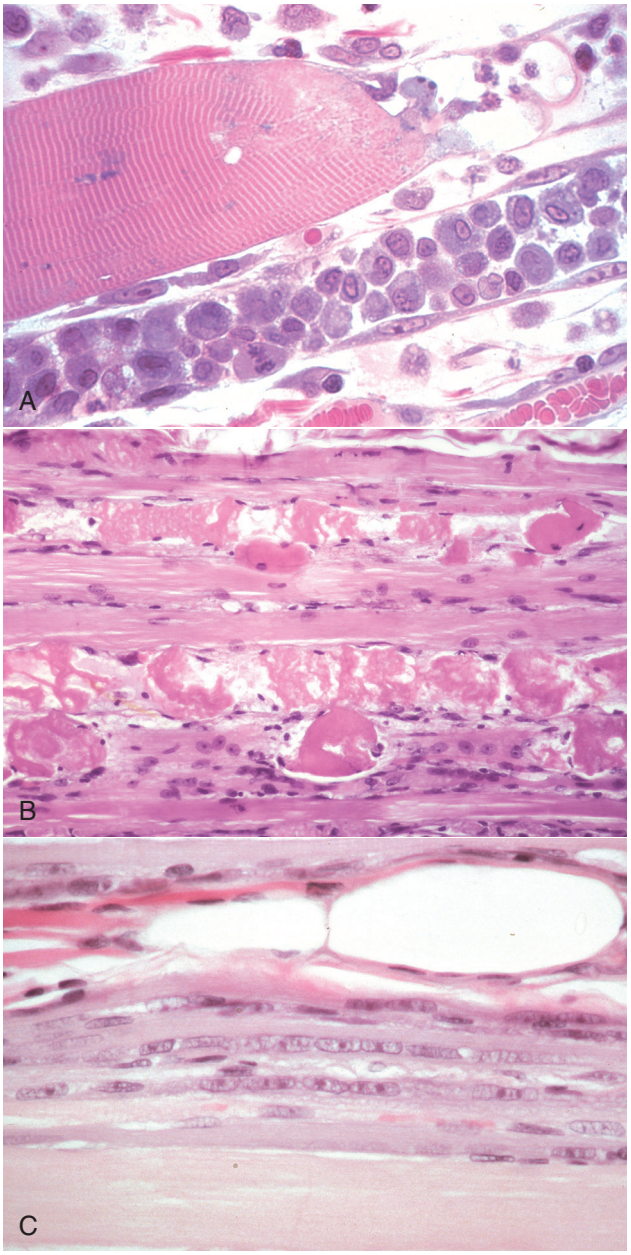


Figure 15-13 Segmental Necrosis and Regeneration. A, Monophasic segmental coagulation necrosis, skeletal muscle, longitudinal section of two myofibers. A segment of the upper fiber *(right)* and all the visible portion of the lower fiber have undergone necrosis, and macrophages have invaded through the intact basal lamina and cleared the cytoplasmic debris. Satellite cells on the inner surface of the basal lamina of the lower fiber are activated, and one *(lower left side)* is in mitosis. One-micron-thick plastic-embedded section, H&E stain. **B,** Polyphasic injury, segmental coagulation necrosis and regeneration of myofibers, muscle, longitudinal section. Between each of the foci of coagulation necrosis in the lowest myofiber is a segment of small-diameter faintly basophilic cytoplasm lacking cross-striations, in which there is an internal chain of euchromatic nuclei. This is a late stage of regeneration. Formalin fixation, H&E stain. **C,** Monophasic injury, late-stage regeneration, skeletal muscle, longitudinal section. The regenerating segment of the myofiber consists of myotubes, which have small diameters, with slightly basophilic cytoplasm and internal rows of large euchromatic nuclei. Formalin fixation, H&E stain. (**A** courtesy Dr. A. Kelly, University of Pennsylvania. **B** courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University. **C** courtesy Dr. B.J. Cooper, College of Veterinary Medicine, Oregon State University.)

tube formed by the basal lamina that remains after segmental myofiber necrosis. Clearly what is now termed the sarcolemma (plasmalemma) of necrotic fiber segments is lost, but this is a misnomer that is firmly entrenched. The important concept to remember is that, if intact, the basal lamina forms a cylindrical scaffold to guide proliferating myoblasts and to keep fibroblasts out. Satellite cells may be seen undergoing mitosis, at which stage they are known as *activated myoblasts*, on the inner surface of this tube (see Fig. 15-13, *A*). Within hours, proliferating myoblasts will fuse end-to-end to form myotubes (Fig. 15-13, *B* and *C*), and within days the myotube produces thick and thin filaments and undergoes maturation to a myofiber, reestablishing myofiber integrity. If the basal lamina is ruptured, myotubes are said to be able to bridge gaps of 2 to 4 mm and larger ones heal by fibrosis (see later discussion). The process of myofiber regeneration recapitulates embryologic development of skeletal muscle and is depicted schematically in Fig. 15-14. A percentage of dividing satellite cells do not fuse with the forming myotube but instead become new satellite cells capable of future regeneration.

In summary, the success of muscle regeneration depends on (1) the presence of an intact basal lamina and (2) the availability of viable satellite cells. The stages of successful muscle regeneration are summarized in Box 15-2.

Thus myofibers undergoing segmental necrosis in which the basal lamina is preserved, as in metabolic, nutritional, and toxic myopathies, regenerate very successfully. However, when large areas of satellite cells are killed (e.g., by heat, intense inflammation, or infarction), the situation is very different. In this case, a return to normal is not possible, and healing is chiefly by fibrosis.

If the insult to the muscle is sufficient to disrupt the myofiber basal lamina but not enough to damage the satellite cells, regeneration attempts are ineffective. Because the basal lamina is not intact, there is no tube to guide the myoblasts proliferating from each end. Myoblast proliferation under these conditions results in formation of so-called muscle giant cells (Fig. 15-15). Thus the presence of muscle giant cells indicates that conditions for regeneration have not been optimal and occurs after destructive lesions, such as those caused by trauma that transects myofibers, infarction, and intramuscular bacterial infection or injection of irritants. Muscle giant cells are often accompanied by fibrosis, which will unite the ends of the damaged myofibers. This also occurs in muscle damaged by invasive or metastatic sclerosing carcinomas. Cytokines released from damaged muscle fibers contribute to the signaling pathways that initiate macrophage infiltration and regeneration, but they also contribute to interstitial fibroblast activation. Collagen is inelastic, and thus large areas of fibrosis inevitably reduce the ability of the muscle to contract and to stretch. Fibrosis within locomotory muscles often results in obvious alteration of the gait.

Because segmental necrosis and regeneration are such a common result of a wide variety of insults (e.g., overexertion, selenium deficiency, and toxic injury), a histologic diagnosis of segmental necrosis is often not helpful in determining the cause of the disease. Pathologic classification of lesions according to distribution (i.e., focal, multifocal, locally extensive, and diffuse) and duration (i.e., acute, subacute, and chronic) has proven to be extremely useful in determining the possible causes of segmental muscle necrosis. Pathologic classification of degenerative myopathies is enhanced by use of the terms *monophasic necrosis* and *polyphasic necrosis*. Monophasic lesions are of the same duration, indicative of a single insult. Polyphasic lesions indicate an ongoing degenerative process. Thus a focal monophasic lesion could be the result of a single traumatic incident such as an intramuscular injection (see Fig. 15-9, *B*). A multifocal monophasic lesion could represent a single episode of overly strenuous exercise (exertional myopathy) or a toxin being ingested on one occasion (e.g., a horse eating one dose of monensin; see Figs. 15-11, *B*, and 15-33, *B*). However, if the insult is repeated or ongoing, such as occurs in muscular dystrophy (see Fig. 15-44), selenium deficiency, or continuous feeding of a toxin, then new lesions (segmental necrosis) will form at the same time that regeneration is taking place; in other words, it will be a multifocal and polyphasic disease (see Fig. 15-11, *B*). Using this approach, it is sometimes possible to rule out a diagnosis (e.g., muscular dystrophy and selenium deficiency myopathy are typically polyphasic), but this is not an invariable rule. For example, in livestock with borderline concentrations of selenium, a sudden stress can cause a monophasic necrosis.

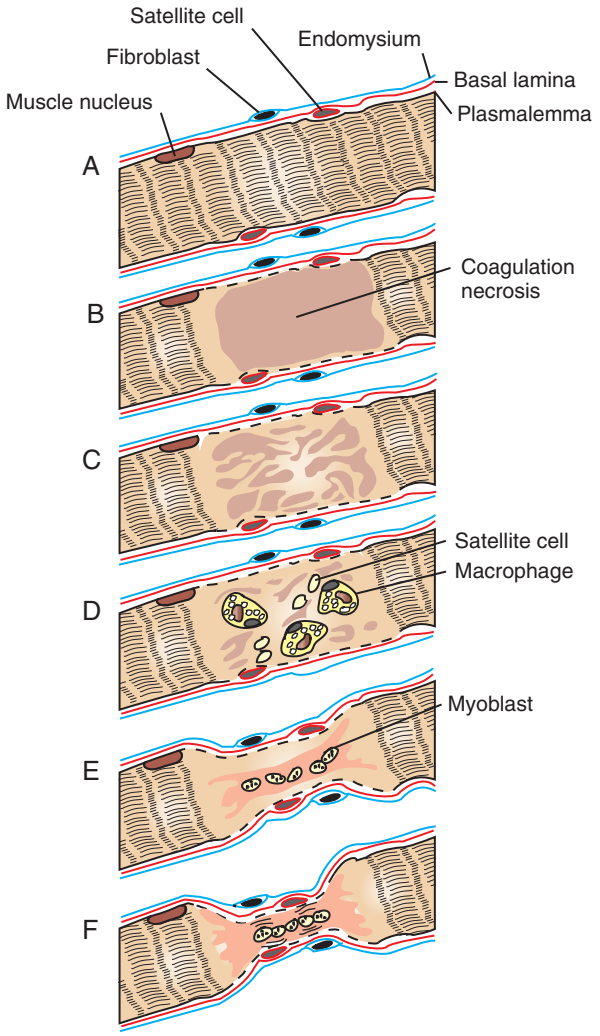


Figure 15-14 Segmental Myofiber Necrosis and Regeneration. **A,** Myofiber, longitudinal section. **B,** Segmental coagulation necrosis. **C,** The necrotic segment of the myofiber has become floccular and detached from the adjacent viable portion of the myofiber. The satellite cells are enlarging. **D,** The necrotic segment of the myofiber has been invaded by macrophages, and satellite cells are migrating to the center. The latter will develop into myoblasts. The plasmalemma of the necrotic segment has disappeared. **E,** Myoblasts have formed a myotube, which has produced sarcoplasm. This extends out to meet the viable ends of the myofiber. The integrity of the myofiber is maintained by the sarcolemmal tube formed by the basal lamina and endomysium. **F,** Regenerating myofiber. There is a reduction in myofiber diameter with central rowing of nuclei. There is early formation of sarcomeres (cross-striations), and the plasmalemma has re-formed. Such fibers stain basophilically with H&E. (Redrawn with permission from Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Box 15-2 Stages of Muscle Regeneration Under Optimal Conditions

Muscle nuclei disappear from the necrotic segment and the sarcoplasm becomes hyalinized (eosinophilic, amorphous, and homogeneous) because of the loss of normal myofibrillar structure (see Fig. 15-15, *B*). The necrotic portion may separate from the adjacent viable myofiber (see Fig. 15-12, *B*; Fig. 15-14, *A* and *B*; and Fig. 15-15, *C*).

Within 24 to 48 hours, monocytes emigrate from capillaries, become macrophages, and enter the necrotic portion of the myofiber (see Fig. 15-13, *B*; Fig. 15-14, *A*; and Fig. 15-15, *D*). Concurrently, the satellite cells, located between the basal lamina and the sarcolemma, begin to enlarge (see Fig. 15-14, *A*; and Fig. 15-15, *C* and *D*), become vesicular with prominent nucleoli, and then undergo mitosis to become myoblasts.

Myoblasts migrate from the periphery to the center of the sarcolemmal tube, admixed with macrophages (see Fig. 15-15, *D*).

Macrophages lyse and phagocytose necrotic debris and form a clear space in the sarcolemmal tube, and the shape and integrity of the sarcolemmal tube are maintained by the basal lamina (see Fig. 15-14, *A*).

Myoblasts fuse with one another to form myotubes, which are thin, elongated muscle cells with a row of central, closely spaced nuclei. Developing myotubes send out cytoplasmic processes in both directions within the sarcolemmal tube (see Fig. 15-15, *E*). When the processes contact each other or a viable portion of the original muscle fiber, they fuse. The regenerating fiber is characterized by (1) basophilia as a result of increased RNA content; (2) internal nuclei, often in rows, that have differentiated to myonuclei; (3) a lack of striations; and (4) a smaller than normal diameter (see Fig. 15-14, *B* and *C*, and Fig. 15-15, *F*).

The fiber grows and differentiates. Its diameter increases, the sarcoplasm loses its basophilia, and longitudinal and cross-striations appear, indicating the formation of sarcomeres.

In most species, within several days, the muscle nuclei of regenerating fibers move to their normal position at the periphery of the fiber, just under the sarcolemma.

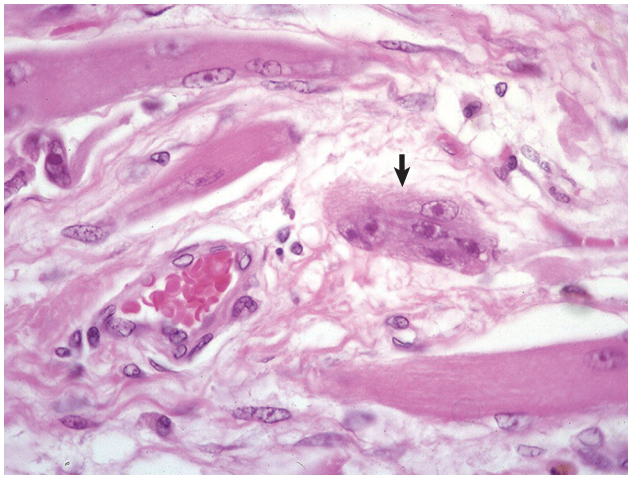


Figure 15-15 Ineffectual Regeneration. Large, bizarre multinucleate muscle giant cells *(arrow)* are indicative of regeneration in an area in which the myofiber's basal lamina has been damaged. Because the wall of the "myotube" of basal lamina is not intact, regenerating sarcoplasm exudes through the defect, and in cross section this appears as a "muscle giant cell." Formalin fixation, H&E stain. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

The term *rhabdomyolysis* is often encountered, particularly in the clinical arena, and especially in association with exercise-induced muscle injury (exertional rhabdomyolysis) in human beings, horses, and dogs. Technically, *rhabdomyolysis* simply means necrosis (lysis) of striated muscle. Rhabdomyolysis generally indicates the presence of a severe degenerative myopathy with a large degree of myofiber necrosis (see Fig. 15-35). In horses, the term *exertional rhabdomyolysis* has become firmly entrenched as a clinical entity in which exercise-induced muscle injury is the presenting sign. The term *recurrent exertional rhabdomyolysis* is often employed in cases in which repeated bouts of exercise-induced muscle damage have been documented.

Alteration in Myofiber Size

The normal myofiber diameter will vary, depending on fiber type, the muscle examined, the species, and the age of the animal. In some species (e.g., horse, cat, and human beings), there are three distinct populations based on diameter: Type 1 fibers are the smallest, type 2B fibers are the largest, and type 2A fibers are intermediate in size. Different sizes in diameters are in part a reflection of the oxidative needs of the fibers; oxygen diffuses more readily into the interior of small-diameter fibers. In the dog, all fiber types are oxidative, and fiber-type diameter is much more uniform. A histogram generated from morphometric analysis of fiber diameters will reveal the characteristics of individual muscles in various species. Not surprisingly, this type of detailed information is more readily available for human patients than for animals. Even without morphometric analysis, however, a pathologist experienced in examination of muscle can often determine whether there is a normal fiber-size distribution (based on fiber diameter in transverse section) or whether there is an increase in fiber-size variation. The finding of increased fiber-size variation suggests that something is wrong but in itself does not give any indication of cause. Increased fiber-size variation can be a result of fiber atrophy, fiber hypertrophy, or both and is considered part of the spectrum of changes included in the term *chronic myopathic change* (Box 15-3).

Atrophy

The term *atrophy* is used to imply either a reduction in the volume of the muscle as a whole or a reduction in the diameter of a myofiber. In the early stages of atrophy, it may be difficult or impossible to detect loss of muscle mass by gross observation, and morphometric evaluation of myofiber diameters may be required. Several cellular physiologic processes can be activated to result in muscle atrophy. These include induction of lysosomal action to result in autophagy of cytoplasmic components, apoptosis (programmed cell death), and activation of the cytoplasmic ubiquitin-proteosomal machinery. Lysosomal activation is prominent in denervation atrophy and is the basis for the positive reaction of denervated fibers in alkaline phosphatase and nonspecific esterase preparations. The causes of muscle fiber atrophy include physiologic and metabolic processes and denervation. In most instances, muscle atrophy is reversible provided the cause is corrected. The type of fiber undergoing atrophy varies, depending on the cause; therefore fiber typing is often required for

Box 15-3 Findings Associated with Chronic Myopathic Change

Excessive fiber-size (diameter) variation	Other cytoarchitectural changes
Internal nuclei	Fibrosis
Fiber splitting	Fat infiltration

Box 15-4 Fiber Types Affected in Different Types of Muscle Atrophy

Denervation: Type 1 and type 2 fibers; reinnervation leads to altered fiber-type patterns (fiber-type grouping)
Disuse: Predominantly type 2 fibers; may vary, depending on the species and cause
Endocrine disease: Predominantly type 2 fibers; associated with hypothyroidism and hypercortisolism
Malnutrition, cachexia, and senility: Predominantly type 2 fibers
Congenital myopathy: Often predominantly type 1 fibers

a definitive diagnosis. Interestingly, type 2 fibers are the most likely to atrophy under a variety of circumstances (Box 15-4). Signaling molecules involved in muscle atrophy include tumor necrosis factor-α (TNF-α) and interleukin (IL)-1 and IL-6.

Physiologic Muscle Atrophy. Decrease in myofiber diameter and therefore in the overall muscle mass is a physiologic response to lack of use (disuse atrophy), cachexia, and aging. Type 2 fibers are preferentially affected (E-Fig. 15-4). Disuse atrophy occurs relatively slowly, and only in muscles not undergoing normal contraction, as is caused by severe lameness or in muscles of a limb that is splinted or enclosed in a cast. The degree of disuse atrophy will be variable, but typically it is not as severe as the atrophy of cachexia or denervation (see later discussion). Disuse atrophy is often asymmetric. Muscle atrophy caused by cachexia can be profound, especially in cases of cancer cachexia in which increased circulating levels of TNF alter the muscle metabolism, favoring catabolic processes rather than anabolic processes. Cachexia also develops relatively slowly and causes symmetric muscle atrophy. Starvation, malnutrition, neoplasia, and chronic renal and cardiac diseases are possible causes of cachexia.

Atrophy Caused by Endocrine Disease. Preferential atrophy of type 2 fibers causing symmetric muscle atrophy also occurs because of various endocrine disorders. The most common are hypothyroidism and hypercortisolism in dogs. Aging horses with pituitary dysfunction or tumors (leading to equine Cushing's syndrome) often develop type 2 muscle fiber atrophy. Myofibers contain a high concentration of surface receptors for several hormones, and atrophy caused by endocrine disease reflects the intimate interrelationship between the endocrine and the muscular systems.

Denervation Atrophy. Denervation atrophy, also known by the misnomer *neurogenic atrophy*, is not uncommon in veterinary medicine. Maintenance of normal myofiber diameter depends on trophic factors generated by an intact associated nerve. Loss of neural input results in rapid muscle atrophy, and more than half the muscle mass of a completely denervated muscle can be lost in a few weeks. This trophic effect is not dependent on contractile activity because denervation atrophy is not a feature of neuromuscular junction disorders such as botulism and myasthenia gravis. In these disorders, there is a failure of neuromuscular transmission, but the nerve to the muscle is intact; therefore the muscle is technically still innervated. Generalized neuropathies or neuronopathies, such as equine motor neuron disease, result in widespread and symmetric muscle atrophy. More commonly, however, only select nerve damage is present, resulting in asymmetric muscle atrophy. One example is equine laryngeal hemiplegia (roaring) secondary to damage to the left recurrent laryngeal nerve (Fig. 15-16). Note that purely demyelinating disorders of peripheral nerves can cause profound

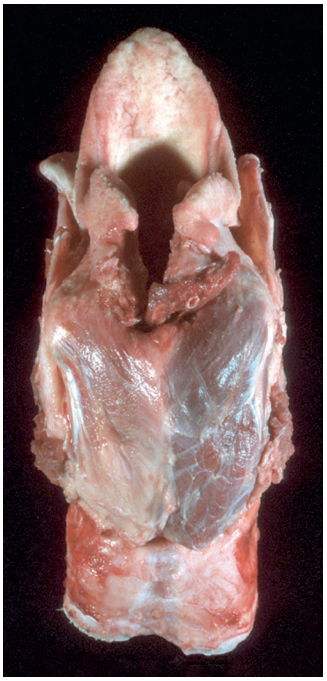


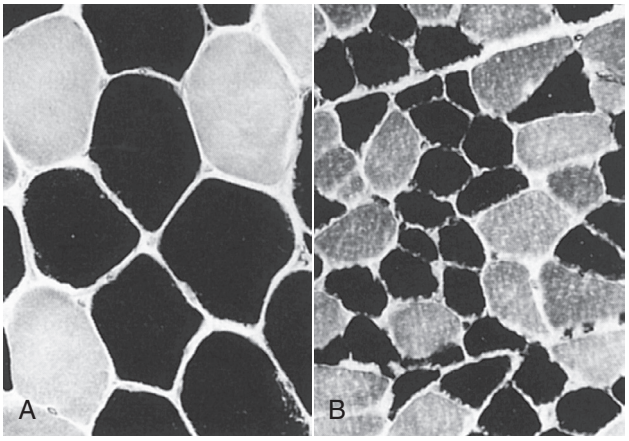
Figure 15-16 Denervation Muscle Atrophy, Left Cricoarytenoideus Dorsalis Muscle, Larynx, Dorsal Surface, Horse. Note the unilateral *(left side)* atrophy and pale gray to white discoloration of the muscle. This horse had a peripheral neuropathy, which led to laryngeal hemiplegia. (Courtesy Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

neuromuscular dysfunction, but axons are still intact. Associated myofibers are not technically denervated and therefore do not undergo denervation atrophy.

After denervation, fibers become progressively smaller in diameter as peripheral myofibrils disintegrate. If an atrophic fiber is surrounded by normal fibers, it will be pressed into an angular shape, called an angular atrophied fiber. The angular atrophied fibers of denervation atrophy most often occur either singly or in small contiguous groups (small group atrophy) (Fig. 15-17, *A*). In more severe denervating conditions, in which many fibers within muscle fascicles are undergoing denervation atrophy, there are no normal fibers to cause compression and angularity, and affected fibers occur as larger groups of small-diameter, rounded fibers (large group atrophy; Fig. 15-17, *B*). Although myofibrils disappear rapidly, muscle nuclei do not do so at the same rate, and therefore denervation atrophy is often associated with a notably increased concentration of myonuclei. The breakdown of glycogen in the myofiber is an early change in denervation atrophy, and therefore denervated fibers stain faintly or not at all with the PAS reaction.

A histologic diagnosis of denervation atrophy may be suspected, based on the characteristic features of routinely processed muscles, but is most reliably documented with histochemistry or immunohistochemistry to detect fiber types. The loss of a nerve fiber to a muscle results in atrophy of all myofibers innervated by that nerve. Because of the intermingling of motor units forming a mosaic pattern of fiber types, myofibers undergoing denervation atrophy are scattered in a section of muscle. Because the motor neuron determines the histochemical myofiber type and because denervating diseases typically involve both type 1 and type 2 neurons or nerves, atrophy of both type 1 and type 2 myofibers in muscle fasciculi is the hallmark of denervation atrophy (Fig. 15-18, *A*).

In denervation atrophy, histologic examination of the intramuscular nerves is warranted because it may reveal axonal degeneration



E-Figure 15-4 **Disuse Atrophy, Dog. A,** Transverse section of normal biceps femoris muscle. **B,** Same muscle, same magnification, 60 days after disuse. Both type 1 *(light)* and type 2 *(dark)* fibers are atrophic, but type 2 fibers are more severely affected. Frozen section, ATPase pH 9.8. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

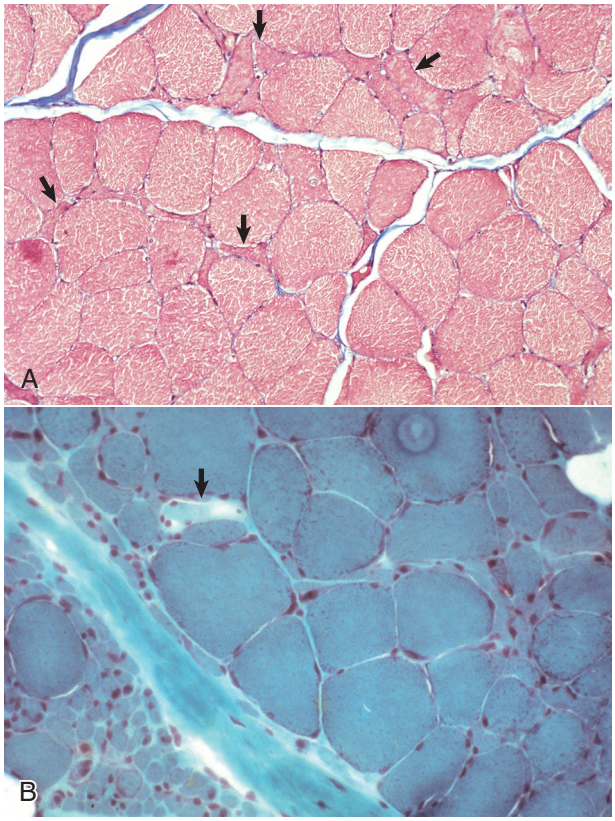


Figure 15-17 Denervation Atrophy, Transverse Sections. Both sections are from horses with equine motor neuron disease. **A,** In relatively mild denervation, severely atrophied and angular fibers form small contiguous clusters indicative of small group atrophy (*arrows*). Formalin fixation, Masson trichrome stain. **B,** In severe denervation, entire fascicles of fibers undergo rounded atrophy characteristic of large group atrophy *(lower left)*. Small group atrophy and admixed fiber hypertrophy are also present. A single pale stained fiber *(arrow)* is undergoing acute necrosis. There is also mild endomysial and perimysial fibrosis and mild fat infiltration *(empty vacuoles in the upper right and lower left)*. Frozen section, modified Gomori's trichrome stain. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

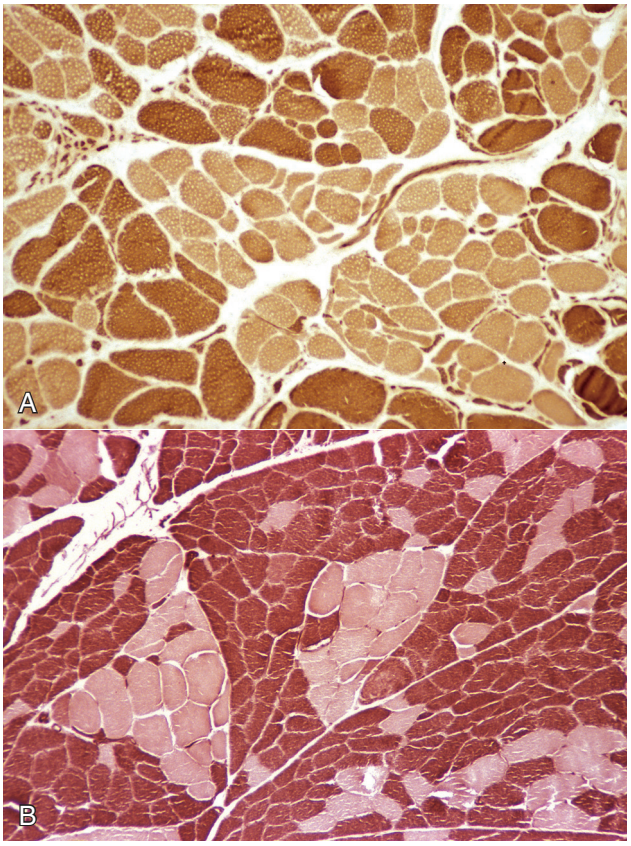


Figure 15-18 Denervation Atrophy and Reinnervation, Skeletal Muscle, Transverse Sections. A, Fiber typing reveals angular atrophy of both type 1 *(light)* and type 2 *(dark)* fibers, characteristic of denervation atrophy. In this case, there is also a loss of the normal mosaic pattern of fiber types, with groups of type 1 and of type 2 fibers indicative of reinnervation. This section is from a horse with laryngeal hemiplegia. Frozen section, ATPase pH 10.0. **B,** Fiber-type grouping in a dog indicative of denervation and reinnervation secondary to corticosteroid therapy. There is a loss of the normal mosaic pattern of fiber types, with grouping of type 1 *(light)* and type 2 *(dark)* fibers. The lack of angular atrophied fibers indicates that active denervation is not occurring at this time. Frozen section, ATPase pH 9.8. (**A** courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University. **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

or loss of myelinated fibers. Masson trichrome stain can be useful here because it will differentiate myelin (red) from collagen (blue). If the nerve damage does not incapacitate the animal and the muscle can still be used (e.g., in locomotion), the remaining innervated myofibers often undergo notable hypertrophy because of increased workload. Often, the hypertrophied fibers in chronic denervation are type 1. Even without fiber typing, a pattern of severe small or large group atrophy (see Fig.15-17, *A*), especially if associated with notable fiber hypertrophy (see Fig. 15-17, *B*), is strongly suggestive of denervation atrophy. A finding of damage in an associated peripheral nerve is definitive.

Under many circumstances, denervated muscle fibers can be reinnervated by subterminal sprouting of axons from adjacent normal nerves. Reinnervation results in return to normal myofiber diameter, but reinnervation is often from sprouts of a different type of nerve. Because muscle fiber type is a function of the motor neuron, the newly innervated myofiber takes on the fiber type determined by that neuron. This process results in a loss of the normal arrangement of type 1 and type 2 myofibers and the formation of groups of the same fiber type adjacent to each other, called *fiber-type grouping* (see Fig. 15-18). Thus fiber-type grouping is the hallmark of denervation followed by reinnervation. What appears to be fiber-type grouping can also occur because of fiber-type conversion (most often to type 1 fibers) in chronic myopathic conditions. Careful evaluation of the structure and function of peripheral nerves helps distinguish neuropathic from myopathic changes. If previously reinnervated fibers are denervated again, the pattern includes large groups of atrophied fibers of a single fiber type, a process known as *type-specific group atrophy*. Type-specific group atrophy is far less common in animals than in human beings. Fiber-type grouping and type-specific group atrophy can only be detected by methods that distinguish fiber types. Changes occurring as a result of denervation and reinnervation are illustrated in Fig. 15-19.

Atrophy Caused by Congenital Myopathy. Congenital myopathy in children is often associated with selective type 1 fiber atrophy. This finding is less common in the congenital myopathies identified thus far in animals. Selective type 1 atrophy is, however, a feature of feline nemaline myopathy, an animal model of congenital nemaline myopathy in children.

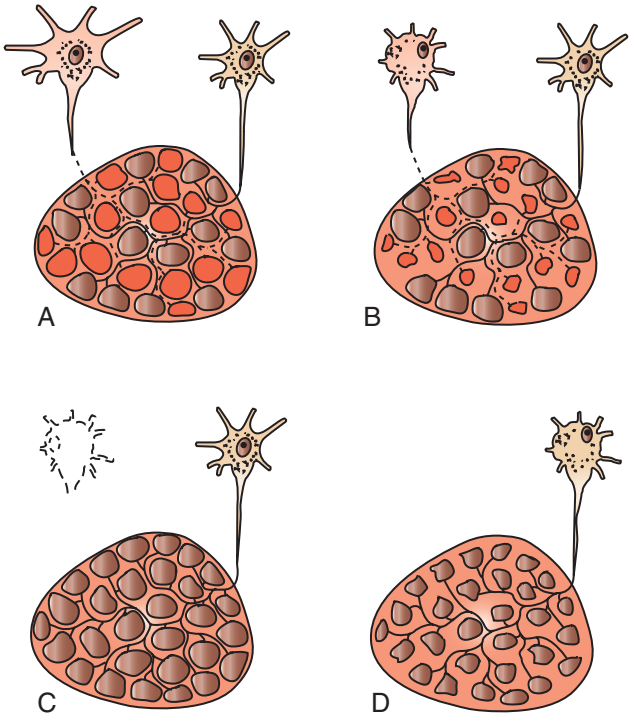


Figure 15-19 Motor Units Undergoing Denervation and Reinnervation. A, Terminal axon branches innervate multiple myofibers, and myofiber type is determined by the electrical activity of the type of neuron innervating the myofiber. Normally the terminal axons of the motor units are intermingled, with the result that the differently stained myofiber types form a mosaic pattern. **B,** If a neuron (or axon) is damaged, the axon will undergo Wallerian degeneration, and the myofibers in that motor unit will undergo denervation atrophy. Small group atrophy is illustrated here. **C,** Axonal sprouts from a healthy neuron can reinnervate affected fibers and cause restoration of their normal diameter. The myofibers will assume the fiber type of the new motor unit, which often causes fiber-type conversion, leading to fiber-type grouping. **D,** If neuronal (or axonal) damage is progressive, denervation atrophy of large groups of fibers of a single type can occur, known as type-specific group atrophy. This type of atrophy is less common in animals than in human beings. (Redrawn with permission from Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

Hypertrophy

Myofibers increase in diameter by the addition of myofilaments. Physiologic hypertrophy is the normal process of myofiber enlargement that occurs with exercise conditioning. Compensatory hypertrophy occurs because of pathologic conditions that (1) decrease the number of functional myofibers and therefore increase the load on remaining fibers or (2) interfere with normal cellular metabolic or other physiologic processes. Compensatory myofiber hypertrophy is therefore considered a relatively nonspecific response to a variety of insults. Fibers undergoing compensatory hypertrophy can enlarge to more than 100 µm in diameter (normal is less than approximately 60 to 70 µm). Fiber hypertrophy often accompanies fiber atrophy, which contributes to increased fiber-size variation in various myopathic and neuropathic conditions.

Compensatory hypertrophy can occur because of a decrease in the number of functional myofibers. Thus, in a partially denervated muscle, the remaining innervated fibers hypertrophy (see Fig. 15-17, *B*), presumably as a result of increased workload. Pathologically, hypertrophied fibers have less oxygen diffusion from interstitial capillaries to internal portions of the myofiber because of the increase in the distance from the capillary to the internal portions of the myofibers, which can lead to myofiber damage. Mechanical overloading of hypertrophied muscle fibers is also possible. For example, overloading of hypertrophied fibers can result in segmental necrosis of the hypertrophied fibers (see Fig. 15-17, *B*), or fibers can undergo longitudinal fiber splitting to generate one or more smaller-diameter "fibers," all contained within the same basal lamina (Fig. 15-20). Serial sections of areas of fiber splitting generally reveal that splits do not extend the entire length of the myofiber. Fiber splitting is considered a form of cytoarchitectural alteration (see later discussion). Insulin-like growth factor 1 (IGF-1) is an important molecular signal involved in skeletal muscle hypertrophy. Genetic inactivation of the regulatory gene myostatin results in muscle hypertrophy caused by an increase in the number of myofibers.

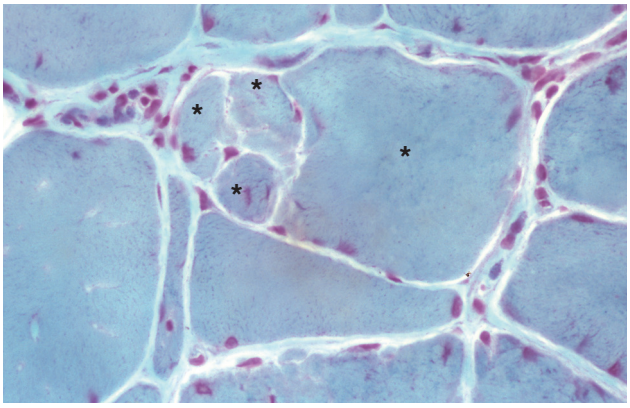


Figure 15-20 Fiber Splitting of Hypertrophied Myofibers, Nemaline Myopathy, Skeletal Muscle, Transverse Section, Cat. Sarcolemmal ingrowth into the myofiber has resulted in multiple partitions with the formation of four myofibers *(asterisks)*; however, all myofibers are enclosed by one basal lamina. Frozen section, modified Gomori's trichrome stain. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

Cytoarchitectural Changes

In addition to fiber splitting, a variety of other cytoarchitectural changes can occur within myofibers. Some are degenerative, the result of an insult that damages the myofiber but does not culminate in myofiber necrosis. Others reflect underlying ultrastructural alterations that may be either pathologic or compensatory in nature. The functional significance of many of the myofiber cytoarchitectural changes is not known.

Vacuolar Change

Vacuolar change is a common cytoplasmic alteration. In formalin-fixed paraffin-embedded sections or in any sample subjected to less than ideal handling, true vacuolar change can be very difficult to distinguish from artifacts. Vacuoles can be an early manifestation of processes leading to necrosis, they can reflect underlying sarcotubular dilation as occurs in many myotonic conditions (see later discussion), and they can be caused by abnormal storage of carbohydrate or lipid, or they can reflect underlying myofibrillar abnormalities. Additional studies are often necessary to determine the nature of the vacuoles. When severe, such as in glycogen storage diseases, the term *vacuolar myopathy* is often employed.

Internal Nuclei

Myonuclei of mature myofibers in domestic animals are normally found peripherally, just beneath the sarcolemma. Nuclei located one nuclear diameter or more from the sarcolemma are known as *internal*

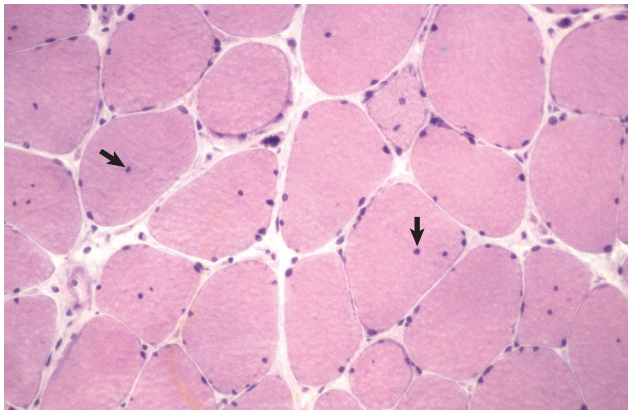


Figure 15-21 Chronic Myopathic Change, Medial Triceps Muscle, Horse. The variation in myofiber diameter and the presence of one or more internal nuclei in most myofibers *(arrows)* are indicative of a chronic myopathic change. Frozen section, H&E stain. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

nuclei. (NOTE: The previously used term *central nuclei* is considered incorrect because few abnormally placed nuclei are exactly centrally located.) Internal nuclei are rare in normal mammalian muscle, but a small percentage can be found normally in avian and reptilian species. Rows of internal nuclei in small-diameter, slightly basophilic myofibers are characteristic of the myotubular stage of regeneration (see Fig. 15-13, *B* and *C*). In most species, myonuclei return to the normal peripheral location early in regeneration, within days of myotube formation. Rodents are the exception. In rodents, internal nuclei are retained after regeneration, which, in these species, provides a handy marker for identification of fibers that have undergone necrosis and regeneration. In other mammalian species, the presence of internal nuclei in normal or hypertrophied fibers is a nonspecific finding indicative of chronic myopathic change (Fig. 15-21; see Box 15-3). In hypertrophied fibers, the migration of myonuclei to the internal portion of the myofiber can precede the sarcolemmal infolding that creates longitudinal fiber splitting.

Whorled and Ring Fibers

The cytoarchitectural rearrangements resulting in whorled and ring fibers are best appreciated in transverse sections. Whorled fibers contain spirals of cytoplasm with internally located nuclei. Whorled fibers can be seen in areas of chronic denervation and also in areas in which myofiber necrosis with incomplete regeneration has occurred. Ring fibers (also known as *ringbinden*) contain a peripheral rim of sarcomeres oriented perpendicular to their normal orientation, resulting in peripheral radiating striations. Ring fibers are visible with many stains, both in frozen sections and in routinely processed sections. In either frozen or routine sections, they are best visualized in sections stained with PAS (Fig. 15-22, *A*) or iron hematoxylin. In human beings, ring fibers are common in a specific form of inherited muscular dystrophy known as *myotonic dystrophy*, but they are also seen in other myopathic and in neuropathic conditions and therefore are not specific for myotonic dystrophy. Similarly, there is no animal disorder in which ring fibers are specific, and these fibers can be seen in a variety of myopathic and neuropathic conditions such as ovine congenital muscular dystrophy. The presence of ring fibers can only be considered a chronic myopathic change. For example, numerous ring fibers were found in muscle from the contralateral weight-bearing limb from a horse with long-standing, non–weight-bearing foreleg lameness.

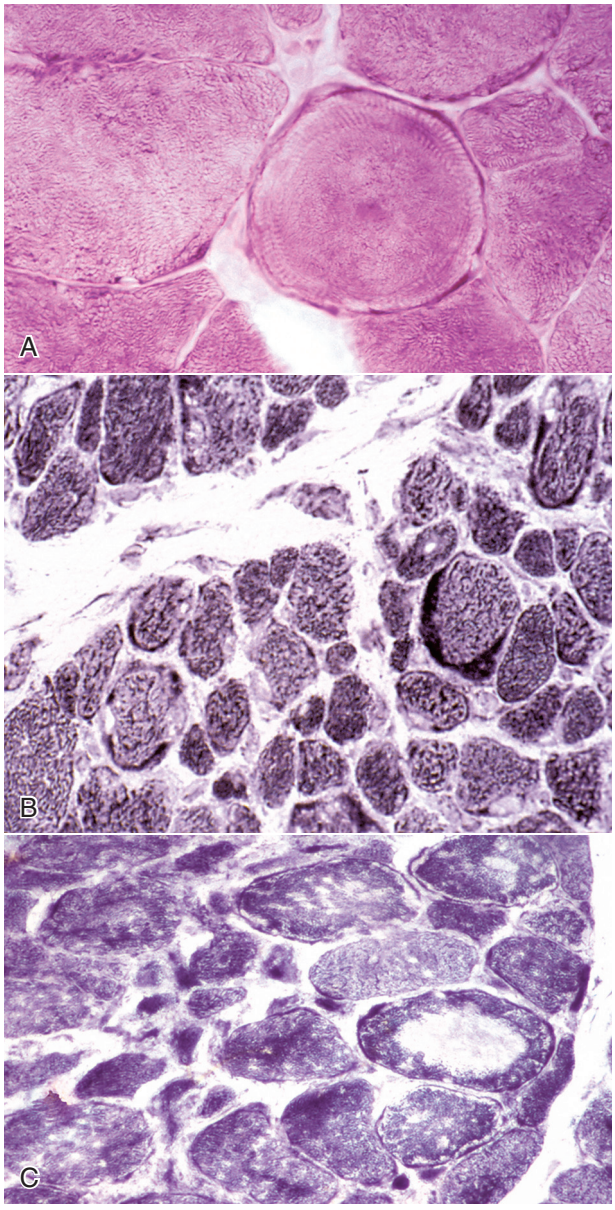


Figure 15-22 Cytoarchitectural Changes, Skeletal Muscle, Transverse Sections. A, Ring fiber, extensor carpi radialis muscle, horse. A ring fiber *(center right)* is characterized by a peripheral rim of sarcomeres, arranged circumferentially around a myofiber and with their length at right angles to the long axis of the myofiber. Frozen section, PAS reaction. **B,** Irregular mitochondrial distribution with peripheral aggregates of blue staining mitochondria, Labrador centronuclear myopathy, temporalis muscle, dog. Frozen section, NADH reaction. **C,** Irregularity of mitochondrial *(blue-stained)* distribution and "moth-eaten" fibers, polyneuropathy, dog. Fibers containing pale zones are characteristic of moth-eaten fibers. Frozen section, NADH reaction. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

Other Cytoarchitectural Changes

Many other cytoarchitectural changes reflect alterations in mitochondrial density or integrity and are best appreciated on examination of frozen sections, in which mitochondria can be visualized, or on ultrastructural examination. The presence of peripheral aggregates of mitochondria, which stain red with modified Gomori's trichrome stain, form the basis of "ragged red" fibers. Ragged red fibers are a hallmark of mitochondrial myopathy in human beings. In

animals, however, ragged red fibers are common in various myopathic conditions and also occur in normal dog and horse muscle. Mitochondrial abnormalities are also detected by oxidative enzyme reactions such as NADH (Fig. 15-22, *B* and *C*) and SDH in frozen sections. Nemaline rods, formed by expansions of the Z-line material, stain purple to red with modified Gomori's trichrome stain in frozen sections. These rods can also be seen in animals with other myopathic conditions. Moth-eaten fibers contain multiple pale zones because of loss of mitochondrial oxidative enzyme activity on frozen sections and occur in denervating disorders and in myopathic conditions (Fig. 15-22, *C*). Sarcoplasmic masses are pale-staining zones usually at the periphery of myofibers but occasionally central. These can be seen in H&E-stained muscle sections and appear as light blue areas with few or no myofibrils. Ultrastructurally they often contain disarrayed myofilaments with or without degenerate mitochondria. Other less commonly encountered alterations in animal muscle are pale central cores visible with mitochondrial stains, tubular aggregates composed of sarcotubular membranes, and target fibers in which mitochondrial oxidative enzyme reactions reveal central clear zones surrounded by a thin rim of highly reactive cytoplasm. Other less commonly encountered alterations in H&E-stained sections of animal muscle are pale central cores. As demonstrated in sections stained by mitochondrial oxidative enzyme reaction (e.g., SDH), these are of three types: (1) cores rich in mitochondria and similar to the peripheral sarcoplasmic masses described previously, (2) target fibers so designated because of a pale center surrounded by a rim of densely staining mitochondria, and (3) aggregates of sarcotubular membranes that do not stain with mitochondrial stains.

Chronic Myopathic Change

Evaluation of abnormal skeletal muscle often reveals chronic myopathic change, which includes alterations in myofiber diameter, cytoarchitectural alterations, and interstitial fibrosis and fat infiltration (see Box 15-3). Chronic myopathic change accompanies a variety of myopathic and neuropathic conditions. In particularly severe cases, a definitive cause may not be identified. Chronic inflammation or denervation and chronic degenerative myopathy resulting in repeated bouts of myonecrosis and regeneration often cause diffuse endomysial and perimysial fibrosis (see Figs. 15-17, *B*, and 15-47, *B*). Interstitial infiltration of muscle by mature adipocytes is less common than fibrosis and occurs most commonly in chronically denervated muscle (see Fig. 15-17, *B*), particularly neonatal muscle that lacks appropriate innervation (Fig. 15-23). Fat infiltration can also occur because of severe chronic degenerative myopathy. A chronically damaged or denervated muscle that develops profound fibrosis and/or fat infiltration can be grossly enlarged, despite atrophy or loss of myofibers—a condition known as *pseudohypertrophy* (see Fig. 15-9, *D*).

Aging

Aging changes in skeletal muscle are well documented in human beings but less well documented in domestic animals. The term *sarcopenia* refers to generalized reduction in muscle mass, strength, and function related to aging, in the absence of underlying disease. In contrast, *cachexia* is generalized muscle atrophy caused by underlying disease or malnutrition. Changes in mitochondrial function and progressive denervation are implicated as possible causes of sarcopenia in aging human beings. Aged animals often exhibit mild to severe muscle atrophy. To what degree this atrophy in animals is due strictly to age-related changes rather than to underlying chronic organ dysfunction (e.g., renal failure, cardiac disease, and neoplasia) is most often unknown. Sarcopenia and cachexia can occur concurrently in aged animals and people. Old cattle can accumulate lipofuscin within skeletal muscle, which can cause a tan-brown discoloration, but there is no apparent clinical significance to this change.

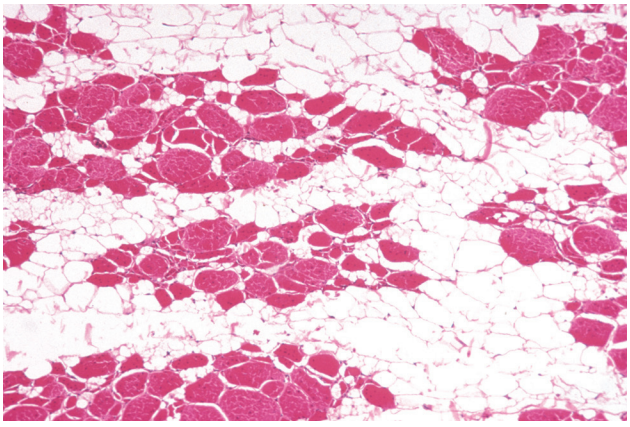


Figure 15-23 Lipomatosis (Steatosis), Calf. Lost myocytes have been replaced by mature adipocytes *(clear [nonstaining] areas)*. Islands of remaining myofibers have groups of angular atrophied fibers admixed with hypertrophied fibers, suggestive of denervation atrophy. Formalin fixation, H&E stain. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Box 15-5 Portals of Entry and Pathways of Spread Into the Muscular System

DIRECT
Penetrating wounds
Intramuscular injections
Bone fracture causing trauma to adjacent muscle
External pressure causing crush injury

HEMATOGENOUS
Blood-borne pathogens, toxins, autoantibodies, and immune complexes
Cytotoxic lymphocytes causing immune-mediated damage
Other inflammatory cells

Portals of Entry/Pathways of Spread

Portals of entry and pathways of spread are summarized in Box 15-5. Injury to muscle can occur secondary to trauma or infection. Muscle lying superficially can be damaged by penetrating wounds, including those created by intramuscular injections (Fig. 15-24; see also Fig. 15-9, *B*), which can also allow entry of infectious agents. Muscles located deeply are often injured after bone fracture. Crush injuries from external forces cause extensive muscle damage, and excessive tension can cause muscle tearing. Muscles are endowed with an extensive vascular network that can allow entry of blood-borne pathogens, immune complexes, antibodies and toxins, and inflammatory cells.

Other routes by which muscle can become dysfunctional are summarized in Box 15-6. Some muscular disorders are genetically determined. Inherited or acquired dysfunction of motor neurons or nerves causes muscle injury in the form of atrophy. Toxins or an altered endocrine or electrolyte status can affect muscle, and physiologic damage can be caused by exhaustive or overexuberant exercise.

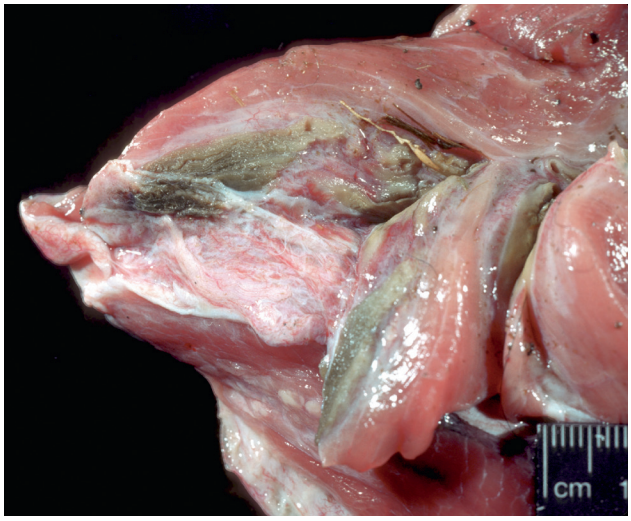


Figure 15-24 Inflammation and Myofiber Necrosis, Injection Site, Muscles, Lateral Thigh, Cow. Necrotic muscle has been stained green by the injected material, which has spread distally down the fascial plane between the two muscles from the original injection site *(top right)*. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Box 15-6 Other Causes of Muscle Dysfunction

PHYSIOLOGIC
Excessive muscle tension causing muscle rupture
Exercise-induced damage to myofibers
Loss of innervation
Loss of blood supply
Endocrine and electrolyte abnormalities

GENETIC
Inborn errors of metabolism
Genetic defects of myofiber structural components
Developmental defects

NUTRITIONAL/TOXIC
Deficiency of selenium and/or vitamin E
Toxic plants or plant products
Feed additives (ionophores)
Other toxins (e.g., some snake venoms)

Defense Mechanisms/Barrier Systems

Defense mechanisms and barrier systems are summarized in Box 15-7. The thick encircling fascia (epimysium) of many muscles provides some protection from penetrating injuries and from extension of adjacent infection. This fascia can, however, also contribute to injury under circumstances that lead to increased intramuscular pressure causing hypoxia (compartment syndrome). Tissue macrophages are not typically found in normal muscle but are recruited rapidly from circulating monocytes in the vasculature. Macrophages can cross even an intact basal lamina and effectively clear debris from damaged portions of myofibers, allowing for rapid restoration of the myocyte through satellite cell activation. Neutrophils and other inflammatory cells are also recruited from the bloodstream in response to injury or infection. The extensive vascular network of muscle includes extensive collateral circulatory pathways that render muscle relatively resistant to ischemic damage caused by thrombosis or thromboembolism. Despite the high vascular density of muscle, metastasis of neoplasms to muscle is quite rare. There is evidence that the capillary endothelium of skeletal muscle is inherently resistant to neoplastic cell adhesion and invasion.

Box 15-7 Defense Mechanisms and Barrier Systems of Skeletal Muscle

SKIN, SUBCUTIS, AND FASCIA
Form structural barriers to protect against external injury

VASCULATURE
Collateral circulation to protect against ischemia
Recruitment of monocytes that become tissue macrophages
Recruitment of neutrophils and other inflammatory cells
Capillary endothelium resistant to tumor metastasis

IMMUNOLOGIC RESPONSES
Innate humoral and cellular immunologic responses

OTHER
Adequate tissue antioxidant concentrations
Physiologic adaptation (e.g., hypertrophy, fiber type alteration)
Regenerative capacity of myofibers

Disorders of Domestic Animals

Types of Muscle Disease

Classification of muscle diseases based on lesions alone is not very satisfactory, and many classifications are based on cause (e.g., toxic myopathy or nutritional myopathy). An example of such a classification is given in Table 15-2. Myopathic conditions can be inherited or acquired. Inherited disorders can affect muscle metabolism or myofiber structure. Acquired muscle disease in livestock is often associated with nutritional deficiency or with ingestion of myotoxins, whereas acquired muscle disease in the dog is most often caused by immune-mediated inflammatory conditions. Other causes of acquired myopathies include ischemia, infectious agents, hormonal or electrolyte abnormalities, and trauma. There are also many neuropathic conditions that result in denervation atrophy (see peripheral nerve discussion). More information on most of the disorders described in this section can also be found under the appropriate species heading or in E-Appendix 15-1.

Degenerative

Degenerative myopathies are those resulting in segmental or global myofiber necrosis in which inflammatory cells are not the cause of the myofiber damage.

Disturbance of Circulation. Given the numerous capillary anastomosis and rich collateral circulation of skeletal muscle, only disorders that result in occlusion of a major artery or that cause widespread intramuscular vascular damage will result in myofiber necrosis (Box 15-8). Vascular occlusion of a major artery, most often aortoiliac thrombosis, occurs most commonly in cats (thromboembolism) and horses (mural thrombosis). Intramuscular vascular damage occurs in many species, and there are a variety of causes.

The basic factor in determining the effect of ischemia on muscle is the differential susceptibility of the various cells forming the muscle as a whole. Myofibers are the most sensitive, satellite cells less sensitive, and fibroblasts the least sensitive to anoxia. Thus obstruction of the blood supply to an area of muscle leads first to myofiber necrosis, then to the death of satellite cells, and finally to the death of all cells, including the stromal cells. The size of skeletal muscle infarcts depends on the size of the vessel obstructed and the

E-Appendix 15-1

Viral Causes of Myositis

Porcine encephalomyelitis is caused by a coronavirus of the *Enterovirus* genus. Besides the destruction of the neurons, which results in paralysis, the virus can also cause multifocal necrosis of myofibers, accompanied by a focal interstitial and perivascular infiltrate of lymphocytes, macrophages, and a few neutrophils.

The major lesions of foot-and-mouth disease virus in ruminants and pigs are vesicles in the skin and mucous membranes. In addition, the heart and skeletal muscles can have yellow streaks and pale foci, which microscopically are areas of segmental myofiber necrosis accompanied by an intense lymphocytic and neutrophilic infiltration.

Akabane virus (Bunyaviridae family) can produce a nonsuppurative myositis in the bovine fetus.

Bluetongue, caused by a virus of the family Reoviridae, is a noncontagious, insect-borne viral disease of sheep that causes vasculitis in a wide array of tissue, particularly the oral mucosa. Gross lesions in muscles are foci of necrosis (infarctions) and hemorrhage. Depending on the age of the lesions, necrosis, calcification, or regeneration may be present. Because of the size of the infarcts, regeneration is usually not possible, and healing is by fibrosis.

Parasitic Myositides

The larval forms of *Ancylostoma caninum* migrate somatically, primarily in human beings. After entering the muscles of paratenic hosts, development is arrested. The larvae cause inflammation and myonecrosis. As they continue to migrate, they leave a trail of inflammation and segmental myofiber necrosis.

Toxocara canis larvae migrate through numerous tissues of the dog (visceral larval migrans). Some larvae are arrested, and granulomas form around them. These have been found in a wide array of tissue, including kidney, liver, lung, myocardium, and skeletal muscle. The lesion in muscle is a focal granulomatous myositis, with the larvae and granulomas lying between myofibers.

Dirofilaria immitis, a nematode normally found in the hearts of dogs and cats, can occasionally involve the external and internal iliac arteries and their branches. Thromboemboli from debris and parasites can cause multiple infarcts in the muscles of the hind limbs (see the section on Disturbance of Circulation).

Cysticercus is a larva with a solid caudal portion and a bladder-like proximal portion. It is the intermediate stage in the life cycle of several tapeworms. *Taenia solium* and *Taenia saginata*, both tapeworms of human beings, have a cysticercus stage in the pig (*Cysticercus cellulosae*) and cattle (*Cysticercus bovis*). These cysticerci preferentially lodge in the most active muscles, especially the heart, masseter, diaphragm, and tongue, where they appear as small white or gray cysts. Histologically, there is displacement of myofibers by the cyst but little myositis; there may be a few lymphocytes, macrophages, and eosinophils around the cyst, which lies in the interstitial tissue, not within the myofiber. With time, the immunologic system of the host kills the cysticercus. *Cysticercus cellulosae* in pigs can become calcified. *Cysticercus ovis* in the heart and shoulder muscles of sheep and goats is the intermediate stage of *Taenia ovis*, a tapeworm of dogs.

Hepatozoon americanum is a protozoal organism, previously classified as *Hepatozoon canis*, that infects multiple tissues, including the skeletal muscle of dogs. It is most common in South Africa and the Middle East but also occurs in areas of the United States (primarily Oklahoma and the Gulf Coast area). Young dogs, up to 6 months of age, are most susceptible to infection. The organism is transmitted by ingestion of an infected tick, such as *Rhipicephalus sanguineus*. Sporozoites invade through the intestinal wall and travel to multiple tissues, particularly liver and skeletal muscle, where they undergo schizogony. Suppurative to granulomatous inflammation occurs after rupture of schizonts within tissue. Encysted stages, however, do not elicit an inflammatory response. Clinical signs include fever, anorexia, weight loss, body pain, and gait abnormalities. Respiratory signs can also occur. Serum CK activity is often mildly increased. Radiographs often reveal a characteristic periosteal proliferation of long bones similar to that of hypertrophic osteopathy. Diagnosis is made by identification of the organism either within peripheral neutrophils or within affected tissue.

In dogs, infection by *Trypanosoma cruzi* (Chagas' disease) causes myocarditis with lesser involvement of skeletal muscle. Inflammation consists of lymphocytes admixed with macrophages. Protozoal organisms are typically readily identified in affected tissues.

Congenital and Inherited Myopathies

Congenital Muscular Hyperplasia (Double Muscling) in Cattle

Congenital muscular hyperplasia (double muscling) is seen in several beef breeds, including Charolais, Angus, Belgian blue, Belgian white, South Devon, Santa Gertrudis, and Piedmontese cattle. This disorder is inherited as an autosomal recessive trait with incomplete penetrance. The genetic defect is inactivation of the myostatin gene, which regulates the number and size of myofibers. Affected calves have large, bulky muscles, especially of the shoulder and rump, because of an increased number of otherwise normal fibers. This increased muscle bulk predisposes to dystocia. Body fat deposits and intramuscular fat are reduced to approximately 60% of normal, which is considered desirable in a meat-producing animal. The diagnosis of this disorder is readily made based on typical clinical findings. There is no treatment.

Muscular Dystrophy

Bovine Diaphragmatic Dystrophy

A muscular dystrophy affecting diaphragm and respiratory muscles has been recognized in Meuse-Rhine-Yssel cattle in Europe and Holstein cattle in Japan. This disorder appears to be inherited as an autosomal recessive trait. The most common clinical sign is recurrent bloat. Clinical signs appear in adults 2 years of age or older and include loss of condition, decreased rumen activity, and recurrent bloat. Serum activity of muscle enzymes is normal. The diaphragm is found to be thickened and pale. Examination of affected muscle indicates a progressive myopathy with severe cytoarchitectural alterations and other chronic myopathic changes, including fibrosis. Scattered necrotic fibers can be found, but this myopathy does not have the characteristic ongoing progressive myofiber necrosis and regeneration of muscular dystrophy. Central corelike lesions are prominent and have been found to contain actin and ubiquitin with immunohistochemical studies. This disorder would be best defined as a progressive inherited myopathy, possibly a myofibrillar myopathy. There is no treatment, and animals producing affected offspring should not be rebred.

Ovine Muscular Dystrophy

A progressive disorder known as *ovine muscular dystrophy* is recognized in Merino sheep in Australia. The underlying defect is not known. The disease is inherited as an autosomal recessive trait. Clinical signs of neuromuscular weakness occur as early as 1 month of age and are characterized by a stiff gait and exercise intolerance. Serum concentrations of CK and AST are increased. Because the disease affects only type 1 myofibers, gross lesions are most easily seen in muscles that consist primarily or only of type 1 myofibers

(e.g., vastus intermedius). The appearance depends on the age of the animal. Initially the muscle is pale and lacks tone but is close to normal size. In the next few years, the muscle becomes firm, more atrophic, and pale gray to almost white as the space formerly occupied by the myofibers is filled with adipocytes and fibrosis. There is atrophy and hypertrophy of the myofibers, along with myopathic features such as internal nuclei and subsarcolemmal masses. Lesions do not have the characteristic ongoing progressive myofiber necrosis and regeneration of muscular dystrophy, and this disorder may be best defined as a progressive inherited myopathy. Diagnosis is based on characteristic clinical and histopathologic findings. There is no treatment for this progressive disorder, and animals producing affected lambs should not be rebred.

Other Canine Muscular Dystrophies

Defects in sarcoglycan, a protein that is part of the sarcolemmal dystrophin glycoprotein complex, have been found in both male and female dogs of various breeds. Affected dogs exhibit signs of neuromuscular disease by 1 year of age. Serum activities of CK, AST, and ALT are increased. EMG detects abnormal spontaneous activity, including myotonic bursts, and histopathologic findings of multifocal polyphasic necrosis are consistent with muscular dystrophy.

Other Muscular Disorders of Cattle

Myopathy of Gelbvieh Cattle

A necrotizing myopathy of juvenile Gelbvieh cattle has been recognized. An inherited basis is suspected. Clinical signs include neuromuscular weakness. The characteristic histopathologic change in affected muscles is necrotizing vasculitis that results in myofiber necrosis. The pathogenesis of this disorder is not known; both vitamin E deficiency and immune-mediated disease have been suggested. Pathologic changes are also found in the kidney, dorsal spinal tracts of the spinal cord, and in peripheral nerves. Cardiac lesions can occur but are uncommon. Treatment with vitamin E may be of some benefit.

Brown Swiss Cattle Neuronopathy

An inherited neuronal degenerative disease designated as a form of spinal muscular atrophy occurs in brown Swiss cattle. Clinical signs of a progressive lower motor neuron weakness appear by 2 to 6 weeks of age. Neuronal degeneration within the ventral gray matter of the spinal cord leads to axonal degeneration of peripheral nerves and denervation atrophy of muscle. The disorder is inherited as an autosomal recessive trait, and pedigree analysis has identified a common ancestor thought to be the founder animal. Animals producing affected calves should not be rebred.

Other Breed-Associated Disorders of Dogs

Canine Dermatomyositis

A condition involving skin and muscle has been described in collies and Shetland sheepdogs, and it has been compared with dermatomyositis of human beings. In human beings, characteristic skin lesions and immune-mediated damage to muscle capillaries occur. In dogs, the dermatopathologic changes are distinctive, but muscle involvement is much less common, and the muscle lesions seen are not always convincingly vascular in nature. In cases studied by the author, occasional muscle inflammation appeared to reflect extension of inflammation from overlying ulcerated skin.

Myopathy of Bouvier des Flandres Dogs

A progressive degenerative myopathy affecting males and females is recognized in Bouvier des Flandres dogs. Onset of clinical signs of neuromuscular weakness varies from approximately 2 months to 2 years of age. Esophageal and pharyngeal muscles are often most severely affected. Generalized muscle atrophy, weakness, and abnormal gait are typical. Serum activities of CK and AST are often moderately increased. EMG reveals abnormal spontaneous activity (myotonic bursts). Generalized muscle atrophy and megaesophagus are common necropsy findings. Histopathologic changes are generally severe chronic myopathic change with notable cytoarchitectural changes. Multifocal fiber necrosis and regeneration occurs but is not common. Cardiac necrosis and fibrosis can also be seen.

Distal Myopathy of Rottweiler Dogs

In distal myopathy of Rottweiler dogs, both males and females are affected. Clinical signs of progressive muscle weakness and development of a plantigrade and palmigrade stance are apparent by approximately 2 months of age. This disorder is characterized histologically by severe fiber atrophy and fat infiltration, primarily of distal limb musculature. Myonecrosis and fibrosis are mild. Serum activities of CK and AST can be normal or slightly increased. EMG reveals rare spontaneous activity (fibrillations and positive sharp waves). Decreased serum and muscle carnitine concentrations suggest that this may be a lipid metabolic disorder.

Myopathy of English Springer Spaniels

A myopathy with involvement of esophageal muscle occurs in English springer spaniel dogs. Affected dogs also have dyserythropoiesis and cardiomegaly. Histologic findings include chronic myopathic change with central linear or granular inclusions within myofibers.

Myopathy of Great Danes

A progressive myopathy characterized by central "corelike" structures occurs in young Great Dane dogs. Clinical signs are progressive weakness and muscle atrophy. Serum concentration of CK is either normal or only mildly increased.

Myoclonus in Wirehaired Miniature Dachshunds

A syndrome of sustained muscle contraction (myoclonus), seizures, and early dementia is recognized in related wirehaired miniature dachshunds. Inclusions of PAS-positive, amylase-resistant polyglucosan bodies similar to Lafora bodies described in human beings occur in skeletal muscle and central nervous tissue.

Other Breed-Associated Disorders of Cats

Feline nemaline myopathy is a congenital disorder described in domestic short-haired cats. Affected cats develop a characteristic progressive gait abnormality and muscle atrophy at an early age. The characteristic pathologic finding of expanded Z-line material (nemaline rods) within skeletal muscle fibers is only apparent in frozen sections or ultrastructurally. The mode of inheritance is not known.

An autosomal recessively inherited muscular dystrophy caused by absence of the dystrophin-related protein α-dystroglycan occurs in Devon rex and Sphinx cats. Clinical signs of neuromuscular weakness are apparent beginning at 1 month to 6 months of age. The disease is either slowly progressive or remains static. Megaesophagus is also possible. Muscular dystrophy associated with deficiency of β-sarcoglycan also occurs in cats.

Myotonia

Equine Species

Congenital or early onset myotonia is seen in thoroughbreds, standardbreds, and quarter horses. Various similar disorders, designated as myotonic dystrophy–like or muscular dystrophy–like, are likely to be the same or similar disorders. As with all congenital myotonias,

an underlying abnormal ion channel leading to continuous abnormal muscle activity is suspected. But to date the defect and potential for inheritance have not been defined. Affected horses have remarkable exercise intolerance, with stiffness of posture and gait apparent at birth or soon thereafter, and often, remarkably well-defined to hypertrophied muscle groups. Clinical signs of stiffness are most apparent when the animals first begin to move, with some decrease in stiffness with exercise. Serum concentrations of CK and AST are generally normal to only slightly increased. Muscles often show prolonged dimpling after percussion. Concentric needle EMG demonstrates characteristic waxing and waning ("dive bomber") myotonic bursts.

No specific gross lesions are present, other than prominent muscling. On histologic examination, affected muscle fibers vary tremendously in size and shape, with numerous internal nuclei, altered cytoplasmic areas beneath the sarcolemma (sarcoplasmic masses), and other cytoarchitectural alterations such as ring fibers. Scattered fiber necrosis and regeneration may be seen but is not a prominent feature. In chronic cases, affected muscles can develop a variable degree of replacement of myofibers by fat, indicating a previous loss of myofibers.

The diagnosis of myotonia is based on characteristic clinical signs in a young horse and can be confirmed by EMG or muscle biopsy. No specific treatment is known at this time.

Feline Species

The pathogenesis of feline congenital myotonia is not known at this time, although a skeletal muscle ion channel defect is suspected. Cats with congenital myotonia have signs similar to those of cats with X-linked muscular dystrophy, but the muscular hypertrophy is less remarkable. A stiff gait is the most obvious sign. Serum concentrations of CK and AST are normal or only slightly increased. Concentric needle EMG reveals waxing and waning ("dive bomber") potentials characteristic of myotonia. Other than mild muscular hypertrophy, there are no findings at necropsy. Significant myofiber hypertrophy and increased variation in myofiber diameter are the only histopathologic findings. Dilation of sarcotubular elements is the characteristic ultrastructural finding. The diagnosis of congenital feline myotonia is based on characteristic clinical findings. At this time, no type of treatment has been attempted.

Metabolic Myopathies

Acid Maltase Deficiency (Glycogenosis Type II; Pompe's Disease)

Acid maltase deficiency (glycogenosis type II; Pompe's disease) is a defect that has been described in shorthorn and Brahman cattle and is inherited as an autosomal recessive trait. The enzyme defect results in blockage of the glycolytic metabolic pathway and in cellular dysfunction, which is most evident in skeletal muscle, Purkinje cells of the heart, and neurons. Myofiber necrosis is thought to be a result of a cellular "energy crisis" (i.e., energy deprivation).

Affected shorthorn cattle often show clinical signs of weakness by 3 to 7 months of age and die as a result of respiratory and cardiac failure. Affected shorthorn cattle may also develop relatively normally until 1 to 1½ years of age, at which time weakness and neurologic deficits are evident. Affected Brahman cattle grow poorly and have muscular weakness and neurologic disease. Electrocardiographic studies reveal abnormalities of cardiac conduction. Serum concentrations of CK and AST can be increased, with notable increases evident in severely weak animals before death.

There may be no obvious changes within the skeletal and cardiac muscle at necropsy, although pale streaks may be evident in those animals undergoing myofiber necrosis before death. No gross pathologic lesions are evident in the nervous system. On histopathologic examination, affected myofibers, cardiac myocytes, and neurons are filled with vacuoles containing glycogen (vacuolar myopathy and neuronopathy), which can be demonstrated by PAS reaction. Glycogen accumulation in skeletal myofibers is segmental, whereas in neurons it is diffuse. Both degeneration and regeneration of skeletal muscle fibers and chronic myopathic change (fiber atrophy, hypertrophy, and internal nuclei) are present.

Diagnosis of a glycogenosis can be made based on characteristic clinical and histopathologic findings. Assay of affected tissue for glycolytic enzyme activities is necessary to determine the specific enzyme defect. There is no effective treatment for this disorder, and cattle known to produce affected calves should not be rebred.

Myophosphorylase Deficiency (Glycogenosis Type V; McArdle Disease)

Myophosphorylase deficiency is an autosomal recessive disorder with glycogen storage similar to acid maltase deficiency but with only skeletal muscle involvement. This disorder has been identified in Charolais cattle. Clinical signs of exercise intolerance and inability to keep up with herd mates are recognized at a relatively early age. If forced to exercise, affected cattle become recumbent for up to 10 minutes. Serum concentrations of CK and AST are often mildly to markedly increased. No specific findings are evident at necropsy. Histopathologic findings in skeletal muscle are similar to those of acid maltase deficiency. Diagnosis can be based on characteristic clinical and histopathologic findings. Affected animals and carriers can be detected after analysis of peripheral blood leukocyte DNA by polymerase chain reaction assay. There is no treatment, and carrier animals should not be used for breeding.

A glycogen storage myopathy caused by myophosphorylase deficiency has been identified in sheep in Australia and is similar to the disease in cattle.

Phosphofructokinase Deficiency (Glycogenosis Type VII)

Phosphofructokinase deficiency (glycogenosis type VII) is an autosomal recessive disorder in dogs caused by a point mutation in the muscle isoenzyme of phosphofructokinase, an important enzyme in the glycolytic pathway. This disorder has been recognized in English springer spaniels and American cocker spaniels. Muscles from older affected dogs can have myopathic changes and inclusions of a PAS-positive, amylase-resistant substance classified as complex polysaccharide. Clinical signs of neuromuscular dysfunction do not occur, however, because skeletal muscle upregulates expression of the liver isoenzyme of phosphofructokinase. Absence of erythrocyte phosphofructokinase results in hemolysis during periods of increased respiratory activity (panting) and resultant mild respiratory alkalosis.

Feline Glycogenoses

Glycogenosis type IV occurs in Norwegian Forest cats because of decreased activity of GBE, resulting in defective carbohydrate metabolism and a generalized glycogen storage disease. The disorder is inherited as an autosomal recessive trait. Affected cats may be stillborn or die within a few hours of birth. Those that survive lack energy and develop muscle tremors and a bunny-hopping pelvic limb gait at approximately 5 months of age. The disease is progressive, resulting in severe generalized muscle atrophy and tetraplegia. Concentric needle EMG reveals abnormal spontaneous activity with normal motor nerve conduction velocities. Serum concentrations of CK and AST are mildly to moderately increased. Muscle atrophy and fibrosis are evident in affected pelvic limb muscles of

cats surviving 1 year or longer. Storage of PAS-positive, amylase-resistant material forming "lakes" within skeletal muscle fibers is the characteristic histopathologic finding. Myofiber atrophy is also prominent, and myofiber necrosis and regeneration can be seen. Cardiac myocytes have similar inclusions and undergo necrosis and replacement by fibrosis. Abnormal glycogen storage is also seen within smooth muscle and neurons in the central nervous system. Diagnosis can be suspected on the basis of characteristic clinical and histopathologic findings. Confirmation is based on assay of GBE concentration in blood leukocytes. There is no treatment for this disorder.

Similar intramyofiber inclusions of PAS-positive, amylase-resistant inclusions resulting in clinical signs of neuromuscular weakness are found rarely in older cats of mixed breeding, suggesting that there is more than one cause for this finding in cats.

Equine Mitochondrial Myopathy

A single case of mitochondrial myopathy in a 3-year-old Arabian filly has been reported. Deficiency of mitochondrial respiratory chain complex I was detected. Clinical signs were stiff gait and profound exercise intolerance. Lactic acidosis developed with minimal exercise. Skeletal muscle samples exhibited increased muscle mitochondrial content with bizarre cristae formation on ultrastructural examination.

Canine Mitochondrial Myopathies

A mitochondrial myopathy has been recognized in Old English sheepdogs. Clinical signs are exercise intolerance leading to episodic weakness and exercise-induced lactic acidosis. A suspected mitochondrial myopathy occurs in Welsh terrier dogs. Involvement of skeletal muscle occurs in Alaskan husky and Australian cattle dogs as part of a mitochondrial encephalomyopathy syndrome.

Other Canine Metabolic Myopathies

Pyruvate dehydrogenase deficiency occurs in Clumber and Sussex spaniels in the United States and Belgium. Clinical signs are profound exercise intolerance with exercise-induced lactic acidosis. No gross or histopathologic lesions are found in muscle.

Table 15-2 Classification of Muscle Disease

Classification	Cause or Type of Disorder
Degenerative	Ischemia
	Nutritional
	Toxic
	Exertional
	Traumatic
Inflammatory	Bacterial
	Viral
	Parasitic
	Immune-mediated
Congenital and/or inherited	Anatomic defects
	Muscular dystrophy
	Congenital myopathy
	Myotonia
	Metabolic
	Malignant hyperthermia
Endocrine	Hypothyroidism
	Hypercortisolism
Electrolyte	Hypokalemia
	Hypernatremia
	Other electrolyte imbalances
Neuropathic	Peripheral neuropathy
	Motor neuronopathy
Neuromuscular junction disorders	Myasthenia gravis
	Botulism
	Tick paralysis
Neoplasia	Primary tumors (rhabdomyoma, rhabdomyosarcoma)
	Secondary tumors (hemangiosarcoma, fibrosarcoma, infiltrative lipoma, other tumor phenotypes)
	Metastatic tumors

Box 15-8 Causes of Muscle Ischemia

Occlusion of a major blood vessel
External pressure on a muscle
Swelling of a muscle in a nonexpandable compartment ("compartment syndrome")
Vasculitis/vasculopathy

duration of blockage. Because of the numerous anastomoses, blockage of capillaries causes less severe ischemia but can result in segmental myofiber necrosis, which is usually multifocal and if the cause is ongoing, polyphasic, with regenerating and necrotic myofibers. However, when larger arteries are blocked, whole areas of muscle, including the satellite cells, are killed, resulting in a monophasic necrosis and healing by fibrosis. Ischemia can also cause peripheral nerve damage and neuropathy, leading to denervation atrophy of intact myofibers.

Increased intramuscular pressure can occur in a recumbent animal of sufficient weight after a prolonged period of recumbency, because of either disease or general anesthesia. Myofiber necrosis caused by recumbency can occur because of (1) decreased blood flow as a result of compression of major arteries, (2) reperfusion injury causing massive calcium influx into muscle cells when the animal moves or is moved and the compression relieved, (3) increased intramuscular pressure causing compartment syndrome (see later definition), or (4) any combination of these factors. Localized myonecrosis caused by recumbency is common in horses, cattle, and pigs;

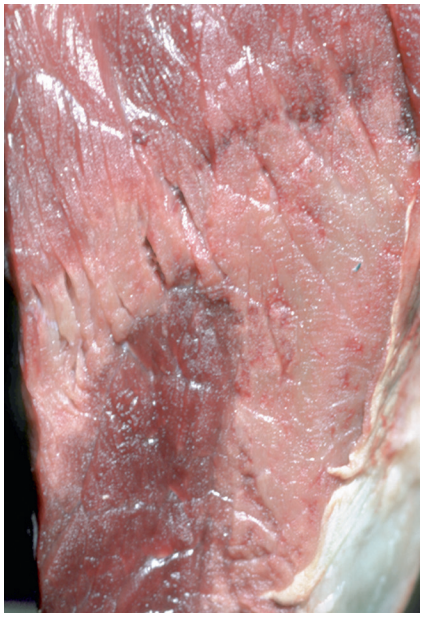


Figure 15-25 Ischemic Necrosis, Downer Cow Syndrome, Pectoral Muscle, Cow. Increased intramuscular pressure during prolonged periods of recumbency has resulted in localized muscle pallor (lighter-colored areas of muscle) from myofiber necrosis secondary to decreased blood flow caused by compression of arteries. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

occurs only in large breeds of dogs; and is virtually unheard of in cats. In downer cows, the weight of the body of the animal in sternal recumbency can cause ischemia of the pectoral muscles and of any muscles of the forelimbs or hind limbs that are tucked under the body. Ewes in advanced pregnancy with twins or triplets can develop an ischemic necrosis of the internal abdominal oblique muscle, which can lead to muscle rupture. Plaster casts or bandages that are too tight can put external pressure on muscles, leading to ischemia. The duration of ischemia determines the severity of necrosis and the success of regeneration (see the section on Necrosis and Regeneration). Postanesthetic myopathy is a monophasic, multifocal necrosis. In the downer cow, the lesions are multifocal to locally extensive (Fig. 15-25) and, depending on the duration since the onset of recumbency, can be either monophasic or polyphasic.

Any severe insult, whether it be ischemia caused by recumbency or another myodegenerative disorder that causes myonecrosis within a muscle covered by a tight and nonexpansible fascia, can result in ischemic injury because early in the necrosis, there is increased intramuscular pressure. The resulting compromise of blood circulation leads to ischemic myodegeneration, which is known as *compartment syndrome*. The phenomenon of compartment syndrome is best illustrated in the anterior tibial muscle of human beings after strenuous exercise. This condition is believed to be a consequence of swelling of the anterior tibial muscle, which is surrounded anteriorly by the inelastic anterior fascial sheath and posteriorly by the tibia. Swelling impedes blood supply, resulting in ischemia. A similar phenomenon occurs in muscles surrounded by tight fascia in animals, particularly horses. Horses that are recumbent because of general anesthesia can develop compartment syndrome affecting gluteal or lateral triceps muscles. Horses can also develop compartment syndrome in gluteal muscles because of exertional rhabdomyolysis and in temporal and masseter muscles because of selenium deficiency. Compartment syndrome is also possible in the temporal and masseter muscles of dogs with masticatory myositis.

Damage to intramuscular blood vessels will also cause myofiber necrosis. Vasculitis can cause areas of muscle damage (e.g., in horses with immune-mediated purpura hemorrhagica because of *Streptococcus equi* infection [see Fig. 15-32] and in pigs with erysipelas). Viral diseases that target blood vessels of many organs, such as bluetongue in sheep, can also affect muscle. Exotoxins produced by clostridial organisms cause myositis and severe localized vascular damage, leading to hemorrhage and myofiber necrosis. The familial myopathy of Gelbvieh cattle is characterized by fibrinoid necrosis of intramuscular blood vessels and associated myonecrosis.

Nutritional Deficiency. Myofibers are particularly sensitive to nutritional deficiencies that result in the loss of antioxidant defense mechanisms. Nutritional myopathies are most common in livestock, including cattle, horses, sheep, and goats (Table 15-3). Although nutritional myopathy of livestock is often referred to as *selenium/vitamin E deficiency*, in the vast majority of cases, it is deficiency of selenium that is the cause of myofiber degeneration. The trace mineral selenium is a vital component of the glutathione peroxidase system, which helps to protect cells from oxidative injury. The high oxygen requirement combined with contractile activity makes striated muscle, both skeletal and cardiac, particularly sensitive to oxidative injury. Neonatal animals, which rely on stores of selenium accumulated during gestation, are most frequently affected. Affected muscle is pale as a result of necrosis (see Fig. 15-39), thus the common name *white muscle disease*. As should be evident from the previous discussion, a gross observation of pale muscle is not specific for necrosis caused by nutritional deficiency; therefore the term *nutritional myopathy* is much preferred.

Toxic Myopathies. Livestock are the animals most prone to develop a degenerative myopathy from the ingestion of a toxin (see Table 15-3). Myotoxins can be present in plants in pastures or hay and in plants or plant products in processed feed. Examples of toxic plants and plant products include *Cassia* (coffee senna), *Karwinskia* (coyotillo), *Eupatorium* (white snakeroot), *Acer negundo* (box elder tree) seeds, and gossypol present in cottonseed. Clinical signs are weakness, often leading to recumbency, and are accompanied by a moderate to severe increase in serum muscle enzyme concentrations. Gross and histologic findings of multifocal necrosis that can be either monophasic or polyphasic are typical. Diagnosis is based on identification of causative plants within feed, pasture, or stomach contents or, when available, detection of toxic compounds in stomach content or liver.

Ionophore antibiotics, such as monensin, lasalocid, maduramicin, and narasin, are often added to ruminant feeds to enhance growth. Ionophores form lipid-soluble dipolar reversible complexes with cations and allow movement of cations across cell membranes, often against the concentration gradient. This causes a disruption of ionic equilibrium that can be detrimental, especially to excitable tissue such as the nervous system, heart, and skeletal muscle. Ionophore toxicity results in calcium overload and death of skeletal (see Figs. 15-11, *B*, and 15-33) and cardiac muscle. Most domestic ruminants are quite tolerant of moderate ionophore levels, but toxicity occurs at very high levels. Most cases of ionophore toxicity involve the ingestion of monensin. The LD_{50} (the dose at which 50% of animals die) of monensin in cattle is 50 to 80 mg/kg, and the LD_{50} for sheep and goats is 12 to 24 mg/kg. Horses are exquisitely sensitive to ionophores and even very low levels are toxic, with an LD_{50} for monensin of only 2 to 3 mg/kg of body weight.

Exertional Myopathies. The ionic and physical events associated with myofiber contraction can under certain circumstances predispose a myofiber to necrosis. Exercise-induced myonecrosis, which can be massive, can occur because of simple overexertion. This outcome is well known in the capture and restraint of nondomesticated species, a syndrome known as *capture myopathy*. More often, however, exercise-induced myofiber damage occurs in animals with preexisting conditions such as selenium deficiency, muscular dystrophy, severe electrolyte depletion, or glycogen storage disease. The term *exertional rhabdomyolysis* (also known as *exertional myopathy*, *azoturia*, *setfast*, *blackwater*, *Monday morning disease*, and *tying up*) has long been applied to a syndrome recognized in horses (see Fig. 15-35). Only recently have underlying myopathic conditions been identified as the most common predisposing cause of equine exertional rhabdomyolysis (see Disorders of Horses). A similar disorder affects working dogs such as racing sled dogs and greyhounds, the cause of which is still unclear.

Trauma. External trauma to muscle includes crush injury, lacerations and surgical incisions, tearing caused by excessive stretching or exercise, burns, gunshot and arrow wounds, and certain injections. Some of these result in complete or partial rupture of a large muscle. The diaphragm is the most common muscle to rupture and in dogs and cats is most often the result of a sudden increase in intraabdominal pressure such as from being hit by a car. In horses, diaphragmatic rupture is thought to occur most often during falls in which the pressure of the abdominal viscera causes diaphragmatic damage. A partial rupture of a muscle results in a tear in the fascial sheath, through which the muscle can herniate during contraction. In racing greyhounds, spontaneous rupture of muscles, such as the longissimus, quadriceps, biceps femoris, gracilis, triceps brachii, and gastrocnemius, can occur during strenuous exercise. In horses, damage to the origin of the gastrocnemius muscle has been linked to overexertion during exercise or while struggling to rise. Tearing of muscle fibers occurs in the adductor muscles of the hind limbs of cattle doing the "splits" (sudden bilateral abduction) on a slippery floor. Because there is often extensive disruption of the myofibers'

Table 15-3 Nutritional and Toxic Myopathies

Disorder	Species Affected	Cause
Nutritional myopathy	Horses, cattle, sheep, goats, camelids, pigs	Selenium or (less commonly) vitamin E deficiency
Ionophore toxicity	Horses, cattle, sheep, goats, pigs	Monensin, other ionophores used as feed additives
Plant toxicity	Horses, cattle, sheep, goats, pigs	*Cassia occidentalis*, other toxic plants; gossypol in cottonseed products
Pasture-associated myopathy (United Kingdom, Midwestern United States)	Horses	Box elder tree *(Acer negundo)* toxicity

basal laminae, most of the healing is accomplished by fibrosis. If muscle trauma is accompanied by fractures of bones and the animal moves the limb, further trauma by laceration by sharp bone fragments can result.

An abnormal response to localized muscle trauma is thought to be a possible underlying cause of two uncommon reactions of muscle: myositis ossificans and musculoaponeurotic fibromatosis. The term *myositis ossificans* is a misnomer, because the lesion does not involve inflammation, but it has attained the status of acceptance by common usage. Myositis ossificans is a focal lesion usually confined to a single muscle and has been seen in horses, dogs, and human beings. The lesion is essentially a focal zone of fibrosis with osseous metaplasia, often with a zonal pattern. The central zone contains proliferating undifferentiated cells and fibroblasts; the middle one, osteoblasts depositing osteoid and immature bone; and the outer one, trabecular bone, which may be being remodeled by osteoclasts. These lesions can cause pain and lameness, which are often cured by surgical excision. A connective tissue disorder in cats, fibrodysplasia ossificans progressiva, has been inappropriately called *myositis ossificans*. Musculoaponeurotic fibromatosis has so far been described only in horses and human beings. It is a progressive intramuscular fibromatosis that has also been called a *desmoid tumor*. Musculoaponeurotic fibromatosis is not, however, considered to be a true neoplastic process. Progressive dissecting intramuscular fibrosis accompanied by myofiber atrophy are the characteristic features. In most cases, the extent of intramuscular involvement makes surgical excision impossible, although wide excision of early lesions has proved to be curative.

Inflammatory Myopathies (Myositis, Myositides [Plural])

In addition to the misnomer "myositis ossificans," the term *myositis* has been inappropriately applied to various other veterinary disorders, such as exertional and nutritional myopathy, in the horse. These two disorders are degenerative myopathies, not inflammatory myopathies. It is vitally important to distinguish between a true myositis and a degenerative myopathy in which there is a secondary inflammatory response. In the normal response to the myofiber necrosis, the necrotic segment is infiltrated by macrophages recruited from the circulating monocyte population (see Figs. 15-12, *B*, and 15-13 *A*), which phagocytose the cellular debris. Severe acute necrotizing myopathy can also be accompanied by a certain degree of infiltrating lymphocytes, plasma cells, neutrophils, and eosinophils. Cytokines released from damaged muscle fibers are likely to recruit a variety of inflammatory cells under various circumstances, but these cells are not involved in causing the muscle cell damage. True myositis occurs only when inflammatory cells are directly responsible for initiating and maintaining myofiber injury and when inflammation is directed at the myofibers and not at the stroma. In some cases, it may take careful evaluation of the overall tissue changes, an understanding of the probable underlying cause, and years of experience with muscle pathology to differentiate a florid cellular response with macrophages on a "cleanup" mission from true inflammation. Lymphocytic myositis must also be distinguished from lymphoma involving skeletal muscle (see the section on Neoplasia).

Bacterial. Bacterial infections of muscle are not uncommon, particularly in livestock. Bacteria can cause suppurative and necrotizing, suppurative and fibrosing, hemorrhagic, or granulomatous lesions (Table 15-4). Bacterial infection can be introduced by direct penetration (wounds or injections), hematogenously, or by spread from an adjacent cellulitis, fasciitis, tendonitis, arthritis, or osteomyelitis (see the section on Portals of Entry).

Table 15-4 Bacterial Causes of Myositis and Neuromuscular Junction Disease

Infectious Agent	Species Affected
Clostridium spp. causing myositis (e.g., *Cl. septicum*, *Cl. chauvoei*, *Cl. sordellii*, *Cl. novyi*)	Horses, cattle, sheep, goats, pigs
Clostridium botulinum causing neuromuscular junction disease	Horses, cattle, sheep, goats, dogs
Pyogenic bacteria causing myositis (e.g., *Trueperella* [*Arcanobacterium*] *pyogenes*, *Corynebacterium pseudotuberculosis*)	Horses, cattle, sheep, goats, pigs, cats
Bacteria causing fibrosing and granulomatous myositis (e.g., *Actinomyces bovis*, *Actinobacillus lignieresii*)	Cattle, sheep, goats, pigs

Various clostridial species, particularly *Clostridium perfringens*, *Clostridium chauvoei*, *Clostridium septicum*, and *Clostridium novyi*, can elaborate toxins that damage myofibers and intramuscular vasculature, resulting in hemorrhagic myonecrosis (see Figs. 15-31 and 15-37). Toxemia is typical and often lethal. *Clostridial myositis* is most common in cattle and horses. *Clostridial myositis* has also been called *gas gangrene* and *malignant edema* in horses and *blackleg* in cattle.

Pyogenic bacteria introduced into a muscle usually cause localized suppuration and myofiber necrosis. This may resolve completely or become localized to form an abscess. In some cases, the infection can spread down the fascial planes (see Fig. 15-24). For example, a nonsterile intramuscular injection into the gluteal muscles of cattle can cause an infection that extends down the fascial planes of the muscles of the femur and tibia and erupts to the surface through a sinus proximal to the tarsus. Although the majority of inflammation involves fascial planes, some bacteria extend into and cause necrosis of adjacent muscle fasciculi. *Streptococcus zooepidemicus* (horses), *Trueperella* (*Arcanobacterium*) *pyogenes* (cattle and sheep), and *Corynebacterium pseudotuberculosis* (horses, sheep, and goats) are common causes of muscle abscesses. After bite wounds from other cats, cats can develop cellulitis caused by *Pasteurella multocida* that extends into the adjacent muscle.

Bacteria causing single or multiple granulomas (focal or multifocal granulomatous myositis) are relatively uncommon. Most such lesions are caused by *Mycobacterium bovis* (tuberculosis), usually in cattle and pigs, but this disease is rare in North America.

Chronic fibrosing nodular myositis of the tongue musculature in cattle is the result of infection with *Actinobacillus lignieresii* (wooden tongue) or *Actinomyces bovis* (the agent causing lumpy jaw). A similar lesion caused by *Staphylococcus aureus* is known as *botryomycosis* and is most commonly seen in horses and pigs. It is most often wound related and can occur at a variety of sites. Histologically, actinobacillosis, actinomycosis, and botryomycosis are similar in that the lesions are encapsulated inflammatory lesions containing a central focus of "radiating clubs" of amorphous eosinophilic material associated with bacteria and neutrophils (Splendore-Hoeppli reaction). Neutrophils admixed with macrophages (pyogranulomatous inflammation) can also be seen. Gram-stained tissue can be used to differentiate between the clusters of Gram-positive cocci in *Staphylococcus* infection, the Gram-positive bacilli causing actinomycosis (*Actinomyces bovis*), and the Gram-negative bacilli causing actinobacillosis (*Actinobacillus lignieresii*).

Viral. Relatively few of these are recognized in veterinary medicine. Spontaneous ones are listed in Table 15-5. Gross lesions may or may not be visible and, if present, are small, poorly defined foci or streaks. Muscle lesions induced by viruses are either infarcts secondary to a vasculitis, as seen in bluetongue in sheep, or multifocal necrosis, presumably because of a direct effect of the virus on the myofibers.

Parasitic. Parasitic infections of the skeletal muscles of domestic animals are not uncommon and include protozoal organisms and nematodes. The most important ones are listed in Table 15-6 and are discussed under the appropriate species heading. Most parasitic diseases have little pathologic or economic importance, with the exceptions of *Neospora caninum*, *Hepatozoon americanum*, and *Trypanosoma cruzi* in dogs and *Trichinella spiralis* in pigs.

As the name *Sarcocystis* suggests, intramyofiber protozoal cysts caused by *Sarcocystis* spp. are a common finding. This protozoal organism is a stage in the life cycle of an intestinal coccidium of carnivores that uses birds, reptiles, rodents, pigs, and herbivores as an intermediate host. Ingestion of oocysts by an intermediate host releases sporozoites that penetrate through the intestinal wall, enter blood vessels, and are hematogenously disseminated and invade tissue, including muscle. This parasite rarely causes clinical disease and is therefore most often considered an incidental finding. *Sarcocystis* infection of muscle is seen most often in horses, cattle, and small ruminants and occasionally in cats. Because they are intracellular, cysts are protected from the host's defense mechanisms; thus there is no inflammatory response (Fig. 15-26).

Immune-Mediated. Immunologically induced myositis, not associated with vascular injury, has been recognized primarily in the dog. Rarely, immune-mediated myositis occurs in cats and horses. Infiltrating lymphocytes, most often cytotoxic T lymphocytes, are the cause of myofiber injury. Although cytotoxic T lymphocytes are the effector cells causing myofiber damage, the inflammatory infiltrate is a mixture of lymphocyte types. The characteristic histologic pattern of immune-mediated myositis is an interstitial and perivascular lymphocytic infiltration (Fig. 15-27, *A*; see also Fig. 15-47), often with invasion of intact myofibers by lymphocytes (Fig. 15-27, *B*). A variety of forms of immune-mediated myositis occur in the dog and can be localized to specific muscles, presumably because of unique myosin isoforms within those muscles. These are listed in Table 15-7. Acquired myasthenia gravis is also an immune-mediated disease and is included in this table for completeness, but this is a disorder causing damage to the neuromuscular junction rather than to myofibers. In cats, feline immunodeficiency virus infection is a cause of immune-mediated myositis. In horses, lesions consistent with immune-mediated myositis are occasionally found after exposure to *Streptococcus equi* ssp. *equi* or infection with equine influenza virus. Note that small perivascular and interstitial infiltrates of lymphocytes, with no apparent myofiber damage, are a frequent incidental finding in equine muscle.

Immune-mediated vasculitis resulting in muscle injury occurs in horses and is known as *purpura hemorrhagica*. Purpura hemorrhagica has been classically associated with *Streptococcus equi* ssp. *equi*, but other bacteria, such as *Corynebacterium pseudotuberculosis*, can also cause purpura hemorrhagica.

Table 15-5 Viral Myopathies

	RNA VIRUSES	
Disease	**Family**	**Causal Agent**
Porcine encephalomyelitis	Picornaviridae	Enterovirus
Foot-and-mouth disease	Picornaviridae	Aphthovirus
Bluetongue	Reoviridae	Orbivirus
Akabane disease	Bunyaviridae	Akabane virus

Table 15-6 Parasitic Myopathies

Infectious Agent	Type of agent	Species Affected
Sarcocystis spp.	Protozoan	Horses, cattle, sheep, goats, camelids, pigs
Trichinella spiralis	Nematode	Pigs
Neospora caninum	Protozoan	Dogs, fetal cattle
Trypanosoma cruzi	Protozoan	Dogs
Cysticercus spp.	Cestode (larval form)	Cattle, sheep, goats, pigs
Nematode larval migrans	Nematode	Dogs
Hepatozoon americanum	Protozoan	Dogs

Congenital and Inherited Disorders

Muscle is subject to numerous hereditary, congenital, and neonatal defects (E-Box 15-1). Muscular disorders that are apparent at birth are congenital, but they may or may not be inherited. Inherited disorders can manifest at birth or soon thereafter, or they may not be apparent for many years. Molecular biologic studies and development of molecular genetic tests have greatly enhanced our understanding of several muscular disorders of animals and the ability to detect affected and carrier animals.

Anatomic Defects. Anatomic defects in skeletal muscle are apparent at birth or soon thereafter. These defects can be either genetic or acquired and result from either abnormal in utero muscle development or abnormal innervation.

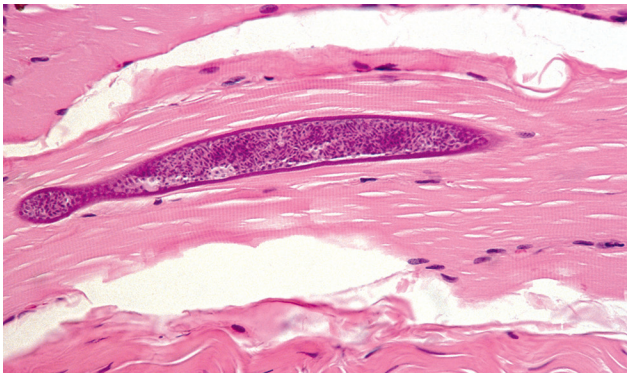


Figure 15-26 Sarcocystosis, Skeletal Muscle, Longitudinal Section, Cow. The horizontally elongate encysted intramyofiber protozoan *(dark purple structure)* is characteristic of *Sarcocystis* spp. There is no associated inflammation. These parasites are common in the muscles of many species of domestic animals and are usually an incidental finding. Formalin fixation, H&E stain. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

E-Box 15-1 Confirmed or Suspected Inherited Myopathies and Neuromuscular Junction Diseases in Animals

Autosomal recessive myopathies, species and breed specific
Arthrogryposis
Carnitine deficiency
Centronuclear myopathy
Congenital myasthenia gravis
Glycogen storage disease
Hereditary spinal muscular atrophy
Hyperkalemic periodic paralysis
Malignant hyperthermia
Mitochondrial myopathy
Muscular dystrophy
Myasthenia gravis
Myotonia congenita
Myostatin defect (double muscling)

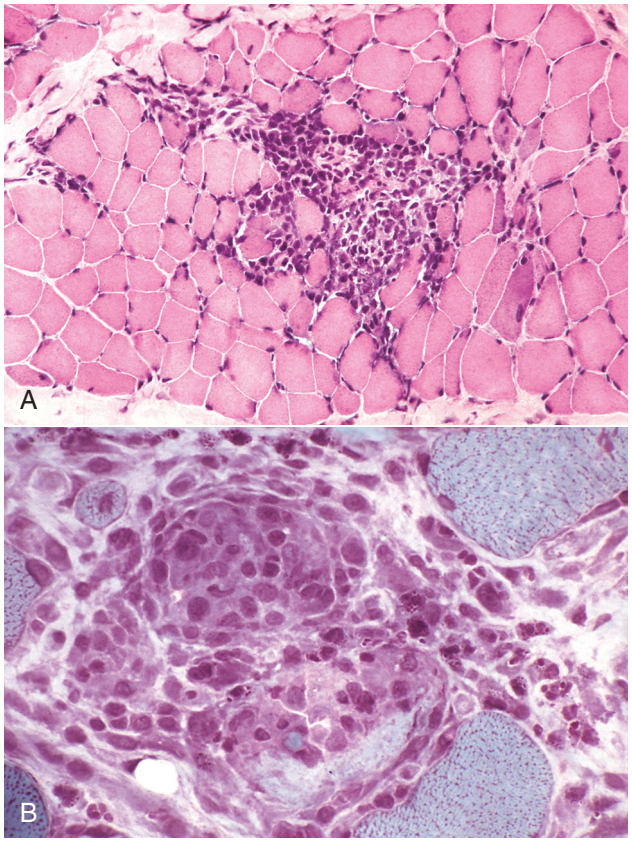


Figure 15-27 Immune-Mediated Myositis, Canine Polymyositis, Skeletal Muscle, Transverse Sections, Dog. A, There is a dense interstitial infiltrate of primarily mononuclear inflammatory cells. Frozen section, H&E stain. **B,** Note the interstitial infiltrate of mononuclear inflammatory cells and mononuclear cells that have invaded intact myofibers causing myofiber necrosis. Frozen section, modified Gomori's trichrome stain. (**A** and **B** courtesy Dr. B.J. Cooper, College of Veterinary Medicine, Oregon State University.)

Table 15-7 Immune-Mediated Muscle Disorders

Disorder	Species Affected
Purpura hemorrhagica	Horses
Viral-associated	Horses, cats
Polymyositis	Dogs, horses (rare)
Masticatory myositis	Dogs
Extraocular muscle myositis	Dogs
Acquired myasthenia gravis	Dogs, cats

Innervation Defects. Congenital defects in the lower motor neuron system, involving motor neurons or peripheral nerves, result in severe alteration of myofiber development. Denervation occurring in fetal and neonatal animals can result in very complex muscle lesions because of the importance of innervation in myofiber development and maturation. Depending on the nature of the nervous system defect, muscular lesions can reflect failure of innervation, denervation of previously innervated fibers, or a combination of both. The most common example of this is arthrogryposis in cattle and sheep in which in utero infection or toxin ingestion causes nervous system lesions that lead to failure of innervation or to denervation of skeletal muscle. In addition, a disorder thought to have a genetic basis has been reported in black Angus cattle and results in failure of innervation of skeletal muscle. Failure of innervation or severe denervation injury in utero most often result in failure of the myofibers to develop and their subsequent replacement by adipose tissue (fatty infiltration). This outcome can be severe in affected muscle and may be the basis for some cases of congenital muscular steatosis in livestock (see Figs. 15-9, *D*, and 15-23).

Genetic Defects. Congenital muscular hyperplasia (double muscling) is a genetic disease causing a congenital anatomic skeletal muscle defect (increased number of myofibers) in cattle, dogs, and children. This disorder is caused by defects in the myostatin gene, which controls in utero muscle development. There is more information on this disease in E-Appendix 15-1. With continued selective breeding and advancement in molecular biologic techniques, it is likely that other genetic defects affecting muscle structure may occur or be recognized.

Failure of Normal Development. In addition to failure of myofiber maturation caused by innervation defects, inherent myofibrillar developmental defects can occur. This is exemplified by myofibrillar hypoplasia causing splay leg in neonatal pigs. A similar condition has been reported in a calf.

Congenital defects in the diaphragmatic muscle (diaphragmatic hernia) can occur in all species but are most well documented in dogs and rabbits. A genetic basis with a multifactorial inheritance is suspected. Clinical signs of respiratory distress caused by herniation of abdominal viscera into the thoracic cavity generally occur at or soon after birth. Defects in the left dorsolateral and central portions of the diaphragm because of failure of closure of the left pleuroperitoneal canal are most common.

Muscular Dystrophy. The term *muscular dystrophy* has been grossly misused in the veterinary literature. Using the definition applied to human beings, muscular dystrophy should only be applied to inherited, progressive, degenerative primary diseases of the myofiber characterized histologically by ongoing myofiber necrosis and regeneration (polyphasic necrosis). Several types of muscular dystrophy occur in human beings and animals. The enormous recent advances in genetic and molecular characterization of muscle diseases have resulted in defining their exact genetic defects, such as those in the dystrophin gene responsible for Duchenne's muscular dystrophy and trinucleotide repeat sequences in myotonic dystrophy, and in the reclassification of others. Similarly, reevaluation of some inherited disorders previously classified as muscular dystrophy, such as muscular dystrophy in sheep and cattle, suggests that they would be better classified as progressive congenital myopathies.

Congenital Myopathies. Those inherited disorders of muscle that do not qualify as anatomic defects, muscular dystrophy, myotonia, or a metabolic myopathy (see later discussion) are classified as congenital myopathies. These include structural defects leading to abnormal myofiber cytoarchitecture. In some cases, the defective gene is known, whereas the cause of others remains undetermined.

Myotonia (Channelopathies). Myotonia is defined as the inability of skeletal muscle fibers to relax, resulting in spasmodic contraction. Various inherited myotonic conditions have been recognized in human beings and animals for many years. Only recently has the basis for many of these myopathies been determined. Most have been found to be related to inherited defects resulting in abnormal ion channel function. Maintenance of ionic equilibrium and control of the ionic fluxes of excitable tissue, such as muscle, are critical to normal muscle functioning. A variety of sarcolemmal ion channels exist that control fluxes of ions such as sodium, potassium, chloride, and calcium. Defective sodium or chloride channels most often result in myotonia.

Metabolic Myopathies. Inherited disorders of muscle metabolism (see E-Box 15-1) are characterized by reduced muscle cell energy production. Clinical signs include exercise intolerance, exercise-induced muscle cramps, and rhabdomyolysis (acute segmental myofiber necrosis). Metabolic defects can involve glycogen metabolism, fatty acid metabolism, or mitochondrial function. Metabolic disorders often cause increased blood lactate after exercise. Inheritance patterns vary. Glycolytic, glycogenolytic, and nonmitochondrial DNA–encoded enzyme defects are generally inherited in an autosomal recessive manner. Defects involving mitochondrial DNA–encoded enzymes are inherited through the dam because all mitochondria are contributed by the oocyte.

The pathways of glycolysis and glycogenolysis are complex, involving a cascade of enzymatic reactions. Deficiency of a glycolytic or glycogenolytic enzyme leads to accumulation of glycogen and in some cases glycogen-related proteoglycans. There are many different types of glycogen storage diseases, and their categorization is dependent on which enzyme is deficient. Of the types of glycogenoses recognized in human beings, five types (II, III, IV, V, and VII) cause glycogen accumulation in muscle. Of the glycogenoses affecting muscle, only types II (acid maltase deficiency), IV (glycogen branching enzyme deficiency), V (myophosphorylase deficiency), and VII (phosphofructokinase deficiency) have so far been recognized in animals. Storage diseases in which glycogen accumulates in muscle have been described in horses, cattle, sheep, dogs, and cats.

Inherited lipid storage myopathies have not yet been described in animals, although dogs appear to have a predilection for development of neuromuscular weakness because of acquired lipid storage myopathy with concurrent reduction in skeletal muscle carnitine activity. Mitochondrial myopathies are rarely recognized in animals, perhaps because of the difficulty in confirming mitochondrial defects. A few such disorders have been described in dogs, and a mitochondrial myopathy has been reported in one Arabian horse. Mitochondrial disorders may affect only muscle, or muscle involvement may be part of an encephalomyopathic condition.

Malignant Hyperthermia. Malignant hyperthermia (MH) is a condition characterized by unregulated release of calcium from the sarcoplasmic reticulum, leading to excessive myofiber contraction that generates heat, resulting in a severe increase in body temperature. MH is often fatal. In human beings, pigs, horses, and dogs, a congenital defect in the sarcoplasmic reticulum calcium-release channel, the ryanodine receptor, causes dysregulation of excitation-contraction coupling leading to MH. Episodes in affected individuals can be triggered by general anesthetic agents, especially halothane, or by stress, thus the name *porcine stress syndrome* for the disorder in pigs (see Fig. 15-42).

An MH-like condition can also occur because of other myopathic conditions, especially those that result in uncoupling of mitochondrial oxidative phosphorylation from the electron transport chain. Inherently uncoupled mitochondria within brown fat are the physiologic basis for production of heat during breakdown of this fat in neonates, and pathologically uncoupled or loosely coupled mitochondria in muscle as a result of an underlying myopathy release energy as heat.

Gross and microscopic lesions are described in the discussion on the disorder in the section on Disorders of Pigs.

Endocrine and Electrolyte Abnormalities

Various endocrinologic abnormalities can result in myopathic conditions (Table 15-8). The most common are hypercortisolism and hypothyroidism in dogs. In horses, pituitary hyperfunction resulting in Cushing's disease also causes muscle disease. In most cases of endocrine myopathy, the end result is myofiber atrophy, particularly of type 2 fibers. A unique syndrome of muscle hypertrophy and pseudomyotonia occurs in dogs associated with hypercortisolism. Endocrine myopathies can also be complicated by the fact that endocrinopathy can also cause pathologic changes in peripheral nerves, leading to a mixture of myopathic (type 2 fiber atrophy) and neuropathic changes (denervation atrophy and alteration in fiber-type pattern) within muscle. Denervation followed by reinnervation leading to fiber-type grouping can be seen in dogs with chronic hypercortisolism (see Fig. 15-18, *B*) and hypothyroidism.

Table 15-8 Myopathies Caused by Endocrine and Electrolyte Abnormalities

Disorder	Species Affected
Hypothyroidism	Dogs
Hypercortisolism	Dogs
Hypokalemia	Cattle, cats
Hypophosphatemia	Cattle
Hypernatremia	Cats
Hypocalcemia	Cattle
Hypothalamic/pituitary dysfunction	Horses

Normal electrolyte status is vital to normal skeletal muscle function. Hypocalcemia, hypokalemia, hypernatremia, and hypophosphatemia can cause profound skeletal muscle weakness, sometimes associated with myofiber necrosis, in various species.

Neuropathic and Neuromuscular Junction Disorders

Dysfunction of the lower motor neurons, peripheral nerves, or neuromuscular junction can have profound effects on muscle function.

Neuropathic Disorders. There are many peripheral nerve disorders and a few motor neuron disorders that can lead to denervation atrophy of muscle in animals. These can be inherited or acquired. Long nerves, such as the sciatic and left recurrent laryngeal nerves, appear to be particularly sensitive to development of acquired neuropathy. Many of the peripheral nerve disorders of animals are discussed in Chapter 14. Characteristic features of denervation atrophy are described in the section on Dysfunction/Responses to Injury, Alterations in Myofiber Size, Atrophy.

Neuromuscular Junction Disorders. The neuromuscular junction is a modification of the postsynaptic myofiber membrane. At the neuromuscular junction, the membrane is folded to increase surface area and is studded with specialized ion channels known as *acetylcholine receptors*. After arrival of an action potential at the distal end of a motor nerve, the terminal axons release acetylcholine, which diffuses across the synaptic space to bind to the acetylcholine receptors. Binding opens these channels, leading to sodium influx, which initiates the skeletal muscle action potential that culminates in muscle contraction. Acetylcholine is rapidly degraded by acetylcholinesterase released from the postsynaptic membrane, which prevents continued stimulation and thus contraction of the muscle fiber.

Disorders that impair the ability of nerve impulses to travel across the neuromuscular junction have profound effects on skeletal muscle function. Technically, however, the myofibers are still innervated, so denervation atrophy does not occur and no light microscopic abnormalities in the muscle or nerve are present. Various neurotoxins (i.e., in snake and spider venom and in curare-containing plants)

and drugs can affect the neuromuscular junction, but the most common neuromuscular junction disorders affecting animals are myasthenia gravis, botulism, and tick paralysis.

Myasthenia Gravis. Myasthenia gravis can be either acquired or congenital. Acquired myasthenia gravis is an immune-mediated disorder caused by circulating autoantibodies against skeletal muscle acetylcholine receptors (Fig. 15-28). Binding of these antibodies to the acetylcholine receptor on the postsynaptic membrane leads to a severe decrease in the number of functional receptors. The mechanisms by which antibodies damage these receptors are (1) direct damage to the neuromuscular junction, which may be visible with electron microscopy as simplification of the folding of the membrane, and (2) formation of cross-linked antibodies leading to receptor internalization. Sufficient functional acetylcholine receptors are present to initially allow normal neuromuscular transmission, but if there is sustained muscular activity the decrease in the number of available receptors leads to progressive weakness and collapse. Therefore acquired myasthenia gravis results in episodic collapse, and repetitive nerve stimulation causes a characteristic rapid decrease in amplitude of the muscle compound motor action potential. Diagnosis of myasthenia gravis can also be made after intravenous injection of cholinesterase inhibitors such as edrophonium chloride (Tensilon, ICN Pharmaceuticals, Costa Mesa, CA) in collapsed animals. The reduction in cholinesterase activity leads to more active acetylcholine being available within the synapse and rapid, although transient, restoration of skeletal muscle contraction. Detection of autoantibodies to acetylcholine receptors in the blood confirms the diagnosis of acquired myasthenia gravis.

The origin of the autoantibodies causing myasthenia gravis is not always known, but there is a strong link between thymic abnormalities and development of myasthenia gravis in both human beings and animals. Specialized cells within the thymic medulla, known as *myoid cells*, express skeletal muscle proteins, including those of the acetylcholine receptor. It is thought that these cells participate in development of self-tolerance. Abnormalities of the thymus, most commonly thymoma in animals and thymic follicular hyperplasia in human beings, can lead to loss of self-tolerance to acetylcholine receptors. In such cases, removal of the abnormal thymus can result in restoration of normal neuromuscular junction activity. When thymic abnormalities are not present, treatment with long-acting anticholinesterase agents and in some cases immunosuppressive agents, such as corticosteroids, is necessary.

Congenital myasthenia gravis is an inherited disorder that is much less common than acquired myasthenia gravis. To date it has been described only in human beings, dogs, and cats. Animals with congenital myasthenia gravis are born with defective neuromuscular junctions that often have a decreased membrane surface area, best visualized with electron microscopy, and as a consequence an inherently reduced acetylcholine receptor density. Such animals may be normal at birth because there are sufficient functional acetylcholine receptors to support muscle contraction in a neonate. However, with rapid postnatal growth, clinical signs of profound, sustained, and progressive weakness occur as a consequence of insufficient functional receptors to support the function of growing muscles.

Botulism. Botulism is a neuromuscular disorder caused by the exotoxin of the bacterium *Clostridium botulinum*. Botulinum toxin is considered one of the deadliest of the known toxins. Botulism is characterized by profound generalized flaccid paralysis. Seven serologically distinct but structurally similar forms of botulinum toxin are designated A, B, C, D, E, F, and G. Sensitivity to these toxin types varies among different species. Dogs are most sensitive to type C toxin, ruminants to types C and D, and horses to types B and C.

Botulinum toxin consists of a light chain and a heavy chain linked by a disulfide bond. Binding of botulinum toxin to receptors on the presynaptic terminals of peripheral nerves is followed by endocytosis of the toxin. Within the endocytotic vesicle of the terminal nerve, the disulfide bond is cleaved, and the released light chain is translocated into the axonal cytoplasm (see Fig. 4-27). Botulinum toxin light chains are metalloproteinases. Numerous proteins are involved in the release of acetylcholine from presynaptic vesicles, and botulinum toxin blocks release of acetylcholine by irreversible enzymatic cleavage of one or more of these proteins. Different forms of botulinum toxin affect different proteins, but the end result is the same. Active neuromuscular junctions are the most

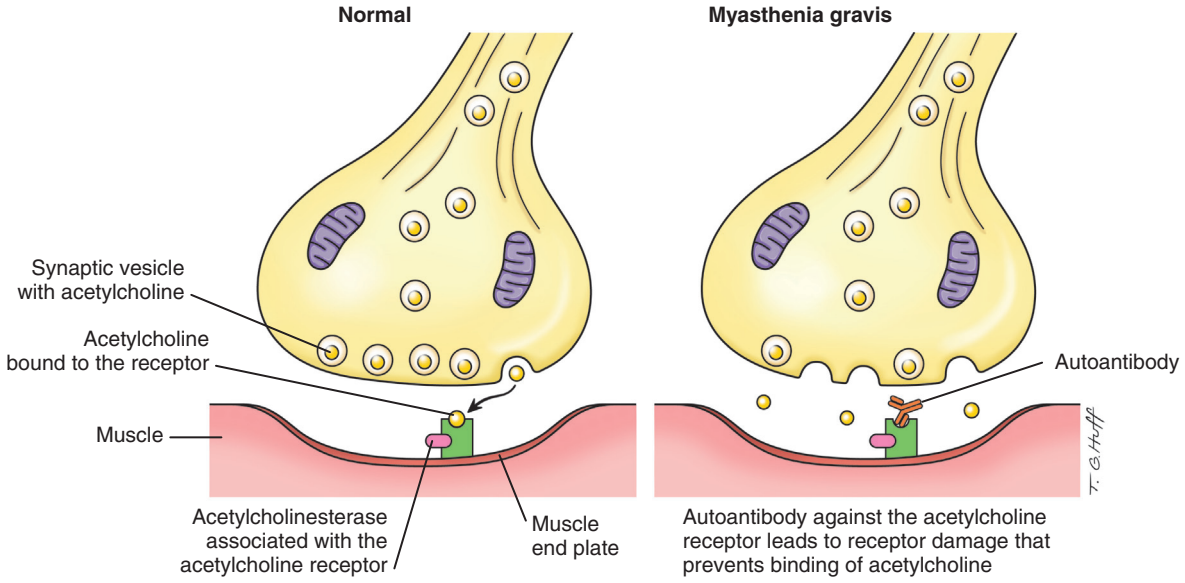


Figure 15-28 Pathogenesis of Acquired (Immune-Mediated) Myasthenia Gravis. Myoneural junction in normal muscle *(left panel)*. When acetylcholine binds to acetylcholine receptors, a signal from the receptor opens ligand-gated sodium channels in the muscle cell membrane leading to contraction. Myoneural junction in myasthenia gravis *(right panel)*. Autoantibody directed against acetylcholine receptors causes receptor injury and blocks the binding of acetylcholine to the receptor, resulting in episodic weakness and collapse.

sensitive, which has led to the use of low concentrations of locally injected botulinum toxin as a treatment for localized muscular disorders resulting in spasm.

Clostridium botulinum spores are commonly present in the gastrointestinal tract of animals and in the soil. Under favorable anaerobic and alkalinic conditions, these spores become active, with resultant toxin production. Botulism can occur because of ingestion of preformed toxin, such as in feed contaminated by dead rodents or soil-borne organisms, or from toxin produced by *Clostridium botulinum* organisms within the gastrointestinal tract or superficial wounds (Box 15-9). Dogs and cats are the species most likely to ingest dead rodents containing botulinum toxin and are quite resistant to developing botulism. In veterinary medicine, horses are the most sensitive to botulinum toxin. Death of horses, most often the result of respiratory muscle paralysis, can result from exposure to only very small amounts of botulinum toxin. The damage to presynaptic axon terminals is irreversible, and recovery from botulism occurs only after terminal axon sprouting and reestablishment of new functioning synapses.

Tick Paralysis. *Dermacentor* and *Ixodes* ticks can elaborate a toxin that also blocks release of acetylcholine from axon terminals. Tick paralysis is seen most often in dogs and children. Recovery after tick removal can be rapid (within 24 to 48 hours), indicating that the mechanism of toxin action in tick paralysis does not result in irreversible presynaptic damage and thus is different from that of botulinum toxin.

Neoplasia

Neoplasms involving skeletal muscle are most often those that arise within the muscle or its supporting structures or that invade muscle from adjacent tissue. Neoplasms metastatic to muscle are rare.

Primary Muscle Tumors. Tumors with striated muscle differentiation are thought to arise from intramuscular pluripotential stem cells rather than from satellite cells. These tumors are uncommon and are either benign (rhabdomyoma) or malignant (rhabdomyosarcoma [Fig. 15-29]). Primary intramuscular tumors can also arise from fibrous tissue, vasculature, or neural elements. The most common tumor to arise from muscle-supporting structures is hemangiosarcoma.

Rhabdomyoma and Rhabdomyosarcoma. Tumors of striated muscle that occur at sites other than within muscle are rhabdomyomas of the heart or lung and botryoid rhabdomyosarcomas of the urinary bladder; these are not discussed in this section. Rhabdomyoma and rhabdomyosarcoma arising within skeletal muscle are most common in the dog, followed by the horse and cat. Morphologic variants include round cell, spindle cell, and mixed round and spindle cell, reflecting the developmental stages of skeletal muscle. Historically, diagnosis of tumors of skeletal muscle has relied on identification of cross-striations indicative of sarcomeric differentiation. Cross-striations are most often seen in elongated multinucleate cells known as *strap cells* (Fig. 15-29, C) and in ovoid cells known as *racquet cells*. They are most easily recognized after staining with phosphotungstic acid hematoxylin (PTAH) stain, but the search for cross-striations can be extremely frustrating and often unrewarding. These days, the diagnosis of tumors of skeletal muscle origin relies primarily on results of immunohistochemical examination using

Box 15-9 Portals of Entry–Equine Botulism

Gastrointestinal colonization of ingesta: Foals up to 6 months of age
Ingestion of preformed botulinum toxin: Adults, usually from rodent carcasses in hay or concentrated feed, or environmental contamination
Wound contamination: Adults, deep wounds, uncommon

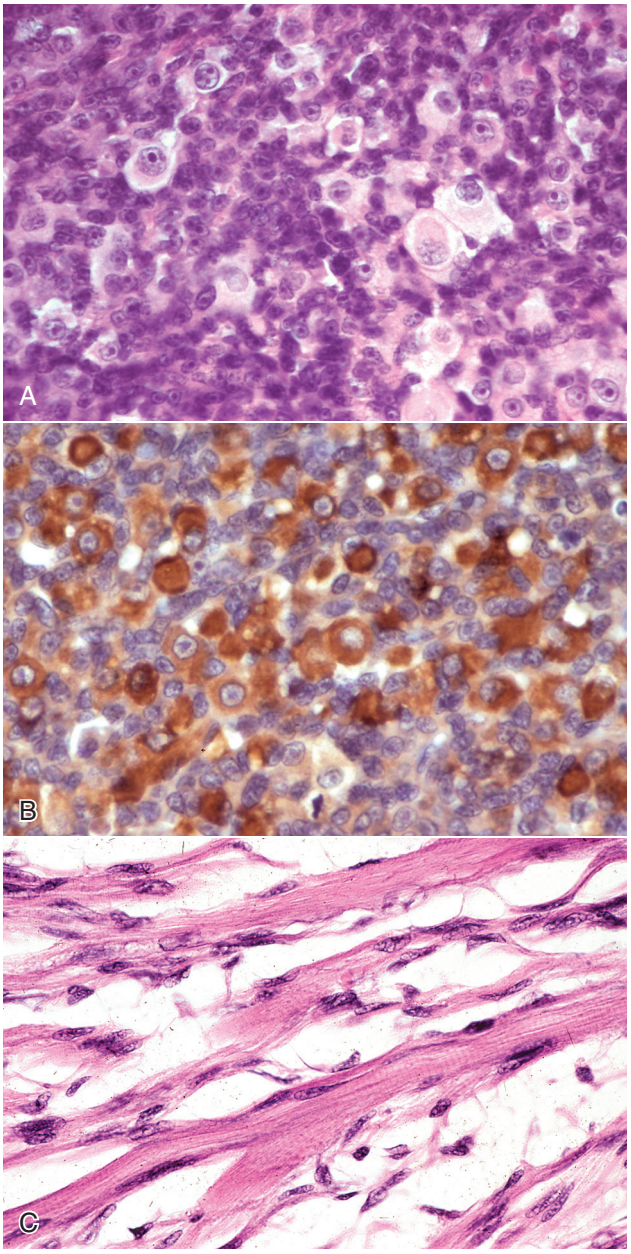


Figure 15-29 Rhabdomyosarcoma. A, Skeletal muscle, cat. An admixture of small round basophilic cells with a lesser number of larger round cells with prominent eosinophilic cytoplasm is characteristic of embryonal rhabdomyosarcoma. Nuclei are central and euchromatic, most often with a single large nucleolus. H&E stain. **B,** Immunostaining reaction of the same rhabdomyosarcoma as depicted in **A,** showing intense cytoplasmic expression of desmin in many tumor cells, indicative of muscle origin (skeletal, cardiac, or smooth). These cells also express myoglobin and sarcomeric actin (not shown), which differentiates skeletal muscle tumors from smooth muscle tumors. Immunoperoxidase reaction for desmin. **C,** Botryoid rhabdomyosarcoma, urinary bladder, large breed dog. Cross-striations, characteristic of a well-differentiated rhabdomyosarcoma, are present in the elongated multinucleate tumor cells. H&E stain. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

antibodies for muscle-specific proteins. Muscle actin and desmin are expressed by smooth and skeletal muscle tumors, but myoglobin, sarcomeric actin, myogenin, and MyoD1 are specific for skeletal muscle. Evidence of muscle differentiation, such as primitive myofilaments and Z-band structures, can also be detected by electron microscopy.

Rhabdomyoma is most often a round cell tumor and occurs most commonly in the larynx of adult dogs. The youngest reported age is 2 years. Tumors are generally smooth and nodular, pink, and unencapsulated. Histologic features are closely packed plump round cells that have central euchromatic nuclei, generally with a single prominent nucleus, and abundant vacuolated to granular eosinophilic cytoplasm. A small number of multinucleate and elongate strap cells can also be seen. Mitoses are rare, and evidence of invasion is uncommon.

Similar to the situation in human beings, rhabdomyosarcomas in animals most often occur at a young age and are most common in the neck or oral cavity, especially in the tongue. These tumors are pink and fleshy, and they often have prominent local invasion. The most common and most distinctive form of rhabdomyosarcoma in animals is embryonal rhabdomyosarcoma, composed of primitive round cells with prominent euchromatic nuclei, a single prominent nucleolus, and either indistinct or prominent eosinophilic cytoplasm ("rhabdomyoblasts"; see Fig. 15-29, *A* and *B*). Rhabdomyosarcoma can also contain elongate multinucleate strap cells (see Fig. 15-29, *C*) and ovoid racquet cells. Cellular and nuclear pleomorphism is common, as is mitotic activity. These tumors are locally invasive and frequently metastasize, although too few cases have been studied to document any pattern of metastasis.

Hemangiosarcoma. Malignant vascular neoplasms (hemangiosarcoma) arising within muscle are most common in the horse and dog (Fig. 15-30). Clinical signs include swelling within a muscle, often with associated lameness. Cytologic preparations frequently reveal only peripheral blood, which is suggestive of a hematoma. Pathologic diagnosis can be difficult if multiple sites within the lesion are not sampled, because the amount of hemorrhage often far exceeds the area composed of proliferating neoplastic endothelial cells. Intramuscular hemangiosarcoma has a high incidence of metastasis, often to the lungs.

Figure 15-30 Intramuscular Hemangiosarcoma, Cervical Skeletal Muscle, Horse. Multiple irregular zones of cavitated *(upper right)* to solid tumor with hemorrhage have replaced normal muscle. Formalin-fixed specimen. (Courtesy Dr. A. de Lahunta, College of Veterinary Medicine, Cornell University.)

Other Tumors Involving Skeletal Muscle. A variant of lipoma, known as infiltrative lipoma, is often located in skeletal muscle. Characteristic gross pathologic and histopathologic findings are mature adipocytes invading skeletal muscle. This tumor is most common in the dog but has also been reported in young horses. Wide excision is the treatment of choice because this tumor recurs as a result of local invasion, but it does not metastasize.

Infiltration of skeletal muscle by neoplastic lymphocytes is not uncommon. Neoplastic lymphocytic infiltrates surround myofibers and can cause myofiber atrophy. These cells do not invade myofibers, however, and myonecrosis is rare. This helps to distinguish intramuscular lymphoma from lymphocytic myositis. Careful examination of infiltrating neoplastic cells typically reveals a relatively monomorphic population of lymphocytes, which may be atypical in appearance. Immunohistochemistry to confirm a single infiltrating cell type is also useful.

Vaccine-associated sarcoma in the muscle of the cat can arise within an intramuscular vaccination site or extend into underlying skeletal muscle from a subcutaneous injection site. Occasionally, mast cell tumors and carcinomas exhibit prominent skeletal muscle invasion. Melanoma arising in the skin of older gray horses often metastasizes to muscle fascia and may exhibit some extension into the muscle itself. Intramuscular metastasis of tumors is rare (see the section on Defense Mechanisms). Intramuscular metastasis of carcinoma, particularly prostatic, and of hemangiosarcoma can occur in dogs. When carcinomas with areas of sclerosis involve muscle, either by extension or by metastasis, the muscle basement membrane of adjacent myofibers is typically destroyed, often resulting in bizarre multinucleate cells representing attempts at muscle regeneration (see Fig. 15-15). These bizarre cells should not be misidentified as tumor cells.

Disorders of Domestic Animals by Species

Adequate muscle function is essential for the survival of any species. Many domestic animals have been selectively bred for improved musculature for meat production, performance, or appearance. Therefore muscle disease in animals can have a significant economic impact. In some cases, it is selection pressure imposed by human beings that has resulted in development and perpetuation of various myopathic conditions in animals. It is likely that continued selection for what appears to be a phenotypically desirable trait will lead to the recognition of new genetic mutations and myopathic conditions in the future.

It is interesting to compare the effects of muscular disorders that affect human beings and animals. The four-footed stance of animals allows for greater stability, which can allow an animal to remain ambulatory for some time, when a similarly affected person would be confined to a wheelchair. However, disorders that result in recumbency, even if it is transitory, can be devastating in livestock. It is much more difficult to nurse a large animal through a period of recumbency than it would be for a hospitalized human or small animal.

The most common and important muscle disorders of animals are discussed by species because this is the way diseases are considered clinically. The same disease may occur in different species. Details of less common muscle disorders are presented in E-Appendix 15-1.

Disorders of Horses

There is perhaps no other domestic animal species for which optimal muscle development and function is so critical as the horse. Selective breeding for better muscling has occurred in virtually all horse

and pony breeds. The ability of such selection pressure to perpetuate equine muscle mutations is exemplified by the relatively recent occurrence of hyperkalemic periodic paralysis (HYPP), in which a muscle mutation results in visually appealing increased muscle bulk and definition. Unfortunately, as noted in the discussion of HYPP later, such mutations do not often result in improved muscle function.

Bacterial and Parasitic Myopathies

Infection by various bacterial organisms and clostridial toxins can cause myopathy in the horse. Protozoa (*Sarcocystis* spp.) are common incidental findings in equine muscle, but *Sarcocystis*-induced muscle damage resulting in clinical signs of muscle disease is rare.

Clostridial Myositis (Malignant Edema; Gas Gangrene). Clostridial myositis in the horse is an often fatal disorder caused by infection by various toxin-producing clostridial species, which are large Gram-positive anaerobic bacilli. *Clostridium septicum* is the most common cause of clostridial myositis in horses, but *Clostridium perfringens* types A to E, *Clostridium chauvoei*, *Clostridium novyi*, and *Clostridium fallax* can also cause infection. Infection can involve more than one clostridial species. *Clostridium* spp. are ubiquitous organisms that form spores within the soil and within the gastrointestinal tract. Unlike cattle, in which nonpenetrating trauma can cause muscle bruising and anaerobic conditions that activate clostridial spores already in the muscle, clostridial myositis in horses is virtually always secondary to a penetrating wound. Most often, this is an injection site of a nonantibiotic substance, but infection of sites of puncture wounds and of perivascular leakage of irritants in intravenously administered compounds are also possible. It is also possible that clostridial bacteria entering the blood from an injured gastrointestinal tract can colonize damaged muscle. This is one possible explanation for the frequent occurrence of signs of colic before development of clostridial myositis at the site of intramuscular injection of medications such as flunixin meglumine that cause localized muscle damage. Under anaerobic conditions, clostridia proliferate and produce toxins that damage blood vessels, resulting in hemorrhage and edema, and cause necrosis of adjacent muscle fibers.

Clinical signs are acute onset of heat, swelling, and pain within a muscle group and adjacent fascia, with concurrent fever, depression, dehydration, and anorexia. If sufficient muscle necrosis is present, serum CK and AST concentrations may be mildly to moderately increased. Death from toxemia and/or septicemia often occurs within 48 hours. Affected muscle and adjacent fascia are swollen and often hemorrhagic, with edema, suppurative inflammation, and necrosis; gas may also be present (Fig. 15-31). Vasculitis is not seen. Gram-positive bacilli characteristic of *Clostridium* spp. are generally demonstrable within affected tissue.

The diagnosis can be made with reasonable certainty based on typical historic, gross pathologic, cytologic, and histopathologic findings. *Clostridium* spp. can also be identified by culture under anaerobic conditions or by a fluorescent antibody test. Treatment must be initiated rapidly and includes surgical incisions into affected muscle to allow drainage and oxygenation, antibiotic therapy, and supportive care.

Botulism. Technically, this disease is a neuromuscular junction disorder and is included in this section for convenience. Botulism is caused by *Clostridium botulinum* toxin and is often not associated with *Clostridium botulinum* infection. The portals of entry of botulinum toxin in horses are summarized in Box 15-9. *Clostridium botulinum* bacteria are found as spores within the gastrointestinal tract of many mammals, and spores are common in the soil. Preformed toxin within contaminated feed or soil is the most common cause of botulism in adult horses. However, in foals, usually between 1 week and 6 months of age, ingestion of *Clostridium botulinum* spores can lead to proliferation of toxin-producing *Clostridium botulinum* within the intestinal tract, resulting in toxicoinfectious botulism (shaker foals). Wound infection is an uncommon cause of botulism in horses.

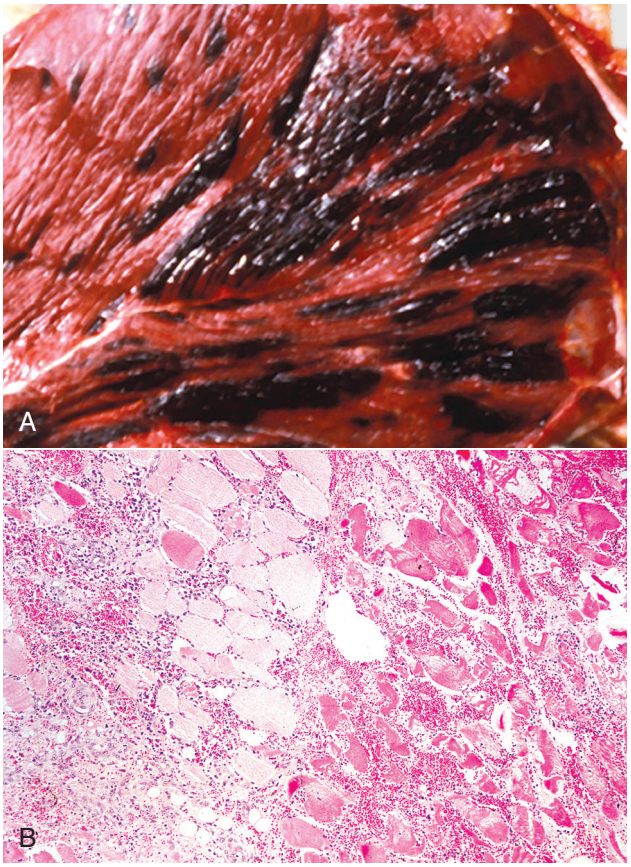


Figure 15-31 Clostridial Myositis, Malignant Edema, Horse. A, *Clostridium septicum* is the most common cause of clostridial myositis in horses. Affected muscle *(shown here)* and adjacent fascia *(not shown here)* are swollen and often hemorrhagic. **B,** Interstitial edema, hemorrhage, and inflammatory cells surround numerous swollen and fragmented necrotic myofibers. Formalin fixation, H&E stain. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

The pathogenesis of botulism has been previously discussed in the section on Neuropathic and Neuromuscular Junction Disorders. Irreversible binding of toxin to presynaptic nerve terminals and blockage of acetylcholine release lead to the profound generalized flaccid paralysis that is the hallmark of botulism. Clinical signs are acute and progress rapidly, generally resulting in recumbency. Dysphagia and tongue weakness are common findings that help to distinguish botulism from other neuromuscular diseases causing recumbency. Serum concentrations of CK and AST are within normal limits (indicating the absence of damage to myofibers) or are possibly slightly increased as a result of ischemic myopathy secondary to recumbency (see later discussion).

No specific gross or histopathologic lesions are present in horses dying with botulism, although aspiration pneumonia caused by dysphagia can occur. Muscle fibers are intact unless recumbency has compromised their blood supply, causing ischemia and localized myofiber necrosis.

Evaluation of stomach contents or contaminated feed may reveal the presence of toxin. However, horses are exquisitely sensitive to botulinum toxin, and because only a small concentration of the toxin may be present in an affected horse, available tests may not detect such a low concentration of toxin. In most equine cases, the diagnosis is made based on the clinical history after elimination of other possible causes of profound muscular weakness. Affected animals should be treated with polyvalent botulinum antitoxin to prevent further binding of toxin. Recovery occurs after terminal axon sprouting and reestablishment of functional neuromuscular junctions. Vaccination with botulinum toxoid is an effective preventive measure.

Corynebacterium pseudotuberculosis (Pigeon Fever). Intramuscular abscesses caused by *Corynebacterium pseudotuberculosis* occur almost exclusively in horses in arid regions of the western United States and Brazil. *Corynebacterium pseudotuberculosis* is a Gram-positive pleomorphic facultative anaerobic bacillus present within the soil. It can enter muscle via penetrating wounds, including injection sites. The biotype most common in horses is different from that which affects sheep and goats because it is unable to reduce nitrates to nitrites. The high lipid content of the bacterial cell wall contributes to the survival of *Corynebacterium pseudotuberculosis* within macrophages. Bacterial exotoxins, such as phospholipase D, contribute to vascular damage and inhibition of neutrophil function. Equine infections occur most frequently during the fall and early winter, and a higher incidence of the disease is often seen after rainy winters. Infections are most common in the pectoral musculature, but other locations are possible. Affected muscles are swollen and edematous and contain variably sized zones of localized suppurative inflammation. Fever is common. The causative agent is readily isolated from affected tissue and can be seen in aspirates from intramuscular abscesses. Treatment is generally curative and includes antibiotic therapy and establishment of drainage of abscesses. Rarely, infection with *Corynebacterium pseudotuberculosis* in horses leads to immune-mediated vasculitis (purpura hemorrhagica; see next section).

Streptococcal-Associated Myopathies. Two distinct degenerative myopathies are associated with infection or exposure of the horse to *Streptococcus equi* ssp. *equi*. One, known as *purpura hemorrhagica*, has been recognized for many years. The other, known as *streptococcal-associated rhabdomyolysis and muscle atrophy*, has only recently been recognized.

Purpura Hemorrhagica. In this disease, muscle damage is not caused by the direct infection of the muscles but, rather, by an immune response to the bacterial pathogen. *Streptococcus equi* is the most common cause of purpura hemorrhagica in horses, but *Corynebacterium pseudotuberculosis* and possibly other bacteria can also cause purpura hemorrhagica. In cases caused by *Streptococcus equi*, circulating immune complexes composed of immunoglobulin A (IgA) antibodies and streptococcal M antigen deposit in the walls of small vessels. This leads to vasculitis and vascular wall necrosis (Fig. 15-32), with resultant hemorrhage and infarction of myofibers. It is also possible that antibodies to streptococcal M protein cross-react with skeletal and cardiac muscle myosins to cause direct injury.

Signs of myopathy often accompany systemic signs of poststreptococcal purpura in horses (i.e., depression, fever, dependent edema, petechiae or ecchymoses, leukocytosis, increased serum fibrinogen, and anemia), but myopathy can also be the primary presenting disease process. Affected horses are weak, may have a short-strided gait, and can become recumbent. Myoglobinuria and very high increases in serum concentrations of CK and AST are common.

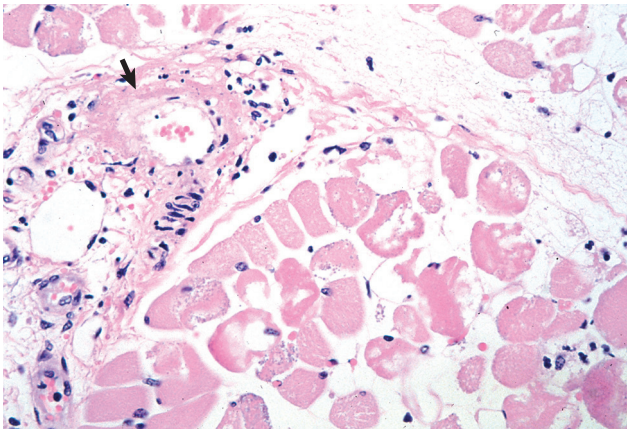


Figure 15-32 Intramuscular Vasculitis, Purpura Hemorrhagica, Skeletal Muscle, Transverse Section, Horse. In the wall of the blood vessel *(arrow)* is a band of circumferential fibrinoid necrosis containing nuclear debris. Many of the adjacent myofibers are necrotic *(center to lower right areas)*. Some of these myofibers are fragmented, and a small number contain fine basophilic deposits of mineral. Formalin fixation, H&E stain. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

Multiple muscles are involved (as opposed to the locally extensive lesion of clostridial myositis), and affected muscles contain multifocal to locally extensive hemorrhage and edema that dissects between necrotic muscle fibers and muscle fasciculi. Gross pathologic findings are similar to those seen in clostridial myositis (see Fig. 15-31, A), but lesions do not contain gas bubbles. Vascular injury (leukocytoclastic vasculitis and fibrinoid necrosis of blood vessels; see Fig. 15-32) is seen on microscopic examination and is the diagnostic feature.

Diagnosis is based on a history of exposure of the horse to *Streptococcus equi* and the typical clinical, clinicopathologic, and histopathologic findings. Because this is an immune-complex disorder, histopathology, cytology, and bacterial cultures of affected muscle do not reveal *Streptococcus equi*. This bacterium or other causative bacteria may be cultured from other affected tissues, especially lymph nodes or guttural pouch. A high serum titer to *Streptococcus equi* M protein is strongly supportive of a diagnosis of streptococcal-associated purpura hemorrhagica. Treatment includes corticosteroid therapy and supportive care, but horses frequently succumb to other sequelae of systemic vasculitis, such as gastrointestinal infarcts.

Streptococcal-Associated Rhabdomyolysis and Muscle Atrophy. A syndrome of severe acute rhabdomyolysis resulting in profound rapidly progressive generalized loss of muscle mass has also been seen in horses with clinical infection by *Streptococcus equi* or in horses that have been exposed to this bacterium but that did not develop obvious clinical signs of infection. This syndrome occurs most frequently in young to young adult quarter horses, but young horses of other breeds can also be affected. Clinically recognizable muscle atrophy is often most evident in paraspinal and gluteal muscles. Some cases have microscopic evidence of concurrent EPSSM (see the section on Inherited or Congenital Myopathies), which may be a predisposing factor. In others, nonsuppurative perivascular and interstitial inflammation has been detected, and the proposed mechanism is immune-mediated damage caused by cross-reaction of streptococcal antibodies with muscle proteins. Affected horses do not show typical signs of purpura hemorrhagica but often have very high serum concentrations of CK (often greater than 100,000 units per liter) and AST (often greater than 10,000 units per liter). Affected horses may respond to corticosteroid therapy.

Most will recover, but recurrence after subsequent exposure to *Streptococcus equi* is possible.

Protozoal Myopathy. Protozoa (*Sarcocystis* spp.) are common incidental findings in equine skeletal and cardiac muscles. Because the protozoa are in cysts within the myofiber itself and thus are protected from the body's surveillance, there is no inflammatory response. Massive infection by *Sarcocystis fayeri* is suspected of causing a degenerative myopathy in horses, but this is rare. Rarely, localized thickening of the tongue has been found in horses with granulomatous myositis, the result of sarcocystis organisms within tongue musculature. The cause of the intense inflammation apparently incited by protozoa in these rare cases is unknown.

Ear Tick–Associated Muscle Spasms. Episodic muscle spasms of various muscle groups can occur in horses with ear ticks (*Otobius megnini*). The mechanism is not known. Dimpling of affected muscles after percussion can be seen, but myotonic discharges are not found with electromyography. Treatment for ear ticks results in rapid recovery.

Nutritional and Toxic Myopathies

Nutritional deficiency, most often of selenium, and various toxins are relatively common causes of degenerative myopathy in the horse.

Nutritional Myopathy. Foals (most commonly up to 2 weeks of age) and young adult horses are most susceptible to nutritional myopathy because of a deficiency of the antioxidants selenium or (less commonly) vitamin E. In severely selenium-deficient areas, such as the Pacific Northwest, selenium deficiency myopathy can occur in horses of any age. Normally the selenium present in the soil is taken up by growing plants. In many areas, the soil is selenium deficient, and selenium supplements to the animal's ration must be provided. Vitamin E deficiency occurs in horses that eat marginal- to poor-quality grass hay and have little or no access to pasture and no supplemental vitamin E. Oxidative injury to actively contracting muscle fibers occurs as a result of a lack of antioxidant activity.

Affected foals are most likely to be those born to selenium-deficient mares. Foals have generalized weakness, which may be present at birth or become apparent soon after birth. Affected foals may become recumbent but are generally bright and alert. They often continue to suckle if bottle fed, but weakness of the tongue and pharyngeal muscles can lead to weak suckling.

Affected adult horses are most often stabled horses fed only selenium-deficient hay, with clinical disease being seen most commonly in the late winter or early spring. In the Pacific Northwest, selenium deficiency myopathy can occur in adult horses fed only pasture or hay, and it can occur at any time of year. Affected adult horses often show preferential involvement of the temporal and masseter muscles (the condition is sometimes inappropriately termed *maxillary myositis* or *masseter myositis*) with swelling and stiffness of these muscles and impaired mastication. Involvement of pharyngeal muscle results in dysphagia and involvement of the tongue results in impaired prehension of food, which can be mistaken for botulism. In more chronic cases, bilaterally symmetric atrophy of the masseter muscles may be evident, which can be mistaken for atrophy secondary to protozoal myeloencephalitis. Careful examination of these horses often reveals generalized weakness, evident as a stiff, short-strided gait. Severely affected horses can have an acute onset of recumbency that mimics neurologic disease.

Serum concentrations of CK and AST are generally mildly to moderately increased, although extremely high concentrations can be seen in severely affected foals and horses. Concentric needle EMG of affected muscles results in abnormal spontaneous activity (positive sharp waves, fibrillations, and myotonic bursts).

Muscles of affected horses appear pale (hence the common name white muscle disease), often in a patchy distribution (see Fig. 15-39). The most severely affected muscles are those that have the highest workload (e.g., cervical muscles in foals used during suckling and "bumping" the udder, proximal limb muscles, tongue, and masticatory muscles). The gross appearance depends on the extent of the necrosis and the stage. In early stages, yellow and white streaks are present, and later pale, chalk white streaks often appear. Horses with impaired swallowing can have cranioventral aspiration pneumonia. Severely selenium-deficient foals and horses also have pale areas of necrosis within the myocardium, especially the left ventricular wall and septum, which are areas that have a high workload. The stage of the necrosis depends on the age of the lesions. In foals with severe, acute myopathy leading to death or euthanasia, lesions are at the stage of massive muscle necrosis and mineralization with minimal macrophage infiltration (monophasic). In animals that have lived longer (i.e., subacute cases), the lesions are polyphasic, and active necrosis, macrophage infiltration, and regeneration are present. Although type 1 fibers may be more likely to develop necrosis because of nutritional myopathy, in severely affected muscles almost all fiber types are affected. In cases with myocardial involvement, myocardiocyte necrosis and mineralization are present. If the animal survives, the necrotic myocardiocytes are replaced by fibrovascular connective tissue that matures to form a scar.

A provisional diagnosis of nutritional myopathy is based on typical history, increases in serum concentrations of CK and AST, and characteristic gross and histopathologic findings. The diagnosis is confirmed by detecting deficient concentrations of selenium or vitamin E in blood of live animals or in liver samples obtained at necropsy. If horses live long enough, myofiber regeneration can restore the muscles to normal. This disorder in foals can be prevented by supplementing the ration of mares with selenium during gestation. Foals born in selenium-deficient areas can also be given injectable vitamin E and selenium soon after birth. Young adult horses should be given sufficient dietary vitamin E and selenium. Treatment with selenium and vitamin E after the onset of clinical signs is far less effective than prevention.

Ionophore Toxicity. The pathogenesis of ionophore toxicity is discussed in the section on Toxic Myopathies. Horses are exquisitely sensitive to ionophores and succumb to very small doses. Ionophores may be present as contaminants within horse feed, or the horse may be accidentally fed ionophore-containing feeds intended for other domestic animals.

Most of the available literature relates to monensin toxicity, but the effects of other ionophores should be similar. In acute monensin toxicity, death occurs because of shock and cardiovascular collapse, and no specific lesions are seen on postmortem examination within the first 48 hours, although these may be stained diffusely pink by myoglobin. If the horse survives 3 to 4 days, affected skeletal and cardiac muscles often contain pale streaks (Fig. 15-33, *A*) and, microscopically, cardiac muscle necrosis and segmental necrosis of skeletal muscle is present (Fig. 15-33, *B*; see Fig. 15-11, *B*), with concurrent increases in serum concentrations of CK and AST, which may be severe. Given the profound sensitivity of horses to ionophores, ionophore toxicity in horses is typically the result of a single dose and thus the lesion is a monophasic multifocal process. This helps to differentiate ionophore toxicity from nutritional

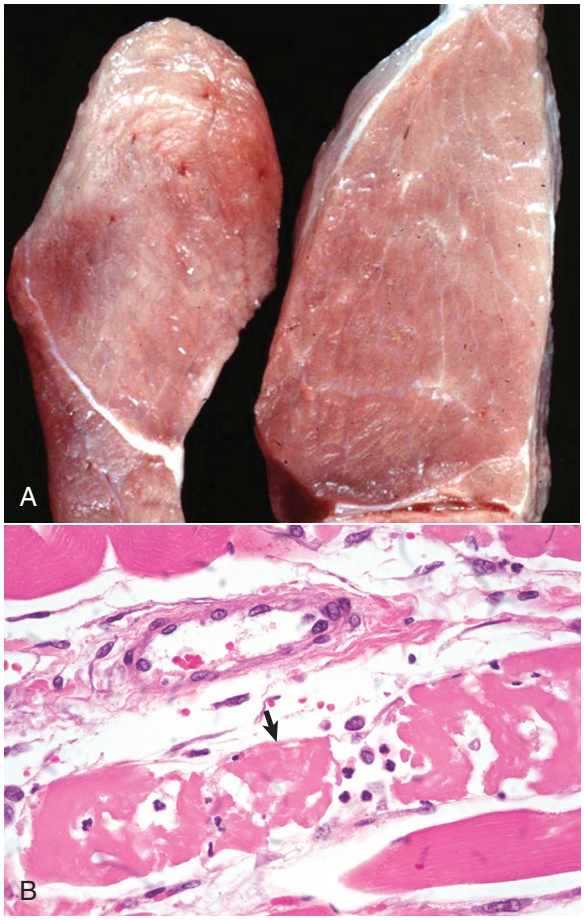


Figure 15-33 Ionophore Toxicity, Monensin, Skeletal Muscle. **A,** Necrosis. The pale white to gray foci are areas of necrotic myofibers. Myocardium will often contain similar lesions. **B,** Segmental myofiber necrosis (2 days old), longitudinal section, horse. The segment of myofiber *(arrow)* visible here is necrotic, fragmented, and infiltrated by macrophages and neutrophils. Note the intact basal lamina and endomysium on both sides of the myofiber, which will contain the regenerating myofiber and thus facilitate resolution. Ionophore toxicity results in calcium overload and death of skeletal (also cardiac) myocytes. Formalin fixation, H&E stain. (**A** courtesy Dr. J. Wright, College of Veterinary Medicine, North Carolina State University; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

myopathy, which is often polyphasic. Both type 1 and type 2 fibers are affected. If the horse survives, necrosis is followed by myofiber regeneration, which can restore the muscles to normal, but necrotic myocardiocytes are replaced by fibrosis because of the lack of significant regeneration by myocardiocytes. Horses dying at 14 days after ionophore exposure often have normal skeletal muscles and extensive myocardial fibrosis. Acute cardiac failure and death because of myocardial scarring can occur months to years after apparent clinical recovery from ionophore exposure.

Diagnosis is based on a history that includes both ingestion of ionophores and the presence of the characteristic gross or histopathologic findings. Analysis of feed or stomach contents for ionophores is definitive. Treatment for ionophore-intoxicated horses is supportive because there is no specific therapy.

Plant Toxicities. A number of toxic plants are known to cause muscle necrosis in horses (see also Toxic Myopathies). These include *Cassia occidentalis* (coffee senna) and *Thermopsis* spp. Most plant-associated toxicities in horses are associated with plants growing in pastures or in baled hay. Necrosis is most often polyphasic, indicating a prolonged period of ingestion. Cardiac myonecrosis may or may not also be present. In the United Kingdom and less commonly in the Midwestern United States, a syndrome of pasture-associated myonecrosis caused by ingestion of the toxin hypoglycin A, contained within seeds of *Acer negundo* (box elder) trees, occurs in horses. This disorder has also been called *atypical myoglobinuria*.

Inherited or Congenital Myopathies and Myotonic Disorders

Hyperkalemic Periodic Paralysis. Hyperkalemic periodic paralysis (HYPP) is a myotonic disorder that affects horses whose ancestry traces back to a quarter-horse stallion named *Impressive*. Affected horses generally have remarkably well-defined muscle groups, which has led to their popularity for showing in halter. The disease is inherited as an autosomal dominant disease; therefore affected horses can be either heterozygotes or homozygotes. Homozygous foals often have a distinctive laryngeal muscle dysfunction that results in laryngospasm and labored breathing. Most homozygous horses do not survive; if they do, they are invalids.

The underlying defect in HYPP is a point mutation in the gene encoding the α subunit of the skeletal muscle sodium channel. This defect causes abnormal (delayed) inactivation of sodium channel activity, resulting in membrane instability and continuous muscle fiber electrical activity, which is reflected in EMG findings (see later discussion). The pathogenesis of clinical signs of HYPP is complex and not entirely understood, either in horses or in human beings with a similar disorder. Affected heterozygotes have a mosaic of abnormal and normal sodium channels, and resting muscle membrane potentials are typically lower than normal. This leads to an increased likelihood of electrical generation of a prolonged muscle action potential, resulting in transient myotonia. When abnormal sodium channels are activated, the response to the resulting abnormally increased intracellular sodium is release of potassium into the extracellular space and bloodstream, resulting in hyperkalemia. Hyperkalemia is not, however, a consistent finding. Feeding of high-potassium feeds, such as alfalfa products or feeds with added molasses, can precipitate clinical signs of HYPP, possibly by activating abnormal sodium channels. Another potential consequence of prolonged activation of abnormal sodium channels is inactivation of normal sodium channels, resulting in flaccid paralysis and collapse. This result would explain the typical signs seen during episodes, which include transient muscle spasm (myotonia), with protrusion of the third eyelid, followed by generalized flaccid paralysis. Decreased muscle temperature, as can occur as a result of a chilling rain, can precipitate episodic collapse in HYPP horses, possibly by decreasing the activity of the muscle sodium-potassium exchanger (the Na-K ATPase), an important means by which affected muscle compensates for abnormal sodium channel activity. Postanesthetic recumbency and anesthesia-associated hyperthermia have also been seen in HYPP horses. Affected horses can appear normal for many years, can have multiple episodes of collapse, or can die acutely. Serum concentrations of CK and AST are generally normal. Abnormal ionic fluxes occur at all times in affected horses, and concentric needle EMG between paralytic episodes reveals characteristic persistent myotonic bursts.

There are no gross pathologic findings in horses with hyperkalemic periodic paralysis other than gross prominent muscling. Skeletal muscle dysfunction in HYPP horses is due to abnormal ionic fluxes that can lead to spasms and weakness; therefore affected skeletal muscle is generally histologically normal. In some cases, scattered

intracytoplasmic vacuoles (vacuolar myopathy) can be present in type 2 fibers. The characteristic pathologic finding of HYPP is only evident at the ultrastructural level, where dilated terminal cisternae of the sarcoplasmic reticulum are found.

Diagnosis can be made with reasonable certainty based on characteristic clinical signs (muscle spasms often leading to flaccid paralysis) and clinicopathologic findings (hyperkalemia) in a horse of Impressive line breeding. Myotonic bursts with concentric needle EMG are also diagnostic. The simplest and most reliable test, however, is a DNA-based test performed on peripheral white blood cells or, as described more recently, on cells obtained from the base of pulled mane or tail hairs. Treatment consists of feeding a low-potassium diet, which means avoiding alfalfa products and molasses. A low-potassium diet can be successful in controlling signs in many cases. More severe cases can be treated with the diuretic acetazolamide, which causes increased urinary excretion of potassium. Acute episodes can be treated with intravenous dextrose or insulin or oral sugar solutions such as sugar syrup. Administration of glucose to stimulate insulin secretion, or of insulin itself, aids in alleviating signs by helping drive the intracellular movement of potassium along with glucose.

Equine Polysaccharide Storage Myopathy. Equine polysaccharide storage myopathy (EPSSM) is a myopathy most commonly recognized in quarter horse, warm blood, Arabian, Morgan, pony of the Americas, and draft-related breeds. It also occurs in many other horse and pony breeds, including miniature horses. Surveys of equine muscle samples have revealed an astonishingly high incidence of approximately 66% in all draft-related horses and approximately 30% in all light horses. Not all affected horses exhibit obvious clinical signs of muscle dysfunction. This disorder is inherited as an autosomal dominant trait.

In contrast to other glycogenoses affecting skeletal muscle, to date no abnormality in the glycolytic or glycogenolytic pathways in skeletal muscle has been identified, making this equine disorder unique, but an underlying carbohydrate metabolic disorder is still suspected. Affected horses appear to have a more rapid intramuscular uptake of blood glucose than controls, although the exact mechanism for this phenomenon is still unknown. A point mutation in the skeletal muscle glycogen synthase 1 (GYS1) gene has been associated with some, but not all, cases of EPSSM. A DNA test for this mutation is available, and horses with GYS1 mutations are sometimes classified as EPSSM type 1. Abnormal accumulation of intracytoplasmic glycogen (confirmed by being PAS-positive, amylase-sensitive) within type 2 fibers is the histologic finding. In severe cases, aggregates of abnormal glycogen are eventually ubiquitinated, resulting in amylase-resistant inclusions composed of glycogen and filamentous protein. Certain breeds, such as quarter horse and draft-related breeds, seem to be most prone to the development of amylase-resistant inclusions, whereas glycogen aggregates are more common in other breeds. The explanation for this difference is as yet unknown, although breeds prone to developing amylase-resistant inclusions are also those breeds most likely to have the GYS1 mutation.

Clinical signs are variable, but all are thought to be caused by insufficient energy production by affected muscle fibers. Abnormal myofiber function caused by architectural alteration secondary to intramyofiber deposition of complex polysaccharide is also a possible mechanism, but the excellent response to therapy, even in horses with severe intramyofiber inclusions of accumulated polysaccharide, suggests that this is less significant than is altered energy metabolism. Recurrent exertional rhabdomyolysis (see later discussion) is a commonly recognized sign, but unexplained pelvic limb lameness is even more common than clinical rhabdomyolysis. Affected horses can also have a stiff gait, symmetric muscle atrophy, back soreness, muscle cramping resulting in abnormal hind limb flexion characteristic of shivers, and bilateral pelvic limb or generalized weakness. In draft horses, sudden onset of spontaneous recumbency or postanesthetic recumbency because of myopathy can occur. Serum concentrations of CK and AST are markedly increased after episodes of exertional rhabdomyolysis but may be only mildly to moderately increased in affected horses after exercise or onset of recumbency. Normal serum concentrations of CK and AST in affected horses are thought to indicate that the muscle dysfunction is not accompanied by overt myonecrosis. Concentric needle EMG may reveal abnormal spontaneous activity (scattered positive sharp waves and fibrillations).

In severe cases, in which horses have died or been euthanatized because of rhabdomyolysis or recumbency, muscles may be pale pink or diffusely red-tinged (myoglobin staining), which can be mistaken for autolysis. Multifocal pale zones may be present (see Fig. 15-35, *A*). In draft horses and sporadically in horses of other breeds, chronic myopathy can result in overall reduction in muscle mass. Muscles in severely affected draft horses can also be of normal size but may contain pale streaks where myofibers have been replaced by fat. The most severely affected muscles are those of the proximal hind limb (especially gluteal, semimembranosus, and semitendinosus muscles) and epaxial muscles of the back (e.g., longissimus), although any of the large "power" muscle groups, including pectoral and shoulder girdle muscles, can be affected. Swollen, dark kidneys (pigmentary nephrosis) caused by myoglobinuria can be seen in horses dying with severe rhabdomyolysis. The extent of overt myofiber necrosis is extremely variable; massive necrosis or regeneration can be seen after severe rhabdomyolysis, whereas only minimal scattered necrotic fibers may be seen in recumbent horses. Lesions are monophasic if there has been only a single bout of exertional rhabdomyolysis, or they are polyphasic if there have been repeated bouts of less severe exercise-induced injury. Abnormal polysaccharide is always present, but fiber necrosis is uncommon in muscle biopsy samples taken from affected horses while they are clinically normal.

The characteristic histologic finding is aggregates of intracytoplasmic material that stain positively with the PAS reaction for glycogen (Fig. 15-34, *A*). In severe cases, multiple pale intracytoplasmic inclusions are also present in H&E stained sections (Fig. 15-34, *B*). These inclusions are PAS-positive (Fig. 15-34, *C*) and resist digestion by amylase and are thus not glycogen. Terms used to describe this amylase-resistant material include *amylopectin*, *polyglucosan*, and *complex polysaccharide*. In chronic cases, myofibers also have chronic myopathic change (atrophy, hypertrophy, or internal nuclei), and fat replacement of myofibers after myofiber loss can occur in severely affected cases.

At this time, the detection of the GYS1 mutation provides a definitive diagnosis of EPSSM, but this test is not very sensitive. The most sensitive test for diagnosis of EPSSM depends on finding characteristic histopathologic changes in muscle samples of horses with appropriate clinical signs. Gluteal, semimembranosus, or semitendinosus muscle samples are preferred, although changes in longissimus muscle are also found, especially in horses with back pain. A presumptive diagnosis of EPSSM can be made based on characteristic clinical findings in a predisposed breed. Treatment has relied on altering the diet to minimize starch and sugar intake (less than 15% of total daily calories) and maximize fat intake (at least 20% to 25% of total daily calories from fat). Grains and sweet feeds are replaced by high-fiber, low-starch, low-sugar feeds, with added fat in the form of vegetable oil, powdered fat, or high-fat rice bran supplements. Providing the horse with regular exercise and as much time

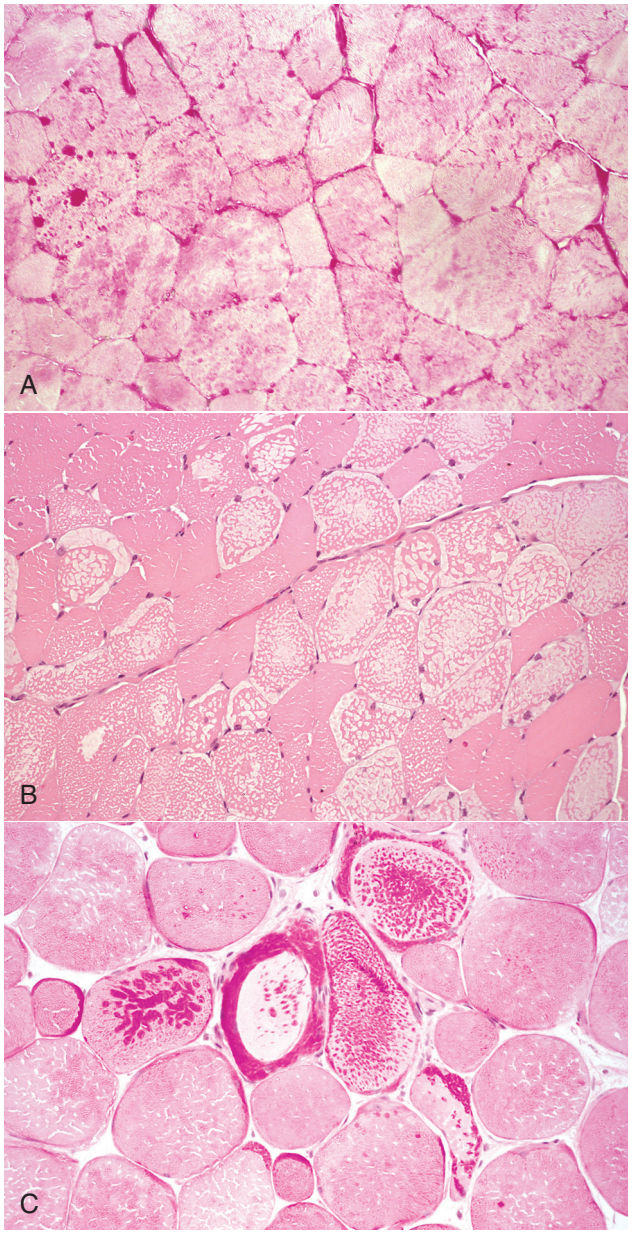


Figure 15-34 Equine Polysaccharide Storage Myopathy, Semimembranosus Muscle, Transverse Sections, Horse. A, Note the increased amount of and irregularly distributed dark-pink staining glycogen. Abnormal aggregates are present both beneath the sarcolemma and within the cytoplasm. Formalin fixation, PAS reaction. **B,** Severe form. Numerous myofibers contain multiple pale *(very light pink moth-eaten appearance)* subsarcolemmal and intracytoplasmic inclusions of stored polysaccharide. Formalin fixation, H&E stain. **C,** These inclusions shown in **B** stain intensely pink-red with PAS but are not digested by amylase *(not shown)* and are characteristic of what is called *complex polysaccharide*, *amylopectin*, or *polyglucosan*. Formalin fixation, PAS reaction. (Courtesy Dr. B.J. Cooper, College of Veterinary Medicine, Oregon State University.)

as possible in a pasture or paddock are also important. Treatment is very successful in most cases.

Glycogen Brancher Enzyme Deficiency. Glycogen brancher enzyme (GBE) deficiency, or glycogenosis type IV, is a disorder caused by a congenital lack of a glycogenic enzyme, GBE, and is an emerging disease in quarter horses and American paint horses. It is inherited as an autosomal recessive trait. Affected foals may be aborted, stillborn, or weak at birth or can have contracted tendons, rhabdomyolysis, or cardiac failure at an early age. The consequence of GBE deficiency is the accumulation of long unbranched chains of glucose within cells that leads to abnormal glycogen formation and intramyofiber deposits. These molecules would normally be converted into glycogen in the presence of GBE in the final step in the formation of glycogen. There are no specific gross pathologic findings. Pulmonary edema may be found in foals that die from cardiac failure. Characteristic histologic findings are round hyaline inclusions resembling amylopectin (polyglucosan bodies) within skeletal and cardiac myocytes, especially Purkinje fibers, and to a lesser degree within hepatocytes. Unlike glycogen, inclusions are PAS-positive and resistant to amylase digestion. As with other carbohydrate metabolic defects, a lack of energy production by affected fibers is thought to underlie cellular dysfunction. Disruption of cytoarchitecture caused by amylopectin deposition may also contribute. Analysis of peripheral blood or skeletal muscle for GBE activity identifies affected animals with severely reduced GBE activity and carriers in which GBE activity is moderately reduced. A DNA test to detect carriers and affected horses using pulled mane or tail hairs is now available. There is no treatment for this disorder.

Myotonia and Mitochondrial Myopathy. A myotonic disorder occurs occasionally in horses, and a mitochondrial myopathy has been described in an Arabian horse. These disorders are discussed in more detail in E-Appendix 15-1.

Other Equine Myopathies

Exertional Rhabdomyolysis. Equine exertional rhabdomyolysis (tying up, azoturia, Monday morning disease, setfast, and blackwater) is characterized clinically by sudden onset of stiff gait, reluctance to move, swelling of affected muscle groups (especially gluteal), sweating, and other signs of pain and discomfort. Serum concentrations of CK and AST are often markedly increased. Signs may appear during or immediately after exercise, but only rarely is exertional rhabdomyolysis associated with exhaustive exercise. In severely affected horses, even minimal exercise, such as walking out of a stall, can cause clinical signs. High grain feeding and lack of regular exercise have been recognized to be factors leading to exercise-induced muscle injury for many years. Previous theories regarding the pathogenesis of equine exertional rhabdomyolysis include development of muscle lactic acidosis, vitamin E and/or selenium deficiency, hypothyroidism, and systemic electrolyte abnormalities. Only recently have studies concluded that lactic acidosis is not a finding in horses with exertional rhabdomyolysis, that hypothyroid horses show no signs of degenerative myopathy, and that electrolyte abnormalities as a primary cause of equine exertional rhabdomyolysis are rare. It is still thought that vitamin E or selenium deficiency can exacerbate signs of exertional rhabdomyolysis in predisposed horses, but neither vitamin E nor selenium deficiency is considered a primary cause. Recent studies have found that affected horses typically have an underlying myopathy, most often equine polysaccharide storage myopathy (EPSSM). There is evidence that recurrent exertional rhabdomyolysis in thoroughbreds is the result of abnormal calcium homeostasis within skeletal muscle, although some affected thoroughbreds have been found to have EPSSM. Because muscle necrosis per se is not painful and does not cause muscle swelling, it is suspected that other factors play a role in this disorder in the horse. These factors include oxidative injury to muscle membranes occurring secondary to segmental necrosis and the subsequent production of oxygen-derived free radical compounds and vascular compromise resulting in ischemia (i.e., compartment syndrome when muscle damage occurs in a muscle with a

tight and relatively nonexpandable fascia such as the gluteal and longissimus muscles). Oxidative injury may explain the perceived benefit of supplemental vitamin E and selenium to affected horses.

Gross findings are similar to those described for equine polysaccharide storage myopathy (EPSSM)—that is, initially areas of muscle that are pale pink or diffusely red-tinged (Fig. 15-35, *A*). Histologic findings are localized or widespread muscle fiber necrosis (Fig. 15-35, *B*), followed by the usual sequence of events: macrophage infiltration and regeneration. Affected fibers are primarily type 2 fibers. Lesions can be either monophasic or polyphasic.

Diagnosis is based on typical clinical signs and clinicopathologic evidence of muscle injury (increased activity of CK or AST). Treatment for an acute episode includes nonsteroidal antiinflammatory agents, acepromazine, and rest. Careful evaluation of the patient for evidence of renal damage ([pigmentary] myoglobinuric nephrosis) because of myoglobin released from damaged muscle is indicated. Long-term treatment and prevention include correction of any concurrent electrolyte, mineral, or vitamin deficiencies and, most important, a change in diet to one that is high in fat and fiber and low in starch and sugar, as described for horses with EPSSM (see the section on Inherited or Congenital Myopathies). Thoroughbreds with recurrent exertional rhabdomyolysis caused by suspected underlying skeletal muscle calcium-handling abnormalities also respond well to this type of diet.

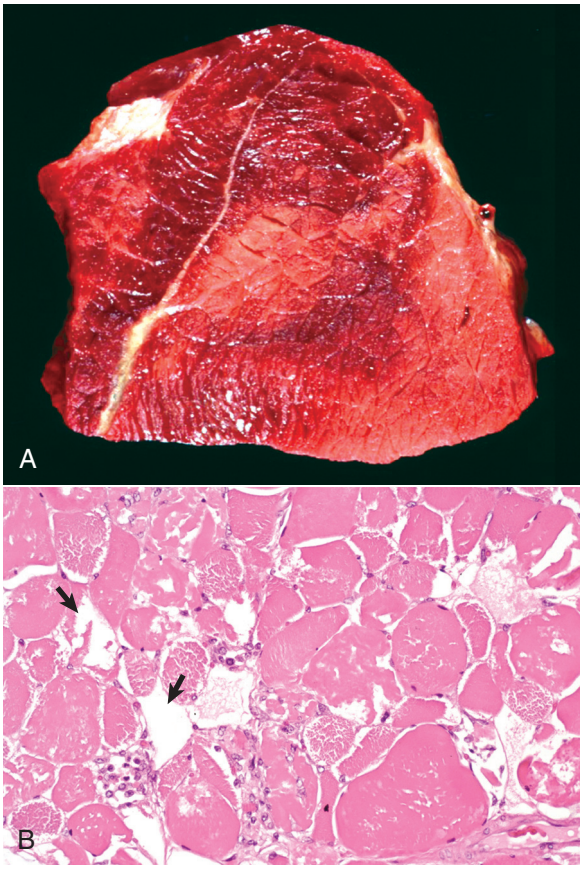


Figure 15-35 Acute Rhabdomyolysis, Skeletal Muscle, Horse. **A,** Affected muscles may be pale pink or diffusely red-tinged, which can be mistaken for autolysis. Multifocal pale zones may also be present. **B,** Segmental myofiber necrosis, semitendinosus muscle, transverse section. Most of the myocytes are necrotic and at the stage of coagulation necrosis. In a few myofibers, necrosis is at a later stage and the necrotic sarcoplasm has lysed, leaving empty sarcolemmal tubes *(arrows)*. A couple of necrotic myofibers are at an even later stage and contain a small number of macrophages. Formalin fixation, H&E stain. (**A** courtesy Dr. W. Crowell, College of Veterinary Medicine, The University of Georgia; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **B** courtesy Dr. B.J. Cooper, College of Veterinary Medicine, Oregon State University.)

Malignant Hyperthermia. In horses, malignant hyperthermia (MH) can occur during general anesthesia. Hyperthermia can also occur during recovery from anesthesia, which is sometimes called *hypermetabolism* to distinguish it from true MH. A genetic defect in the skeletal muscle ryanodine receptor, similar to that in MH in human beings, dogs, and pigs, has been identified in some horses with MH triggered by anesthetic agents. A genetic test for the MH mutation is available. Some horses affected with a hyperthermia-like syndrome during anesthesia or during recovery from anesthesia have hyperkalemic periodic paralysis (HYPP) or equine polysaccharide storage myopathy (EPSSM), but in some cases the exact cause of the hyperthermia is not clear. It is likely that, as is similar to hyperthermia in human beings, a variety of underlying myopathies, especially those that result in uncoupling of mitochondria within skeletal myocytes (see the section on Malignant Hyperthermia), can predispose animals to anesthesia-associated hyperthermia. Studies of muscle from horses with exertional rhabdomyolysis have detected loosely coupled mitochondria, which could predispose them to MH–like episodes. The extent of overt muscle fiber necrosis caused by hyperthermia varies but is often severe.

Ischemic Myopathy. In addition to vascular damage resulting from clostridial toxins or immune-mediated vasculitis, ischemic myopathy of pectoral and limb muscle can be seen in recumbent horses as the result of pressure interfering with vascular perfusion. Once the horse is moved or is standing, reperfusion injury can occur. Development of compartment syndrome can contribute to ischemic injury (see the section on Disturbance of Circulation). Ischemic myopathy of the abdominal muscles can be seen after prolonged pressure from being supported in a sling. In these cases, affected muscles generally show degenerative or regenerative changes that are all at about the same stage (monophasic necrosis). Concurrent necrosis and regeneration (polyphasic necrosis) can also be seen in horses that are in a sling or recumbent for an extended period of time such as for several days. Recovery depends on the extent of the ischemic area and the ability of the muscle to regenerate (i.e., depending on whether the basal lamina is intact and whether satellite cells have become necrotic from ischemia).

Transient pelvic limb muscle ischemia as the result of aortoiliac mural thrombosis occurs in horses. The cause of the thrombosis is unknown, although it has been attributed to migration of strongyle larvae through the aortic wall, damaging the intima. Typically the thrombus is not occlusive, and clinical signs of pelvic limb dysfunction occur only during or after strenuous exercise, such as racing. A short-stride gait and a decreased surface temperature of the distal portion of the affected limb during episodes are characteristic. Because the ischemia is transient, pathologic studies are few. But overt myofiber necrosis is thought to be minimal, and recovery is typically rapid. Surgery to remove the thrombus can be curative.

Postanesthetic Myopathy. Degenerative myopathy can occur in horses undergoing prolonged recumbency during general anesthesia. In some cases, muscle damage may be the result of ischemia from systemic hypotension leading to muscle hypoxia or from pressure caused by the weight of large muscle masses during recumbency, especially when adequate padding has not been provided. Underlying myopathy of various types also predisposes to postanesthetic myopathy. In ischemic damage, the location of the lesions depends

on the position of the horse during anesthesia. In dorsal recumbency, the gluteal and the longissimus muscles are ischemic; in lateral recumbency, the triceps brachii, pectoralis, deltoideus, and brachiocephalicus muscles of the leg under the body become ischemic. The basic mechanism is that the pressure in the muscle exceeds the perfusion pressure in the capillaries. The use of adequate padding under the recumbent horse and the maintenance of normal blood pressure during anesthesia have greatly reduced the incidence of postanesthetic myopathy from muscle ischemia in horses. These days, underlying myopathy, particularly equine polysaccharide storage myopathy (EPSSM), appears to be the most common cause of postanesthetic myopathy in horses.

Endocrine Myopathies. Although hypothyroidism is often suggested to be a cause of muscle dysfunction in the horse, studies of experimentally thyroidectomized horses have failed to support hypothyroidism as a cause of equine myopathy. Pituitary hyperfunction caused by adenoma or hyperplasia in older horses, causing equine Cushing's disease, is the most common equine endocrine disorder causing muscle atrophy (preferentially of type 2 fibers) and weakness. The characteristic pot-bellied appearance of affected horses is thought to be secondary to abdominal muscle weakness.

Denervating Diseases

Localized or generalized muscle dysfunction can be caused by disorders affecting motor neurons or peripheral nerves. Several syndromes of peripheral nerve dysfunction are recognized in the horse.

Peripheral Neuropathy. Injury to the motor nerves in a peripheral nerve results in localized muscle atrophy and dysfunction of those myofibers innervated by those nerves. Damage to the suprascapular nerve results in unilateral scapular muscle (supraspinatus and infraspinatus) atrophy, and the clinical condition is known as sweeney. In working draft horses, this nerve can be compressed by a poorly fitted harness collar. In nonharness horses, trauma is the most common cause. Traumatic injury to the radial nerve or axillary plexus is also relatively common in horses.

Stringhalt is a sporadic pelvic limb neuropathy characterized by an exaggerated flexion of one or both hind limbs. It can be caused by trauma to the hind leg, ingestion of plant toxins, or can be of unknown cause. Outbreaks of stringhalt in pastured horses in Australia and New Zealand are the result of ingestion of *Hypochoeris radicata* and related species, also known as flatweed, false dandelion, and hairy cat's ear. Lesions of denervation atrophy are found in the distal lateral digital extensor muscle, and surgical removal of this muscle is one method of correction. *Hypochoeris radicata* grows prolifically in the Pacific Northwest, and a similar syndrome of plant-induced stringhalt is said to occur there, but evidence to support this hypothesis has been difficult to find. Feeding trials at Oregon State University have failed to reproduce the syndrome.

Fibrotic myopathy is a condition most often attributed to hamstring (semitendinosus, semimembranosus, and biceps femoris) muscle trauma, but pelvic limb neuropathy as a result of trauma or unknown causes can also cause fibrotic myopathy. Fibrotic myopathy causes a restriction of the forward swing of the affected pelvic limb. Gross examination often reveals pale, firm muscle caused by collagen deposition. When fibrotic myopathy is actually the result of neuropathy, affected muscle shows characteristic microscopic lesions of chronic denervation atrophy.

Laryngeal hemiplegia is a well-documented condition in horses in which degeneration of nerve fibers within the left recurrent laryngeal nerve results in unilateral laryngeal muscle denervation atrophy (see Fig. 15-16) and laryngeal dysfunction. Affected horses often make a characteristic respiratory noise during exercise, hence the name *roaring*. There are many possible causes of injury to the left recurrent laryngeal nerve, including extension of infections from the guttural pouches or tumors in that area, lead toxicity, and direct trauma. Most cases, however, are considered idiopathic. Although the exact cause of idiopathic laryngeal hemiplegia in horses is not known, the fact that it occurs only in tall, long-necked horses, and virtually never in ponies, suggests that whatever the mechanism of injury, very long nerves (particularly the very long left recurrent laryngeal nerve of tall long-necked horses) are predisposed.

Lead intoxication can also cause generalized peripheral neuropathy resulting in muscle atrophy and weakness mimicking equine motor neuron disease (see later discussion). Polyneuritis equi (neuritis of the cauda equina) and peripheral nerve lymphoma also cause denervation atrophy in horses. Polyneuritis equi most often involves the caudal nerve roots and facial nerves, and lymphoma has been found affecting multiple nerve roots or selectively involving the facial nerve.

Motor Neuronopathy. Damage to motor neurons in the nuclei of the brainstem or in the ventral horns of the spinal cord will result in Wallerian degeneration of peripheral nerves. In the horse, protozoal myeloencephalitis caused by *Sarcocystis neurona* is a common cause of unilateral denervation atrophy, usually of facial or gluteal musculature because of preferential damage to cranial nerve nuclei in the brainstem or motor neurons of the lumbosacral intumescence. Affected horses often also have Wallerian degeneration in spinal cord white matter and exhibit ataxia and proprioceptive deficits.

Equine motor neuron disease occurs as the result of severe and prolonged vitamin E deficiency, which leads to motor neuron degeneration. Clinical signs are sudden onset of rapid muscle wasting, weakness, trembling, and increased time spent in recumbency. Type 1 motor neurons and muscles are preferentially affected, supporting the proposed pathogenesis of oxidative injury to motor neurons secondary to vitamin E deficiency. The severe denervation atrophy occurring in postural muscles (medial head of the triceps, vastus intermedius, and sacrocaudalis dorsalis medialis) in horses with motor neuron disease often results in a remarkable pale yellow-tan color (Fig. 15-36; see Fig. 15-9, C) and gelatinous texture of the affected muscle. Severely affected horses may become persistently recumbent, leading to death or euthanasia. In some cases, high-dose vitamin E supplementation (10,000 IU or more per day) can halt the progression of the disorder, and affected horses on vitamin E therapy can even develop some compensatory muscle hypertrophy and regain muscle mass. There is little or no evidence of reinnervation in this disorder, and affected horses are considered disabled for life.

Disorders of Cattle

Although cattle have not been selected for muscle performance, many breeds have been selected for meat quality. This process has led to selection for at least one genetic disorder. Disorders affecting muscle can have a profound economic effect on the cattle industry.

Bacterial and Parasitic Myopathies

Clostridial Myositis (Blackleg). Clostridial myositis (blackleg), due to *Clostridium chauvoei*, is an extremely economically important disease that is most common in beef cattle. It can also occur in dairy cattle, especially those housed in free-stall barns where jostling and muscle bruising are possible. *Clostridium chauvoei* is a spore-forming, Gram-positive anaerobic bacillus. Its spores are ubiquitous in the soil and manure, and after ingestion they are

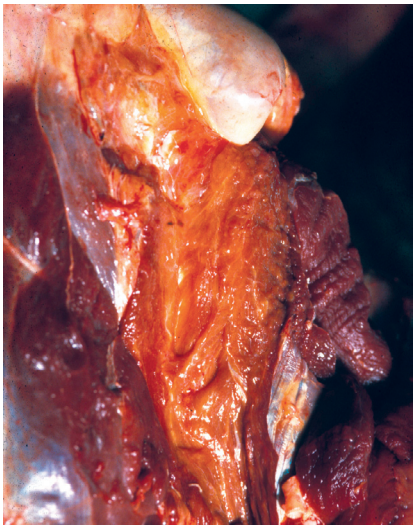


Figure 15-36 Denervation Atrophy, Equine Motor Neuron Disease, Medial Triceps Muscle, Horse. The medial triceps muscle *(center, top to bottom)*, a type 1 predominant postural muscle deep in the foreleg, is diffusely pale tan and gelatinous in appearance because of severe denervation atrophy. The adjacent muscles (*left* and *right*) have a normal appearance *(dark red)*. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University. For histopathologic findings, see Fig. 15-18.)

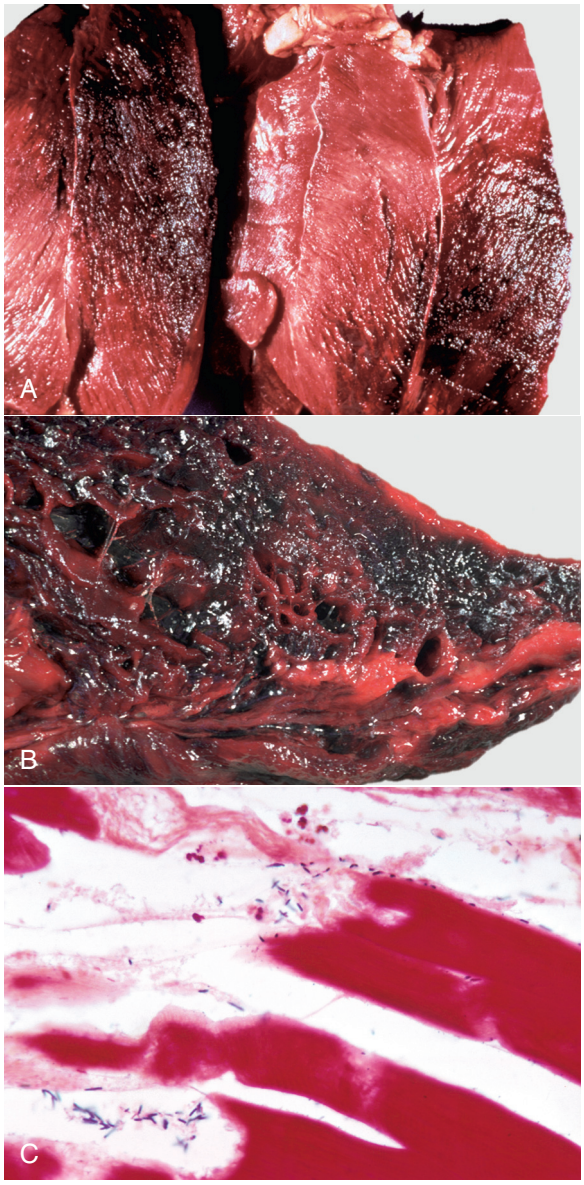


Figure 15-37 Blackleg, Hemorrhagic-Necrotizing Myositis (*Clostridium Chauvoei*), Thigh Muscle, Cow. A, The dark red areas are caused by hemorrhagic necrosis of the affected muscle. These lesions are characteristic of blackleg. **B,** *Clostridium chauvoei* can also produce substantial quantities of gas within infected tissues as shown here by the numerous ("pseudocystic") spaces within hemorrhagic and necrotic muscle. **C,** Gram-positive bacilli *(blue-stained rods)* are present in the affected tissue. Formalin fixation, Gram stain. (**A** courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University. **B** and **C** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

capable of crossing the intestinal mucosa, entering the bloodstream, and being carried to skeletal muscles. The spores lie dormant until localized trauma to the muscle, which in cattle is most often caused by bruising during handling in a chute or from trauma in a crowded feedlot, results in muscle damage and localized hypoxia and anoxia. The resultant anaerobic conditions allow the spores to activate and the bacteria to proliferate and produce toxins that cause capillary damage with resultant hemorrhage, edema, and necrosis of adjacent myofibers.

The most common presentation is acute death. Signs before death are referable to toxemia; to the heat, swelling, crepitus, and dysfunction of the affected muscle group; and to fever. Serum concentrations of CK and AST are typically increased. Locally extensive hemorrhage and edema, often with crepitus caused by gas bubbles, are seen in affected muscles and in overlying fascia and subcutaneous tissue. Necrotic muscle fibers appear dark red to red-black. Lesions are either wet and exudative (early lesions) or dry (later lesions) (Fig. 15-37, A). A characteristic odor of rancid butter from butyric acid is typical. Cardiac muscle can also be involved. In other parts of the body, hemorrhages and edema can occur from the toxemia. Affected carcasses autolyze rapidly, likely because of the effects of clostridial toxins on tissue and of high body temperature before death. Histologically, locally extensive areas of muscle fibers undergoing coagulation necrosis and fragmentation are seen, as are interstitial edema and hemorrhage. Overt vasculitis is not seen. Gas bubbles are typical. Gram-positive bacilli whose appearance is compatible with that of *Clostridium chauvoei* may be demonstrable within affected muscle (Fig. 15-37, C).

Isolation of *Clostridium chauvoei* on anaerobic media or visualization by fluorescent antibody techniques are useful for the diagnosis of blackleg but are confirmatory only if typical gross and histopathologic lesions are present because dormant spores of *Clostridium chauvoei* can be found in normal muscle. The vaccination history and evaluation of husbandry practices are also important; unvaccinated or inadequately vaccinated (i.e., vaccinations not up to date) animals in situations in which muscle trauma is possible are most at risk. There is generally no effective treatment for cattle with blackleg, and death occurs rapidly. Prevention is the best approach. Vaccination against clostridial toxins and maintenance of a safe environment are critical.

Botulism. Botulism caused by ingestion of *Clostridium botulinum* toxin from contaminated feed or soil occurs in cattle, and clinical signs of flaccid paralysis and pathogenesis are similar to those in the adult horse. Cattle are most susceptible to type C and D botulinum toxins, and herd outbreaks are possible. Cattle, however, are much more resistant to botulism than are horses. Botulinum toxin, most

often from animal cadavers such as mice or rats, within silage, haylage, or hay is the most common cause of outbreaks of botulism in cattle. Abnormal eating habits (pica) can result in ingestion of *Clostridium botulinum* toxin from the soil or carrion. Botulism in cattle is usually fatal.

Pyogenic Bacteria. Cattle are prone to develop abscesses and cellulitis (fasciitis) from infections with pyogenic bacteria, most commonly *Trueperella* (*Arcanobacterium*) *pyogenes*. Abscesses in muscle occur most commonly in the hind leg. Swelling and lameness of the affected limb caused by widespread necrotizing cellulitis and myositis are seen.

Trueperella (*Arcanobacterium*) *pyogenes* is a ubiquitous bacterium that can infect muscle by two routes: by direct contamination of wounds and injection sites and hematogenously. The bacterium can be found within the reproductive tract of cows and within the rumen wall, and it has been speculated that *Trueperella* (*Arcanobacterium*) *pyogenes* from a transient bacteremia after parturition or from disruption of the rumen wall can result in colonization of damaged muscle. Lesions vary, depending on the virulence of the bacteria and the age of the lesions. They vary in extent from encapsulated intramuscular abscesses adjacent to the site of injection to a diffuse purulent cellulitis extending down the tissue and fascial planes (see Fig. 15-24). The cellulitis may be so severe as to involve much of the musculature of the affected limb. When abscesses are present, the gross appearance is of an encapsulated mass filled with thick, yellow-green, foul-smelling pus. In cases of cellulitis, pus dissects along fascial planes outside the muscle and between perimysial sheaths within muscles. Inflammation extends into the adjacent myofibers, resulting in myonecrosis and subsequent replacement by fibrous tissue. The greenish color of the exudate is distinctive, and small Gram-positive pleomorphic bacteria are often seen within tissue sections or cytologic preparations. *Trueperella* (*Arcanobacterium*) *pyogenes* is readily isolated on aerobic culture.

Actinobacillus lignieresii (Wooden Tongue). Infection of oral tissue, particularly of the tongue musculature (see Figs. 7-26 and 7-27), by *Actinobacillus lignieresii* results in a severe chronic granulomatous to pyogranulomatous and fibrosing myositis. Infection occurs through oral wounds or by penetrating plant fragments. Affected cattle have difficulty prehending and swallowing and often have excessive salivation. Histologic features include marked fibrosis caused by tissue destruction and chronicity and foci of inflammation containing eosinophilic material ("radiating clubs") and characteristic Gram-negative bacilli. Aggressive antibiotic therapy can be curative.

Actinomyces bovis (Lumpy Jaw). *Actinomyces bovis* frequently involves bones of the jaw, causing chronic granulomatous to pyogranulomatous and fibrosing osteomyelitis (see Fig. 16-58). Occasionally *Actinomyces bovis* involves the musculature of the tongue, causing gross and histologic lesions similar to those caused by *Actinobacillus lignieresii*. Gram stain reveals Gram-positive bacilli, which distinguishes this lesion from the Gram-negative *Actinobacillus lignieresii* infection.

Protozoal Myopathies. *Sarcocystis* spp. forming intracytoplasmic cysts (see Fig. 15-26) is a common incidental finding that may even be grossly visible as nodules within skeletal and cardiac myofibers of cattle (see Fig. 15-40). Massive infection may result in fever, anorexia, and progressive wasting, but this is uncommon. More often, *Sarcocystis* infection is diagnosed as an incidental finding at necropsy or during meat inspection at slaughter. If the cyst wall breaks down, a focus of myofiber necrosis and later granulomatous inflammation result.

Eosinophilic myositis is a disease of cattle thought to be a relatively uncommon manifestation of *Sarcocystis* infection that may involve hypersensitivity. There is overt green discoloration (see Fig. 15-10) of affected muscles caused by the massive infiltration of eosinophils (Fig. 15-38, *A* and *B*). This is accompanied by myofiber necrosis and, in chronic cases, fibrosis. Fragments of degenerating intralesional protozoa can sometimes be found (Fig. 15-38, *C*).

Neospora caninum can also infect cattle. Adults have no clinical disease, but infection of the fetus can cause multifocal nonsuppurative inflammation of skeletal muscle and heart and brain.

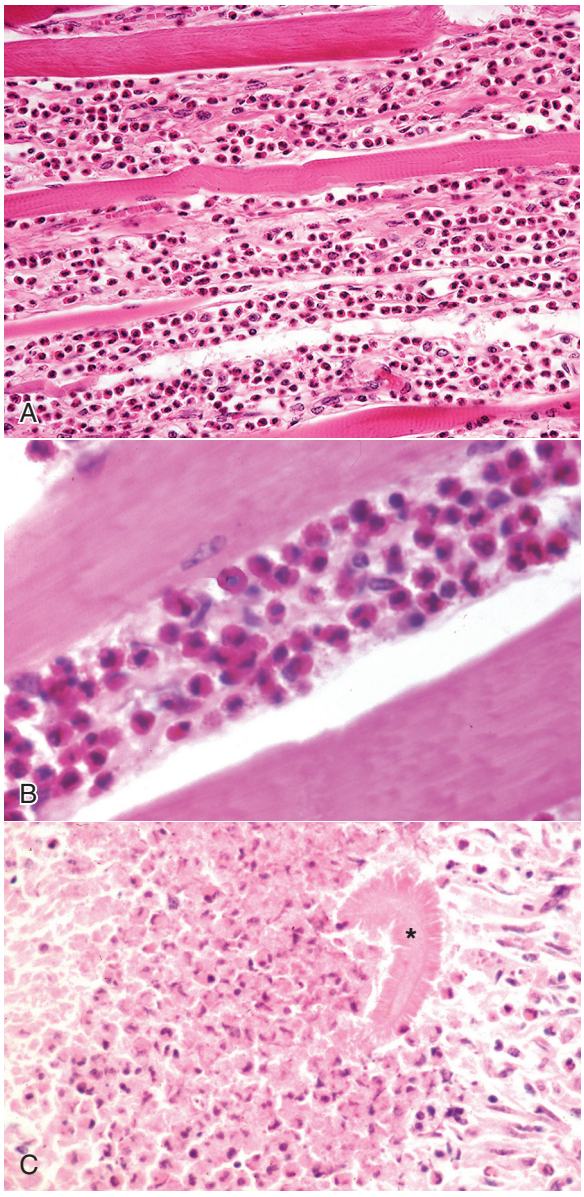


Figure 15-38 Bovine Eosinophilic Myositis, Skeletal Muscle, Longitudinal Section, Cow. A, Dense interstitial infiltrate of eosinophils has separated the muscle fibers, some of which are atrophic. Formalin fixation, H&E stain. **B,** Higher magnification demonstrating the large population of eosinophils in the inflammatory exudate. Formalin fixation, H&E stain. **C,** Degenerate *Sarcocystis* organism *(asterisk)* surrounded by degenerate eosinophils. Formalin fixation, H&E stain. (**A** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **C** courtesy Dr. R. Bildfell, College of Veterinary Medicine, Oregon State University.)

Nutritional and Toxic Myopathies

Nutritional Myopathy. Similar to horses, calves and young cattle are susceptible to nutritional myopathy caused by a selenium or (less commonly) vitamin E deficiency. But the profound involvement of temporal and masseter muscles ("maxillary myositis") that can occur in horses is not seen in cattle. In the latter species, the postural muscles and muscles of locomotion are most commonly affected. Muscles of affected calves appear pale pink to white, often in a patchy distribution and in cervical muscles used during suckling and "bumping" the udder. The gross appearance depends on the extent of the necrosis and the stage of the lesion. In early stages, yellow and white streaks are present, and later pale, chalk white streaks from calcification often appear, thus the common name *white muscle disease* (Fig. 15-39). Confirmation of the diagnosis is based on blood or liver analysis for selenium and vitamin E.

Plant Toxicities. *Cassia occidentalis* (coffee senna, coffee weed) is the most common cause of degenerative myopathy in cattle as the result of plant toxicity. This plant grows throughout the southeastern United States. Pale areas within skeletal muscle, with lesser involvement of cardiac muscle, are caused by myofiber necrosis, generally with minimal to no mineralization. Other plant toxicities are discussed in the toxic myopathies section.

Ionophore Toxicity. The pathogenesis of ionophore toxicity is discussed in the toxic myopathy section. Ionophore toxicity in cattle is seen only with overdoses because of improper feed mixing. Anorexia, diarrhea, and weakness are the primary clinical signs. Serum concentrations of CK and AST are often extremely high (e.g., CK greater than 50,000 U/L and AST greater than 5000 U/L). Pale areas within skeletal and cardiac muscle are due to myofiber necrosis. In animals that survive, regeneration will restore the skeletal muscle completely, but cardiac lesions heal by fibrosis.

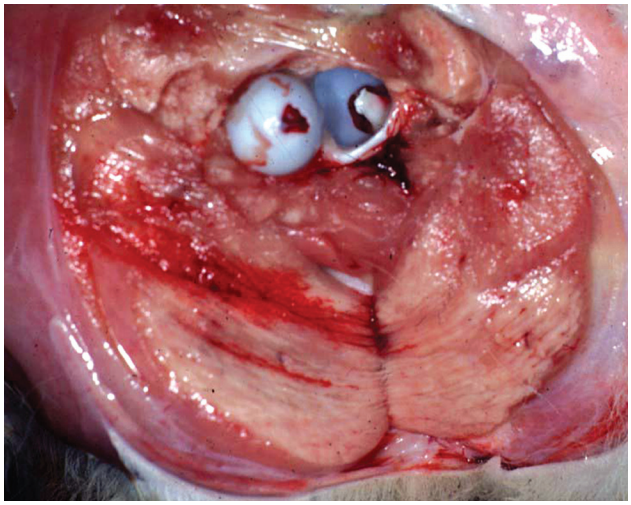


Figure 15-39 **Nutritional Myopathy (White Muscle Disease), Skeletal Muscles of the Caudal Thigh, Sagittal Section, Calf.** In this early stage, affected muscles have yellow and white streaks, often in a patchy distribution. These streaks are areas of necrotic myofibers. Later as the necrotic myofibers calcify, white streaks (chalky texture, mineralization) are visible grossly. (Courtesy Dr. G.K. Saunders, Virginia-Maryland Regional College of Veterinary Medicine; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

Congenital or Inherited Disorders

Steatosis. Steatosis in cattle, sometimes called *lipomatosis*, is most often recognized as an incidental finding at necropsy or at slaughter. This disorder is thought to be the result of defective in utero muscle development, in which large areas of myofibers are replaced by adipocytes. An inherited basis has not been established. Lesions can be symmetric or asymmetric, with the most severely affected muscles being those of the back and loin (longissimus muscles; see Fig. 15-9, *D*). The most severely affected muscles are composed entirely of fat, whereas less severely affected muscles appear streaked because of partial replacement by fat. Histologically, the space normally occupied by myofibers is filled with mature adipocytes. In utero denervation or failure of innervation results in a similar muscle lesion (see Fig. 15-23), and careful evaluation of the peripheral nerves and spinal cord is indicated.

Diagnosis is readily made on gross examination and can be confirmed by histologic examination, specifically in frozen sections stained with Oil Red O or Sudan black for fat. Because this condition is usually not diagnosed during life and the loss of myofibers is irreversible, treatment is neither necessary nor possible.

Other Bovine Congenital or Inherited Myopathies and Neuronopathies. Congenital muscular hyperplasia ("double muscling") resulting from defects in the myostatin gene occurs in a variety of cattle breeds. An unusual multisystemic disease with characteristic necrotizing vasculopathy occurs in young Gelbvieh cattle. Glycogenosis type II (acid maltase deficiency) has been recognized in shorthorn and Brahman cattle, and glycogenosis type V (myophosphorylase deficiency) occurs in Charolais cattle. An inherited motor neuron degenerative disease occurs in Brown Swiss cattle. These disorders are discussed in more detail in E-Appendix 15-1.

Electrolyte Abnormalities

Hypokalemic Myopathy. Decreased potassium interferes with normal muscle cell function and can lead to muscle weakness and myofiber necrosis. Type 2 fibers are preferentially affected. The pathogenesis of hypokalemic myopathy is not clear, but myofiber necrosis may be the end result of either decreased myofiber energy production or focal ischemia secondary to vasoconstriction. Hypokalemia can also interfere with normal cardiac conduction, and atrial fibrillation is common. Hypokalemia in cattle can be the result of anorexia. A history of ketosis occurring within a month of parturition is common. Glucocorticoids with high mineralocorticoid activity, such as isoflupredone acetate used to treat ketosis, are a recognized cause of hypokalemic myopathy in cattle. Activation of glucose transport into cells by intravenously administered glucose or insulin also causes intracellular movement of potassium and can result in hypokalemia. No specific findings are present at postmortem examination, although ischemic necrosis secondary to recumbency can be seen in muscles of the hind limbs (see later discussion). Lesions of multifocal polyphasic myofiber necrosis and vacuolated myofibers (vacuolar degeneration) are present in all muscles, including those not involved in weight-bearing, and are indicative of myodegeneration as a direct effect of hypokalemia.

Affected cows are profoundly weak and become recumbent and unable to support the weight of their heads. Serum concentration of potassium is below normal (<2.3 mEq/L), and CK and AST levels are moderately high (CK up to approximately 25,000 U/L and AST up to approximately 2000 U/L). The diagnosis is based on typical historic and clinical findings and a low serum potassium concentration. Intravenous and oral supplementation with potassium salts and supportive therapy may result in recovery in some cases, but this disorder is often fatal.

Other Electrolyte Abnormalities. Both hypocalcemia and hypophosphatemia can result in profound muscle weakness and recumbency in cattle. In hypocalcemia, weakness is primarily the result of disruption of neuromuscular transmission. Significant changes are not seen in affected muscles, although ischemic necrosis can occur secondary to recumbency (see later discussion). Diagnosis relies on clinical findings and identification of abnormally low serum calcium or phosphorus concentrations. Treatment includes correction of the electrolyte defect by intravenous administration of the appropriate electrolyte-containing fluids, supportive care, and correction of any dietary abnormalities that may predispose to electrolyte problems.

Ischemic Myopathy

Ischemic muscle necrosis caused by recumbency is common in cattle. The muscular lesion is similar to that seen in other species, but in cattle, prolonged sternal recumbency is more common than lateral recumbency, and pectoral muscles and muscles of limbs tucked under the body or splayed out limbs are most prone to injury (see Fig. 15-25).

Disorders of Sheep and Goats

Selection pressures and economic consequences of muscle disorders similar to those in beef cattle exist in small ruminants raised for meat. In goats, selection for an interesting mutant has resulted in perpetuation of myotonia.

Bacterial and Parasitic Myopathies

Clostridial Myositis (Blackleg). Clostridial myositis (blackleg) occurs occasionally in sheep and goats and is similar to the disease in cattle.

Botulism. Botulism can occur in small ruminants, but, as in cattle, it is rare.

Protozoal Myopathy. Intracytoplasmic cysts of *Sarcocystis* spp. are commonly found within skeletal and cardiac muscle fibers of sheep and goats as an incidental finding, similar to findings in muscle and heart of cattle. Eosinophilic myositis as a result of sarcocystosis is rare in sheep and is not recognized in goats. In camelids, massive infection with *Sarcocystis* can occur (Fig. 15-40), especially in animals imported from South America where sarcocystosis is common. In rare cases, *Sarcocystis* infection in camelids is associated with widespread eosinophilic myositis.

Nutritional and Toxic Myopathies

Degenerative myopathy caused by nutritional deficiency or toxin ingestion is relatively common in many small ruminant species. The nonselective eating habits of goats make them particularly likely to ingest poisonous plants.

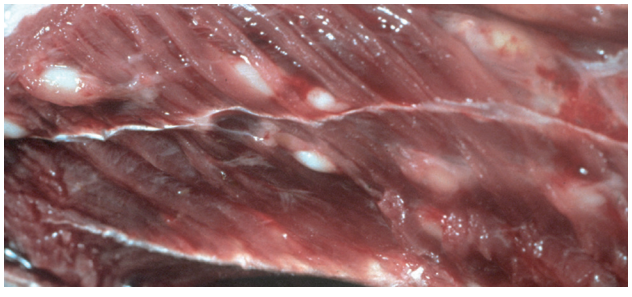


Figure 15-40 Sarcocystosis, Skeletal Muscle, Alpaca. Multiple pale gray-white nodules within the muscle indicate the location of *Sarcocystis* cysts. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

Nutritional Myopathy. Young goats and sheep are susceptible to degenerative myopathy associated with selenium or, less commonly, vitamin E deficiency. A similar disorder occurs rarely in young camelids. The disease in these species is similar to the disease in young cattle.

Toxic Myopathies. Sheep and goats are susceptible to plant and ionophore toxicities, similar to those in cattle. In goats, ingestion of honey mesquite (*Prosopis glandulosa*) causes degeneration of the motor nucleus of the trigeminal nerve, resulting in denervation atrophy of the muscles of mastication, and consequent inability to adequately chew feed, leading to progressive emaciation.

Congenital or Inherited Myopathies

Myotonia in Goats. Myotonia in the goat is inherited as an autosomal dominant trait, and the variable clinical severity is attributable to increased severity in homozygotes compared with heterozygotes. The genetic defect affects the skeletal muscle chloride channel, resulting in decreased chloride conductance and associated ionic instability of the sarcolemma. Starting at approximately 2 weeks of age, affected goats develop severe muscle spasms in response to sudden voluntary effort, for example, when startled by the blowing of a locomotive's horn. Episodes of myotonia can last from 5 to 20 seconds and are characterized by generalized stiffness and adoption of a "sawhorse" stance. Goats often fall over. Sustained dimpling of muscle occurs after percussion. Serum concentrations of CK and AST are normal. Concentric needle EMG reveals the characteristic waxing and waning ("dive bomber") spontaneous activity of myotonia. There are no gross pathologic findings. Histologically, muscle fibers in affected goats may show moderate hypertrophy. But characteristic abnormalities are revealed only with ultrastructural examination in which dilated and proliferated T tubules and terminal cisternae of sarcoplasmic reticulum are seen. Diagnosis is based on characteristic clinical signs and EMG findings. There is no treatment for this disorder, and it is rarely fatal. Affected animals are actually prized by collectors of so-called fainting goats. If nothing else, housing for these animals is simplified because fencing need not be nearly as high as that required for normal goats.

Other Inherited Myopathies. An inherited myopathy (ovine muscular dystrophy) in Merino sheep and an inherited glycogen storage myopathy have been identified in sheep in Australia. These disorders are discussed in more detail in E-Appendix 15-1.

Megaesophagus in Camelids

The tunica muscularis of the esophagus of camelids contains a large amount of skeletal muscle, and adult llamas and alpacas are prone to develop abnormal motility and dilation of the esophagus (megaesophagus). Affected animals often lose body condition and exhibit abnormal rumination of feed boluses. Histopathologic findings of angular atrophy of type 1 and type 2 fibers in the esophagus of affected older llamas suggest that this disorder is an acquired denervating disease, but further studies are necessary. Megaesophagus in alpacas occurs in young animals, and to date no diagnostic muscular lesions have been detected.

Disorders of Pigs

The economic impact of muscle disease in pigs is profound. The high percentage of pigs with the genetic defect that predisposes to

malignant hyperthermia is another example of selection pressure leading to skeletal muscle genetic mutations.

Bacterial and Parasitic Myopathies

Clostridial Myositis (Malignant Edema). Pigs occasionally develop clostridial myositis (usually *Clostridium septicum*), particularly at sites of intramuscular injection. The resulting disease is similar to that seen in cattle, sheep, and goats, although heart involvement appears to be rare.

Pyogenic Bacteria. Abscesses within muscles and their fascia as a result of infection by pyogenic bacteria, such as *Trueperella* (*Arcanobacterium*) *pyogenes*, are common in pigs and are similar to those in cattle.

Trichinosis. Infection of pigs by the nematode parasite *Trichinella spiralis* is of major economic importance to the porcine industry and poses a serious health hazard to human beings. Pigs infected with *Trichinella spiralis* show no clinical signs.

The adult nematode resides in the mucosa of the small intestine. Larvae penetrate the intestinal mucosa and enter the bloodstream, through which they gain access to the muscle. Larvae invade and encyst within myocytes. Encysted larvae are typically not visible on gross examination, although dead larvae can calcify and be visible as 0.5- to 1-mm white nodules (Fig. 15-41, A). Active muscles, such as the tongue, masseter, diaphragm, and intercostal, laryngeal, and extraocular muscles, are preferentially affected. Focal inflammation consisting of eosinophils, neutrophils, and lymphocytes occurs associated with invasion of the muscle by *Trichinella* larvae. After cyst formation, the larvae are protected from the host's immune response and inflammation is minimal to absent (Fig. 15-41, B).

Diagnosis is based on identification of the characteristic nematode larvae encysted within muscle fibers. In those cases in which the larvae have died and calcified, a presumptive diagnosis of trichinosis can still be made.

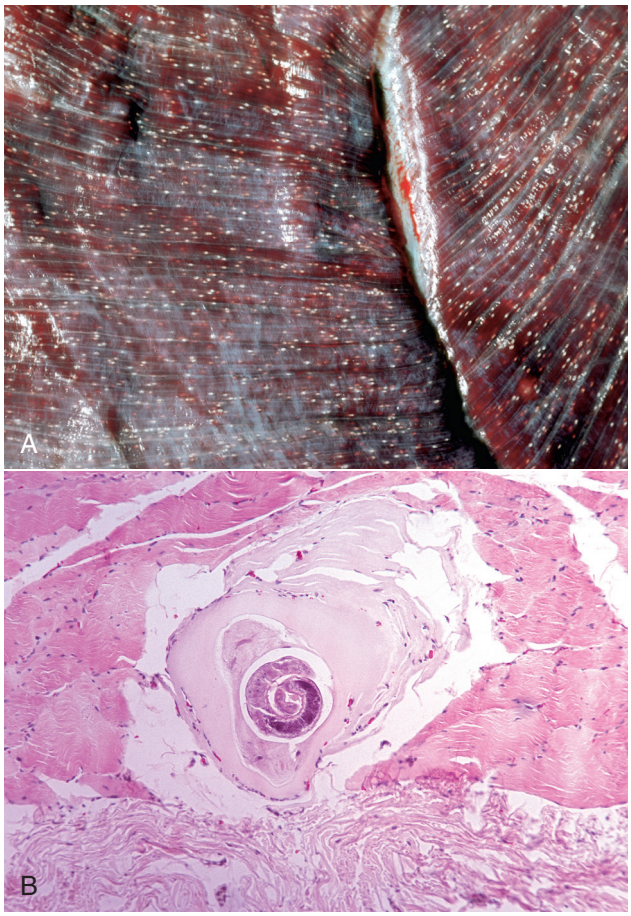


Figure 15-41 **Trichinosis, Encysted Larvae, Diaphragm, Bear. A,** Encysted larvae of *Trichinella spiralis* appear as pale elongated gray-white foci in the muscle. **B,** Encysted larvae *(center)* of *Trichinella spiralis* incite minimal inflammation until they die. Formalin fixation, H&E stain. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Protozoal Myopathies. Intracytoplasmic cysts of *Sarcocystis* spp. are not common in pigs but can occasionally be found in the skeletal and cardiac muscle fibers as an incidental finding. Eosinophilic myocarditis has been reported after experimental infection.

Nutritional and Toxic Myopathies

Nutritional Myopathy. Young pigs are susceptible to degenerative myopathy caused by selenium or vitamin E deficiency, and the pathologic changes are similar to those seen in calves. A distinctive clinical disorder seen in very young Vietnamese pot-bellied pigs, in which affected piglets have a short, stilted gait and tend to stand on their toes, is thought to be related to selenium or vitamin E deficiency. Histologically, there is multifocal polyphasic myofiber necrosis. Affected piglets appear to recover spontaneously.

Toxic Myopathies. Pigs are susceptible to poisoning by *Cassia occidentalis* and develop segmental necrosis of myofibers, especially in the diaphragm. Monensin toxicity results in segmental necrosis of skeletal muscle and necrosis of cardiac muscle, particularly of the atria. The pathogenesis of ionophore toxicity is discussed in the previous section on Toxic Myopathies. Gossypol present in cottonseed products is toxic to pigs when these products are fed at 10% or more of the ration and causes skeletal and cardiac muscle necrosis, as well as lesions in the liver and lung.

Congenital and Inherited Myopathies

Myofibrillar Hypoplasia (Splay Leg). Myofibrillar hypoplasia (splay leg) is a congenital disorder that affects young piglets and results in splaying of the limbs laterally (abduction). Affected animals propel themselves by pushing against the ground with the pelvic limbs. This posture results in progressive flattening of the sternum. Although delayed myofibril development has been suggested, the histopathologic findings are inconclusive because similarly poorly developed myofibers can be seen in normal littermates. Affected piglets can recover with treatment, which includes the use of a harness that partially supports their bodies, holds their legs under their bodies, and encourages locomotion. Providing affected pigs with a nonslip floor is also important.

Steatosis. Pigs can have large areas of muscle replaced by mature adipose tissue, similar to that described in cattle.

Malignant Hyperthermia (Porcine Stress Syndrome; Pale Soft Exudative Pork). MH (porcine stress syndrome, pale soft exudative pork) affects several strains of pigs, most commonly those with unpigmented hair coats. A similar syndrome occurs in Vietnamese pot-bellied pigs. Incidence varies but can be very high within certain herds. The disease in pigs is an accurate animal model of the disease in human beings and is an important cause of economic losses in the pig industry. Susceptibility to MH is inherited as an autosomal recessive trait. The genetic defect results in abnormal activity of the skeletal muscle ryanodine receptor. The

ryanodine receptor is a calcium release channel located in the sarcoplasmic reticulum terminal cisternal membrane that links the T tubule to the sarcoplasmic reticulum during excitation-contraction coupling. Uncontrolled intracytoplasmic calcium release because of abnormal ryanodine receptor activity leads to excessive contraction with resultant heat production. Clinical disease occurs only in pigs homozygous for the defect, although human heterozygotes can also be susceptible to hyperthermic episodes after halothane anesthesia. It is suspected that this defect originated more than 50 years ago in a foundation animal and resulted in offspring with increased muscling and reduced body fat. Affected pigs are clinically normal until an episode of hyperthermia is triggered by a precipitating factor such as halothane anesthesia or stress. Episodes consist of severe muscle rigidity and dramatically increased body temperature. Severe cases progress rapidly to death. Serum concentrations of CK and AST are markedly increased during episodes.

In animals dying during a hyperthermic episode, affected muscles are pale, moist, and swollen and appear "cooked" (Fig. 15-42), thus the common name "pale, soft, exudative pork." Muscles of the shoulder, back, and thigh are preferentially affected. Affected fibers are either hypercontracted or, if the animal has survived for some hours, are undergoing coagulation necrosis. Histopathologic findings in susceptible pigs sampled during clinically normal periods include chronic myopathic change (fiber-size variation, internal nuclei) and rare necrotic fibers.

This disorder is most commonly diagnosed in pigs dying acutely and is made based on the clinical history of a precipitating stress and on the characteristic gross and histopathologic findings. Given that the precise defect is known, genetic testing allows for identification of carrier and affected animals. Avoidance of precipitating stress factors in susceptible pigs and removal of carrier and affected animals from the breeding stock reduce the incidence of this disorder.

Ischemic Myopathy

Large pigs are susceptible to ischemic myopathy secondary to recumbency, resulting in ischemic necrosis similar to that seen in horses and cattle. The proximal limb muscles are most susceptible.

Disorders of Dogs

Selection pressures for a certain type of muscular development are far less frequent in dogs than in livestock. A few disorders, such as myotonia, have been suggested to occur more often in dogs originally bred for meat, but this is pure speculation. The canine genome may have genes prone to new mutations, similar to human beings, leading to genetic disorders, such as X-linked muscular dystrophy. In general, the impact of muscular disorders in dogs is much less than in livestock. Dogs with muscular weakness can still make good house pets.

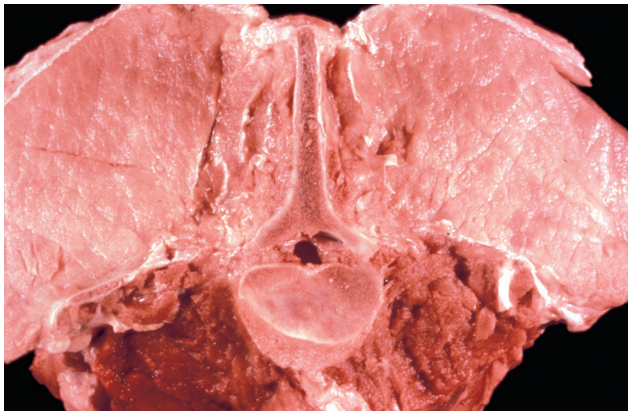


Figure 15-42 Malignant Hyperthermia (Porcine Stress Syndrome, Pale Soft Exudative Pork), Lumbar Epispinal Muscles, Transverse Section, Pig. The affected muscles are pale pink, moist, and swollen and have a "cooked" pork appearance ("parboiled"). (Courtesy Dr. J. Wright, College of Veterinary Medicine, North Carolina State University; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

Parasitic Myopathies

Protozoal Myopathy. The parasitic diseases affecting skeletal muscle in the dog are primarily caused by protozoal organisms, of which *Neospora caninum* is the most important. It is now suspected that early reports of myositis and radiculoneuritis attributed to *Toxoplasma gondii* in young dogs were actually the result of *Neospora caninum* infections. *Neospora caninum* is often transmitted in utero, and evidence suggests that affected bitches are chronic carriers of the organism. Both the peripheral nervous system and the skeletal muscle are invaded by organisms. Ventral spinal roots are preferentially involved, and damage results in denervation atrophy of muscles. Signs of progressive neuromuscular weakness, most profound in the pelvic limbs, begin in affected pups several weeks of age. Marked muscle atrophy of the pelvic limb muscles occurs rapidly, and fixation of pelvic limb joints occurs as a result of denervation of muscle in an actively growing limb. Serum concentrations of CK and AST may be slightly increased. Concentric needle EMG reveals dense, sustained spontaneous activity (fibrillations and positive sharp waves) consistent with denervation.

Pelvic limb muscles are severely atrophied, firm, and pale. Fixation of the pelvic limb joints persists after anesthesia or death. Scattered foci of mixed inflammation with associated segmental myofiber necrosis are often seen within skeletal muscle, and characteristic intracytoplasmic protozoal cysts may be present.

Neospora caninum infection should be suspected based on characteristic progressive neuromuscular dysfunction in a young growing pup. Infection of older dogs is also possible but is uncommon. The finding of a mixed inflammatory-neuropathic lesion within affected skeletal muscle should prompt a search for protozoa, although these are often present in small numbers and may not be seen. Serologic tests can detect antibodies to *Neospora caninum*, and antibodies are available for immunohistochemical studies of paraffin-embedded, formalin-fixed tissue. Antiprotozoal treatment may kill the organisms, but denervation atrophy and pelvic limb fixation will persist.

Hepatozoon americanum and *Trypanosoma cruzi* are other protozoal organisms that can affect canine skeletal muscle. These parasitic diseases are discussed in more detail in E-Appendix 15-1.

Other Parasites. Rarely, cysts of *Trichinella spiralis* are found as an incidental finding in canine muscle.

Congenital or Inherited Myopathies

X-Linked Muscular Dystrophy (Duchenne's Type). X-linked muscular dystrophy (Duchenne's type) has been confirmed or suspected in several breeds of dogs, including Irish terrier, golden retriever, Labrador retriever, miniature schnauzer, Rottweiler, Dalmatian, Shetland sheepdog, Samoyed, Pembroke Welsh corgi, Japanese spitz, and Alaskan malamute. This canine disorder is homologous to Duchenne's muscular dystrophy of human beings and involves defects in the dystrophin gene, which codes for a membrane-associated cytoskeletal protein present in skeletal and cardiac muscle. The absence of dystrophin renders skeletal muscle fibers susceptible to repeated bouts of necrosis and regeneration. Necrosis of cardiac myocytes also occurs and is followed by replacement with connective tissue, resulting in a progressive cardiomyopathy. This

disorder is inherited as an X-linked recessive trait, affecting approximately 50% of males born to a female carrier. Experimentally, affected females have been produced from breeding of an affected male to a carrier female. It is suspected that new mutations in the canine dystrophin gene may be relatively common, as is the case in human beings. Therefore this disorder could occur in any breed, including crossbreeds. There is variable severity of clinical disease even within littermates, and small breed dogs are often less severely affected than are large breed dogs.

Severely affected pups develop a rapidly progressive weakness and die within the first few days of life. In less severely affected dogs, clinical signs are a stiff, short-strided gait and exercise intolerance beginning at 8 to 12 weeks of age, followed by progressive weakness and muscle atrophy. Development of a degree of joint contracture and splaying of the distal limbs is typical (Fig. 15-43). Weakness of the tongue, jaw, and pharyngeal muscles results in difficulty with prehension and swallowing of food, and affected dogs often drool excessively. Involvement of skeletal muscle within the esophagus can result in megaesophagus, which can cause regurgitation, and aspiration pneumonia. Markedly increased concentrations of serum CK, AST, and ALT are characteristic, even before the onset of obvious clinical disease. Concentric needle EMG reveals remarkable spontaneous activity in the form of pseudomyotonic bursts. Muscles do not dimple with percussion.

In pups dying within the first few days of life, the thin superficial muscles of the shoulder, neck, and pelvic limbs (trapezius, brachiocephalicus, deltoid, and sartorius) and the diaphragm have pale yellow-to-white streaks throughout (see Fig. 15-9, A). Death in these cases is thought to be caused by respiratory failure related to severe diaphragmatic myonecrosis. In animals with clinical disease beginning at 8 to 12 weeks, pale streaks within muscle are much less evident, although affected muscles often appear diffusely pale and may be fibrotic. All skeletal muscles, with the exception of the extraocular muscles, appear to be affected to varying degrees. Overt myofiber necrosis is most severe in earlier stages of the disorder and typically affects small clusters of contiguous myofibers. Scattered large, darkly stained myofibers ("large dark fibers") in the early stages of hypercontraction and segmental necrosis are common (see Fig. 15-11, A). Regeneration of affected segments occurs rapidly, and characteristically both myofiber necrosis and fiber regeneration are present within the same section (i.e., the lesion is a multifocal polyphasic necrosis) (Fig. 15-44). Scattered mineralized fibers can also be found. With time, ongoing necrosis and regeneration are less common, and endomysial fibrosis occurs. Chronically affected muscles can have remarkable fibrosis, infiltration by adipocytes, and other chronic myopathic changes. Fiber-type conversion can also be seen as a chronic myopathic change.

In all dogs 6 months of age or older, multifocal pale yellow to white zones will be present within the heart, predominantly involving the subepicardial region of the left ventricular wall, the papillary muscles, and the ventricular septum. Histologically, necrosis, mineralization, and progressive dissecting myocardial fibrosis are found. Death in older animals is the result of either progressive cardiac failure or aspiration pneumonia secondary to dysphagia, although affected dogs may survive for many years.

The diagnosis should be suspected based on characteristic clinical findings in a young male dog but must be confirmed by muscle biopsy and analysis of muscle for dystrophin. The absence of dystrophin in muscle fibers of affected dogs can be confirmed using immunohistochemical staining on frozen sections (Fig. 15-45) or by Western blot analysis. There is no treatment for this disorder.

Carrier females show no clinical signs, but scattered necrotic and regenerating fibers and moderate increases in serum CK and AST are common in young carriers. At birth, dystrophin in carriers is expressed as a mosaic pattern in individual cardiac and skeletal myofibers (Fig. 15-45, C). Because they are multinucleate, skeletal myofibers are able to eventually upregulate and translocate dystrophin to restore this protein to those segments where it is missing throughout the entire myofiber. Fiber necrosis is therefore rare in older carriers. Cardiac muscle, however, remains mosaic for life. Foci

Figure 15-43 Canine Muscular Dystrophy, X-Linked Muscular Dystrophy, Adult Golden Retriever. Note the diffuse muscle wasting and splaying (outward rotation) of the forelimbs. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

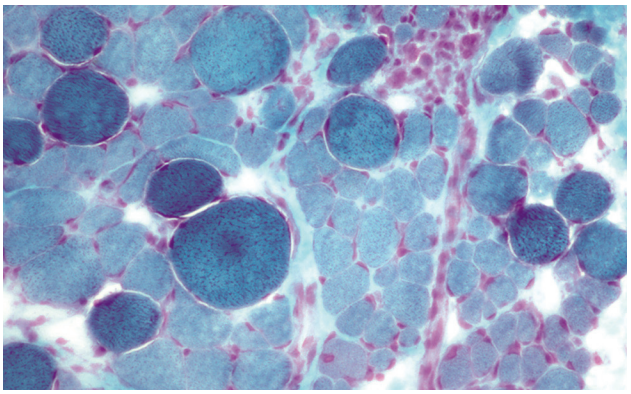


Figure 15-44 Canine Muscular Dystrophy, X-Linked Muscular Dystrophy, Biceps Femoris Muscle, Transverse Section, Dog. The numerous large dark blue staining fibers *(left)* are undergoing acute necrosis, and the cluster of small-diameter fibers with large prominent nuclei *(top right)* are regenerating. The presence of both necrotic and regenerating fibers is indicative of polyphasic necrosis. Frozen section, modified Gomori's trichrome stain. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

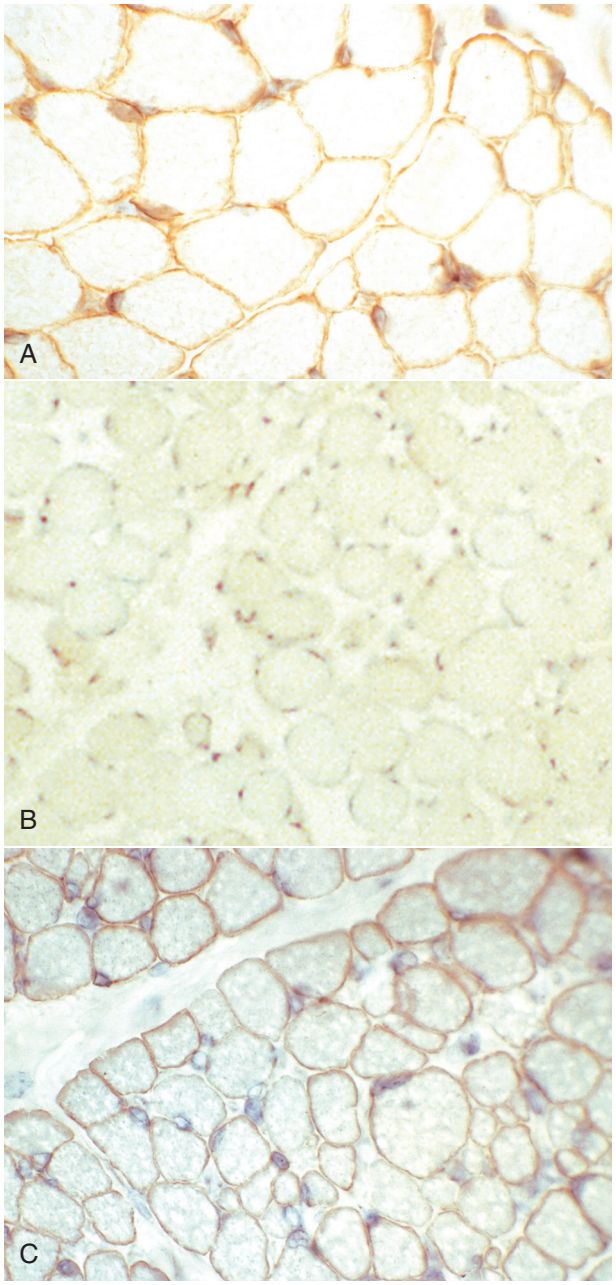


Figure 15-45 Dystrophin Localization *(Brown Stain)* in Transverse Sections of Canine Muscle, Immunostain for Dystrophin, Skeletal Muscle. A, Normal dog. Note that the dystrophin is localized at the sarcolemma. Frozen section, immunoperoxidase reaction for dystrophin. **B,** X-linked muscular dystrophy, dog. Dystrophin is completely absent. Frozen section, immunoperoxidase reaction for dystrophin. **C,** X-linked muscular dystrophy carrier, young carrier female dog. Note the mosaic pattern in which some fibers contain normal dystrophin and others completely lack dystrophin. Frozen section, immunoperoxidase reaction for dystrophin. (Courtesy Dr. B.J. Cooper, College of Veterinary Medicine, Oregon State University.)

of necrosis and development of fibrosis occurs in the cardiac muscle of carrier females, but to date, none have developed overt cardiac failure. Any female dog producing affected pups is a carrier, and approximately half of all of her female offspring will also be carriers. Carrier females can also be identified by either dystrophin or DNA analysis and should be spayed.

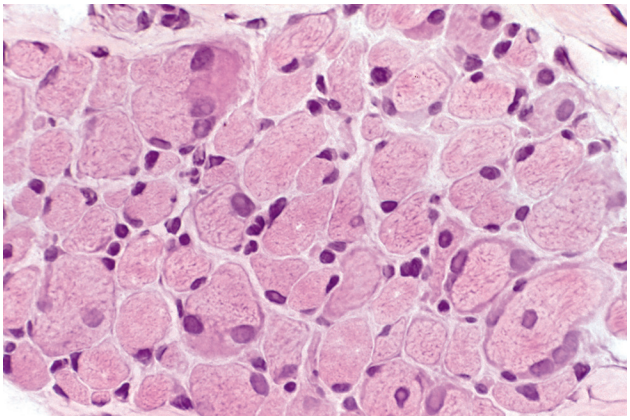


Figure 15-46 Labrador Retriever Centronuclear Myopathy, Skeletal Muscle, Transverse Section, Labrador Retriever Dog. There is excessive fiber-size variation, and some fibers contain one or rarely two internal nuclei. Nuclei are abnormally large. Frozen section, H&E stain. (Courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

Other Canine Muscular Dystrophies. Dystrophin has been found to be associated with a series of dystrophin-associated proteins, forming a membrane complex. The genes for many of these proteins are autosomally inherited; therefore not all canine muscular dystrophies are X-linked disorders. Autosomal recessive inheritance of dystrophin-associated gene defects leading to muscular dystrophy is common in human beings, and defects in dystrophin complex proteins leading to non-Duchenne's type muscular dystrophy have also been identified in various breeds of dogs. These are discussed in more detail in E-Appendix 15-1.

Labrador Retriever Centronuclear Myopathy. Labrador retriever centronuclear myopathy is inherited as an autosomal recessive trait. Affected dogs occur within the working or sporting breed lines rather than the show dog lines. Studies suggest similarity to inherited centronuclear myopathy of human beings, and a genetic test to detect carrier and affected dogs has been developed. Affected Labrador retrievers develop signs of neuromuscular weakness within the first 6 months of life. Exercise intolerance leads to collapse during prolonged exercise, and episodes of collapse can also be elicited by exposure to cold. Loss of triceps and patellar reflexes is characteristic. Affected dogs usually do not develop normal muscle mass. Concentric needle EMG reveals intense and abnormal spontaneous activity with normal motor nerve conduction velocities. Serum concentrations of CK and AST are often normal, although they can be mildly to moderately increased. Megaesophagus can be present.

The only specific abnormalities seen at necropsy are generalized poor muscling and possibly megaesophagus. On histologic examination, affected dogs have remarkable myopathic changes characterized by clusters of atrophic myofibers, myofiber hypertrophy, and internal nuclei (Fig. 15-46). Abnormal mitochondrial distribution, often with peripheral mitochondrial aggregates (identified as ragged red fibers in frozen sections stained with modified Gomori's trichrome stain), can also be seen (see Fig. 15-22, *B*). Segmental necrosis and regeneration are rare; therefore this disorder does not qualify as a muscular dystrophy. The initial reports described this disorder as a type 2 deficiency myopathy, but further studies have shown that fiber-type proportions vary remarkably between muscles and between dogs, although an increase in type 1 fibers (type 1 fiber predominance) is often seen. Alteration of the normal mosaic

pattern of myofiber types is also seen. There is fiber-type grouping, usually considered a neuropathic change, despite the absence of peripheral nerve lesions. These changes are thought to reflect fiber-type conversion unassociated with denervation.

Based on the clinical findings, the diagnosis may be suspected but should be confirmed by genetic testing. There is no treatment for the disorder, although the disease is nonprogressive after 6 months to 1 year of age, and affected animals can still be kept as pets. Dogs producing affected pups should not be rebred.

Congenital Myotonia. Myotonia is seen most commonly in the Chow Chow dog, miniature schnauzer, and Staffordshire terrier. Autosomal recessive inheritance has been confirmed in the miniature schnauzer, and available evidence supports similar inheritance in the Chow Chow. The underlying cellular defect in miniature schnauzers is decreased chloride conduction, and a similar defect is suspected in Chow Chow dogs. Affected pups can begin to show signs of a stiff gait as early as 6 weeks of age. The signs progress for several months and then stabilize with variable severity. Affected dogs move with splayed, stiff thoracic limbs and often a "bunny hop" gait in the pelvic limbs. Signs are most severe on initiation of movement and improve with continued exercise. But affected dogs are never clinically normal. During severe episodes, dogs can fall over, and laryngospasm can result in transient dyspnea and even cyanosis. The musculature becomes remarkably hypertrophied, and sustained muscle dimpling occurs after percussion. Characteristic waxing and waning ("dive bomber") myotonic bursts are found with concentric needle EMG. Serum concentrations of CK and AST are normal or mildly increased.

Overall muscle hypertrophy, with prominently defined muscle groups, is the only finding on postmortem examination. In early stages of the disease, muscle appears relatively normal on histologic examination. With time, myofiber hypertrophy and myofiber atrophy of both type 1 and type 2 fibers and rare scattered segmental necrosis or regeneration are seen. Fibrosis is mild to inapparent.

Diagnosis is based on clinical signs and can be confirmed by concentric needle EMG or by examination of a muscle biopsy. Molecular testing is available to detect carrier and affected miniature schnauzers. Therapeutic agents that act to stabilize excitable cell membranes, such as quinidine, procainamide, and phenytoin, can relieve some of the signs of myotonia.

Swimmer Pups. Swimmer pups are clinically similar to piglets with splay leg. Affected pups cannot adduct the limbs beneath their bodies and develop a characteristic "swimming" gait and, because of the weight of the body, progressive dorsoventral flattening of the sternum and thoracic wall. Although this syndrome can occur in pups with neuromuscular disease of any sort that leads to weakness, it is more commonly associated with overfeeding leading to excess body weight. Affected overfed pups often recover completely after reduction in total daily milk intake, provision of a nonslippery floor surface, and development of harnesses and physical therapy to encourage them to bring their legs underneath their bodies and walk. In pups that die or are euthanized, sternal flattening and abnormal lateral deviation of the limbs are consistent necropsy findings. Histopathologic abnormalities in muscle vary, depending on the cause (e.g., myofiber necrosis and regeneration in pups with muscular dystrophy, and denervation atrophy in denervating disease) and are absent in pups in which this disorder simply reflects overfeeding.

Endocrine Myopathies

Hypothyroidism. Because of its role in muscle metabolism, decreased thyroid hormone often results in skeletal myofiber weakness and atrophy. Hypothyroidism can also cause a peripheral neuropathy, and damage to motor nerves can cause denervation atrophy and contribute to the neuromuscular weakness. Signs of neuromuscular dysfunction caused by hypothyroidism are extremely varied and include generalized weakness, muscle atrophy, laryngeal paralysis, and megaesophagus. EMG studies are often normal; abnormal spontaneous activity and decreased motor nerve conduction velocities can be found if there is concurrent peripheral neuropathy. Serum concentrations of CK and AST are generally normal. Other systemic manifestations of hypothyroidism may or may not be present.

At necropsy, overall muscle atrophy can be seen. Thyroid glands are often bilaterally atrophied, and megaesophagus can be present. Symmetric alopecia (endocrine dermatopathy) can also be seen. Type 2 myofibers are preferentially atrophied. Axonal degeneration can occur in peripheral nerves and, because of denervation, can lead to angular atrophy of both type 1 and type 2 fibers and to fiber-type grouping as a result of reinnervation.

Diagnosis is suspected on the basis of clinical findings and selective type 2 atrophy or evidence of denervation or reinnervation in affected muscles, but it should be confirmed by evaluation of thyroid function. In many cases, replacement thyroid hormone improves the signs of neuromuscular weakness.

Hypercortisolism. Hypercortisolism can occur because of either increased adrenocortical cortisol production or administration of exogenous corticosteroids. Clinical findings of neuromuscular weakness can be very similar to those in hypothyroidism. A unique manifestation of hypercortisolism in some dogs is development of a remarkably stiff, stilted pelvic limb gait, with increased bulk and tone of proximal thigh muscles (Cushingoid pseudomyotonia). The cause of Cushingoid pseudomyotonia is not known, although induction of sarcolemmal ionic instability is postulated. Concentric needle EMG of these muscles reveals myotonic bursts that do not wax and wane (pseudomyotonic activity). Muscles do not dimple after percussion. Other systemic signs of hypercortisolism, such as symmetric muscle atrophy and alopecia, can also be present. Serum concentrations of CK and AST are normal. Adrenal glands have bilateral cortical atrophy caused by exogenous corticosteroid administration or bilateral hypertrophy caused by stimulation secondary to pituitary neoplasia. Adrenal cortical neoplasia causes enlargement of the affected gland and atrophy of the contralateral gland. Findings in affected muscle and peripheral nerves are similar to those seen in hypothyroid myopathy (i.e., selective type 2 fiber atrophy), and evidence of axonal degeneration in peripheral nerves, type 1 and type 2 fiber atrophy indicative of denervation atrophy, and fiber-type grouping reflecting reinnervation are possible (see Fig. 15-18, *B*).

Diagnosis is suspected on the basis of clinical and histopathologic findings but should be confirmed by evaluation of adrenocortical function and total serum cortisol. Cessation of exogenous corticosteroids, removal of adrenal neoplasms, or chemical destruction of hyperplastic adrenal cortical tissue results in improvement in muscle mass and strength, although signs of pseudomyotonia may persist.

Immune-Mediated Myopathies

Polymyositis. Polymyositis is the result of immune-mediated inflammation that attacks components of the skeletal myofibers and results in myofiber necrosis (Fig. 15-47; also see Fig. 15-27 and Table 15-8). The immunologic injury can be directed against skeletal muscle only or can be part of a more generalized immune-mediated disease such as systemic lupus erythematosus. Polymyositis can also occur in dogs with thymoma. This inflammatory myopathy can have

an acute and rapidly progressive course or an insidious onset of muscle atrophy and generalized weakness. Muscles throughout the body are affected, but atrophy of temporal and masseter muscles may be most obvious, mimicking the appearance of dogs with masticatory myositis (see later discussion). Esophageal muscle involvement can lead to esophageal fibrosis and esophageal dysfunction, including megaesophagus. Respiratory muscle involvement can occur and, if severe, will cause respiratory distress. Pain on palpation of muscles is rare. Serum concentrations of CK, AST, and ALT can be increased, but in chronic cases these concentrations can also be within normal limits. Concentric needle EMG often reveals scattered foci of abnormal spontaneous activity, and motor nerve conduction velocities are normal.

At necropsy, overall muscle atrophy may be the only finding. Aspiration pneumonia can occur secondary to megaesophagus. Histologic findings within affected muscles are extremely variable. In acute, fulminating cases, the muscle sections are filled with inflammatory cells, predominantly lymphocytes (Fig. 15-47, *A*), although interstitial eosinophils and neutrophils can also be present. The degree of myofiber necrosis is variable. Necrotic fibers in early stages are surrounded by lymphocytes that can be seen to invade intact myofibers (see Fig. 15-27, *B*). Similar to human polymyositis, $CD8^+$ cytotoxic/suppressor T lymphocytes are the primary infiltrating cells. Necrosis is followed by regeneration, but basal lamina damage is common and results in some degree of healing by fibrosis. In more chronic and insidious cases, the only lesion consists of scattered lymphocytes in the interstitial tissue adjacent to myofibers, with a variable degree of fibrosis and chronic myopathic change (Fig. 15-47, *B*). Sampling multiple muscles for histopathologic examination is recommended.

Polymyositis should be suspected based on the clinical findings, but identification of characteristic changes within muscle sections is often necessary to confirm the diagnosis. A positive circulating antinuclear antibody titer (ANA) is useful but is not always present. Treatment with immunosuppressive drugs, such as corticosteroids, can be curative, but affected animals may require lifelong therapy.

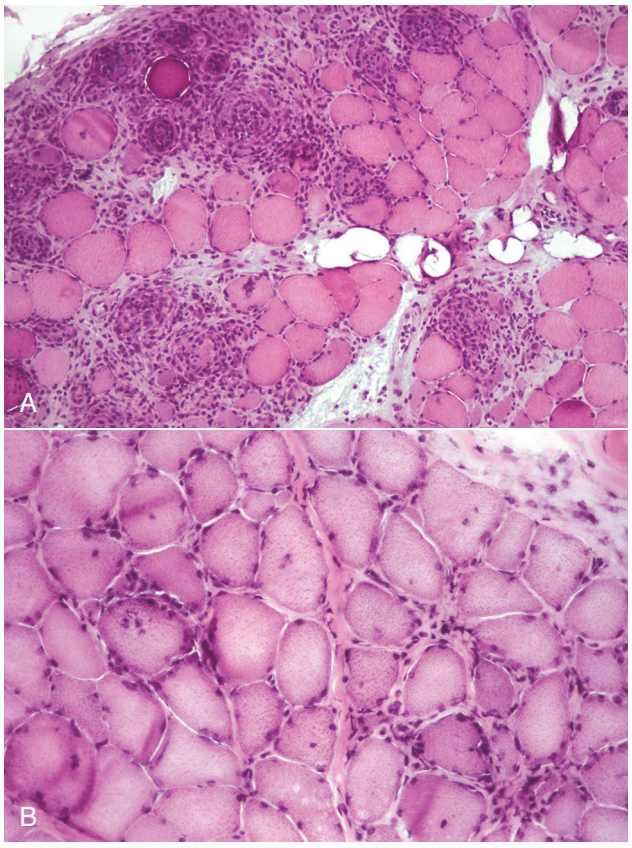


Figure 15-47 Canine Polymyositis, Skeletal Muscle, Transverse Section, Dog. A, Acute polymyositis. Dense interstitial and intramyofiber mononuclear inflammatory cell infiltrates are associated with myofiber necrosis. Frozen section, H&E stain. **B,** Chronic polymyositis. At this stage, there are only scattered interstitial mononuclear inflammatory cell infiltrates, scattered degenerate fibers, and chronic myopathic change (excessive fiber-size variation, internal nuclei, endomysial fibrosis). Frozen section, H&E stain. (**A** courtesy Dr. L. Fuhrer, Clinic Vétérinaire de St. Avertin, France. **B** courtesy Dr. B.A. Valentine, College of Veterinary Medicine, Oregon State University.)

Masticatory Myositis (Eosinophilic Myositis; Atrophic Myositis). The type 2 myofibers in the masticatory muscles of the dog contain a unique myosin isoform (type 2M myosin). Occasionally, antibodies to this myosin form, and the result is an inflammatory myopathy confined to the temporalis and masseter muscles. Severe, acute cases display bilaterally symmetric swelling of, and pain in, those muscles and an inability to fully open the jaw. Affected dogs can have difficulty prehending food. More chronic or insidious cases have bilaterally symmetric atrophy of the temporal and masseter muscles (Fig. 15-48 and Table 15-8) and decreased jaw mobility. Pain may or may not be evident at this stage. Concentric needle EMG often reveals foci of spontaneous activity in active cases but can be normal in more chronic cases. Serum concentrations of CK and AST are normal or only mildly increased.

Severely atrophied muscles often contain pale streaks. The degree and nature of the inflammation are variable. In acute cases, infiltrates of lymphocytes and plasma cells, similar to those in polymyositis, are present. But, in contrast to canine polymyositis, the infiltrating cells in masticatory myositis are primarily B lymphocytes. There can also be numerous eosinophils, and these can be the predominant cell type. Neutrophils are much less common. Inflammation is associated with myofiber necrosis. Regeneration can restore myofibers, but because the basal lamina is often damaged, healing by fibrosis is common. The presence of fibrosis is an important prognostic indicator because fibrosis is an irreversible change.

Figure 15-48 Chronic Masticatory Myositis, Skeletal Muscle, Dog. Note the severe atrophy of the temporalis and masseter muscles. (Courtesy Dr. W. Hornbuckle, College of Veterinary Medicine, Cornell University.)

The diagnosis is suggested on the basis of characteristic clinical findings. Masticatory myositis must be differentiated from polymyositis, which can also have severe involvement of the temporal and masseter muscles. Serologic testing to detect anti–type 2M myosin antibodies specific to masticatory muscle myositis is available, and serum from affected dogs will bind to type 2M fibers (Fig. 15-49). EMG and histopathologic evaluation of multiple muscles can also help to differentiate these two disorders. Treatment with immunosuppressive doses of corticosteroids generally alleviates pain and results in increased mobility of the jaw and an increase in muscle mass. Some degree of atrophy and loss of complete jaw mobility can persist. A single course of corticosteroids can be curative; however, some cases require extended therapy.

Extraocular Muscle Myositis. An immune-mediated attack directed specifically at extraocular muscles is the suspected cause of this disorder. Acute onset of bilateral exophthalmos is seen (see Table 15-8). Affected dogs are usually younger than 2 years of age, and golden retriever dogs appear to be predisposed. Serum concentrations of CK and AST are generally normal.

The extraocular muscles, with the exception of the retractor bulbi muscle, are swollen and pale yellow. A predominantly lymphocytic inflammation resulting in myofiber necrosis and regeneration is seen. Because it is difficult to obtain a biopsy sample of the extraocular muscles, diagnosis is generally based on typical clinical findings. Corticosteroid therapy is effective, but episodes can recur.

Disorders of the Neuromuscular Junction

Myasthenia Gravis. The pathogenesis of myasthenia gravis is discussed in the section on neuropathic and neuromuscular junction disorders (see Fig. 15-28). In most cases, myasthenia gravis is an acquired disease, with circulating antibodies directed at the acetylcholine receptors of the neuromuscular junction. An inherited predisposition to development of acquired myasthenia gravis has been reported in Newfoundland dogs. In some cases, onset of myasthenia gravis occurs because of thymoma or, less commonly, thymic hyperplasia. Myasthenia gravis associated with hypothyroidism also occurs in dogs but is rare. Congenital myasthenia gravis is due to abnormal development of the neuromuscular junction and is inherited as an autosomal recessive trait in Jack Russell terriers, smooth fox terriers, and springer spaniels. Congenital myasthenia gravis also occurs in smooth-haired miniature dachshunds. Typical signs of acquired disease are episodic collapse in an adult dog, with normal gait and strength after rest. Clinical signs can, however, be variable. The canine esophagus contains a large percentage of skeletal muscle throughout the length of the tunica muscularis; therefore megaesophagus is common in dogs with myasthenia gravis and may be the only presenting sign. This differs from human beings, in which only the proximal one-third of the esophageal muscularis is completely skeletal muscle and the lower third is completely smooth muscle. In some cases, mild weakness persists between episodes. Clinical signs of congenital myasthenia gravis appear at an early age (6 to 8 weeks of age) and in most affected breeds are progressive and typically quite severe. Affected dachshunds, however, appear to recover by 6 months of age. Repetitive motor nerve stimulation reveals an initial sharp decremental response, followed by relatively uniform amplitude potentials. Serum concentrations of CK and AST are normal.

No findings are evident at postmortem examination unless megaesophagus, thymic abnormalities, or thyroid abnormalities are present, and no abnormalities in muscle are seen on light microscopic examination. Ultrastructural abnormalities of the neuromuscular junctions (simplification of the postsynaptic membrane) may be present.

Diagnosis is suspected on the basis of typical clinical findings and results of repetitive nerve stimulation. In patients with acquired myasthenia gravis, dramatic transient improvement in muscle strength after administration of intravenous acetylcholinesterase inhibitors such as edrophonium (Tensilon) is seen, and the diagnosis is confirmed by identification of circulating antibodies to skeletal muscle acetylcholine receptors. In cases of acquired myasthenia gravis, the presence of a thymic abnormality should be determined because removal of a thymoma or of a hyperplastic thymus results in resolution of clinical signs. In other cases, long-acting acetylcholinesterase inhibitor therapy, sometimes combined with corticosteroid therapy, is often beneficial. There is no effective treatment for congenital myasthenia gravis.

Tick Paralysis. In a dog with flaccid tetraparesis, a diagnosis of tick paralysis should be considered along with polyradiculoneuritis (coonhound paralysis; see Chapter 14) and botulism. Clinical signs of tick paralysis appear 5 to 7 days after infestation with causative *Dermacentor* or *Ixodes* ticks. Initial clinical signs are pelvic limb weakness, with progression to recumbency within 48 to 72 hours. Cranial nerve function is normal. Clinical signs of tick paralysis are very similar to those of coonhound paralysis (see Chapter 14). Treatment for tick infestation can result in recovery within a few days, although death from respiratory muscle paralysis is still possible.

Botulism. Botulism occurs in dogs, resulting in rapid onset of flaccid tetraparesis, but is rare. Reported cases of canine botulism are most often the result of types C and D of *Clostridium botulinum* neurotoxins. Diagnosis is often presumptive, based on a failure to identify other causes of diffuse neuromuscular weakness and, with luck, a history of consumption of a rotted carcass. Recovery has been reported in dogs with botulism, although many cases are fatal.

Other Canine Myopathies

Exertional Rhabdomyolysis. Massive acute rhabdomyolysis associated with exertion occurs in racing greyhounds and sled dogs. Muscles of the back (longissimus) and thigh (gluteal) are most often affected and may be severely swollen. Predisposing factors are not clear, but in sled dogs a change to a very high-fat diet has resulted in a decrease in exercise-induced muscle injury.

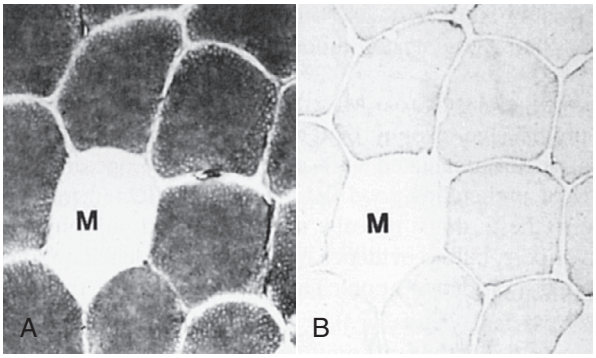


Figure 15-49 **Canine Masticatory Myositis, Skeletal Muscle, Temporalis Muscle, Transverse Sections, Normal Dog. A,** A single type 1 fiber *(light staining, M)* surrounded by type 2 fibers *(dark staining)*. Frozen section, ATPase pH 9.8. **B,** After incubation with serum from a dog with masticatory myositis, type 2 fibers stain positively because of binding of anti–type 2M myosin antibodies from the affected dog. Notice that the type 1 fiber *(M)* is unstained. Frozen section, staphylococcal protein A-peroxidase. (Courtesy Dr. G.D. Shelton, University of California, San Diego.)

Malignant Hyperthermia. Malignant hyperthermia (MH) occurs sporadically in dogs, and breeding studies indicate an autosomal dominant inheritance. The cause has been determined to be a genetic defect in the muscle ryanodine receptor, which is also the cause of MH in pigs and human beings. MH-like episodes can also occur in any dog after ingestion of hops used for brewing beer.

Other Breed-Specific Myopathies. A number of breed-specific myopathies have been reported in the dog, including dermatomyositis in collies and Shetland sheepdogs; mitochondrial myopathy in Old English sheepdogs and other breeds; central core myopathy in Great Danes; exercise-induced collapse in Labrador retrievers; and myopathy of Bouvier des Flandres dogs, English springer spaniels, and Rottweilers. Myoclonus and intramuscular Lafora-like bodies occur in wirehaired miniature dachshunds. These are discussed in more detail in E-Appendix 15-1.

Idiopathic Masticatory Muscle Atrophy

Dogs can develop a progressive atrophy of temporal and masseter muscles that is not associated with pain or difficulty opening the jaw or prehending food. Examination of affected muscle from these dogs reveals mild generalized atrophy of myofibers, but there is no evidence of inflammation, degeneration, fibrosis, or denervation. The cause is not known, and there is no treatment.

Denervating Diseases

There are numerous causes of inherited and acquired peripheral nerve disorders causing axonal damage and resultant denervation in dogs (see Chapter 14). Motor neuron disease is most often inherited, as in the Brittany spaniel and Rottweiler. Such disorders cause symmetric atrophy of affected muscles. Neoplasms arising in peripheral nerves (nerve sheath neoplasms) cause compression of the nerve resulting in Wallerian degeneration, leading to progressive gait abnormalities and ultimately denervation atrophy of muscles of the affected limb.

Disorders of Cats

Relatively few muscular disorders have thus far been identified in cats. This may in part be the result of low performance expectations of the average house cat. It is entirely possible that there are many cats lying around with muscular disorders that have as yet gone unrecognized.

Inherited or Congenital Myopathies

X-Linked Muscular Dystrophy (Duchenne's Type). Dystrophic cats lack the muscle cytoskeletal protein dystrophin, which is also the cause of Duchenne's dystrophy in boys and X-linked muscle dystrophy in the dog. Affected cats develop a progressive, persistent, stiff gait associated with marked muscular hypertrophy. The cause of the remarkable muscular hypertrophy seen in affected cats, as opposed to the muscle atrophy seen in the dog and in human beings, and the pseudohypertrophy as a result of fat infiltration into affected muscle that can occur in human beings, is not known. Age of onset is from a few months to 21 months of age. Affected cats have difficulty grooming, jumping, and lying down. Concentric needle EMG reveals dense and sustained abnormal spontaneous activity, similar to findings in the dystrophic dog. Serum concentrations of CK, AST, and ALT are elevated, typically to very high levels. Affected cats can die under anesthesia or after restraint or sedation because of an MH-like syndrome.

At necropsy, all muscles are severely hypertrophied and may contain pale areas. Focal pale or chalky areas within the myocardium are typically found. Histologically, muscles show a range of changes. Concurrent segmental myonecrosis and myofiber regeneration (polyphasic necrosis) are characteristic. Chronic myopathic changes, found in older animals, include severe myofiber hypertrophy, myofiber atrophy, internal nuclei, and mild to moderate endomysial fibrosis. Myocardial lesions consist of multifocal necrosis and mineralization of cardiac myofibers and fibrosis, primarily in the left ventricular free wall, papillary muscles, and septum. Affected cats may have a relatively normal life span, although unexpected death during anesthesia or forced restraint is common. The exact cause of this is unclear.

The diagnosis is suspected on the basis of characteristic clinical, clinicopathologic, and histopathologic findings in a young male cat. Confirmation relies on assay of muscle samples for dystrophin or on immunohistochemical staining for dystrophin in frozen sections.

Other Feline Inherited or Congenital Myopathies. A form of autosomal recessively inherited muscular dystrophy due to deficiency of the dystrophin complex protein α-dystroglycan occurs in Sphinx and Devon rex cats. Glycogenosis type IV (GBE defect) affecting skeletal muscle is seen as an inherited disorder in Norwegian Forest cats. A histologically similar condition occurs occasionally in other breeds. Feline nemaline myopathy is a rare congenital myopathy in the cat. These disorders are discussed in more detail in E-Appendix 15-1.

Myopathies Caused by Electrolyte Abnormalities (Hypokalemia and Hypernatremia)

Similar to cattle, cats with severe electrolyte abnormalities can show signs of neuromuscular weakness that can be caused by degenerative myopathy. Although degenerative myopathy has been reported secondary to increased blood sodium concentrations (hypernatremia), hypokalemic myopathy occurs far more frequently.

The cause of the weakness and myofiber necrosis associated with electrolyte abnormalities is complex and involves abnormal skeletal muscle energy metabolism and possible ischemia because of vasoconstriction. Hypokalemia (serum potassium concentration less than 3.5 mEq/L) can occur because of decreased dietary intake or increased urinary excretion of potassium. In cats, hypokalemia is often a consequence of chronic renal disease. A genetic defect in the nephron causing renal potassium loss has been linked to periodic hypokalemic myopathy in Burmese related cats. Hypokalemia can also occur secondary to gastrointestinal disease or inappropriate fluid therapy. Hyperthyroidism has been associated with development of hypokalemic myopathy in cats. Hypernatremic myopathy is less common but has been reported in a 7-month-old cat with hydrocephalus and transient hypopituitarism.

Affected cats show severe generalized weakness, with notable ventroflexion of the neck. Concentric needle EMG often demonstrates foci of abnormal spontaneous activity. Serum concentrations of CK, AST, and ALT are often increased, sometimes severely. Clinically diagnosed cases of hypokalemia and hypernatremia can be confirmed by determining if the serum potassium is low or the serum sodium is high, respectively.

No specific gross pathologic findings are present except in cats with hypokalemia as a result of chronic renal disease, in which the kidneys are small and fibrotic. In hypokalemic myopathy, myofiber necrosis and regeneration of variable severity are present concurrently (polyphasic necrosis). Chronic renal disease is commonly due to chronic interstitial nephritis. No abnormalities were detected in a muscle biopsy from a cat with hypernatremic myopathy, although the mildly increased serum concentration of CK and the abnormal EMG suggest mild and perhaps transient myofiber necrosis and regeneration.

Diagnosis is based on characteristic clinical findings of weakness and concurrent hypokalemia or hypernatremia. Treatment of affected cats has been very successful. Immediate fluid therapy is used to correct the electrolyte abnormality, followed by diet change to maintain normal electrolyte concentrations. If there is an underlying hyperthyroidism, this should also be treated.

Immune-Mediated Disorders

An immune-mediated myositis has been described in cats infected with feline immunodeficiency virus (FIV). Serum concentration of CK is moderately increased, but clinical signs of muscle dysfunction are not apparent. Infiltration of muscle by $CD8^+$ lymphocytes, similar to human immunodeficiency virus (HIV)-associated polymyositis, is characteristic.

Disorders of the Neuromuscular Junction

Myasthenia Gravis. Feline acquired and congenital myasthenia gravis are similar to these disorders in the dog but occur less commonly.

Botulism. Although theoretically possible, confirmed or highly suspicious cases of botulism in cats have not been reported. This result likely reflects both an inherent resistance to botulinum toxin and the typical feline fastidious appetite.

Denervating Diseases

Disorders affecting peripheral motor nerves are much less common in cats compared to dogs. A chronic relapsing polyneuritis primarily affecting ventral spinal roots has been seen in young adult cats, which can cause denervation atrophy in affected muscles. Diabetes mellitus can also result in peripheral neuropathy in cats.

Suggested Readings

Suggested Readings are available at www.expertconsult.com.

Suggested Readings

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