

Systems Pathology: Muscle System

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About

These notes are a fairly comprehensive collection of information to complement the lectures and labs delivered in VETM2220, Systems Pathology II, on the topic of skeletal muscle. Although all of the information is useful, certain areas will have been emphasized in lecture, let the areas focussed on in lectures and lab guide your studying. There are a few rare conditions that are not discussed in these notes, and you are encouraged to read through the relevant chapters in the textbooks recommended below.

The notes are available online at <http://russfraser.ca/muscle/>, as a PDF on Moodle, and as an Epub (E-book format, suitable for a tablet). Please feel free to provide feedback, whether on content, style, or typos!

Contact me

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Reference material

- Zachary, J. F., & McGavin, M. D. (2016). Pathologic Basis of Veterinary Disease Expert Consult. Elsevier Health Sciences.
- Maxie, G. (2015). Jubb, Kennedy & Palmer's Pathology of Domestic Animals-E-Book (Vol. 1). Elsevier Health Sciences.

Acknowledgements

These lecture notes were prepared in R (R Core Team, 2018) using the bookdown (Xie, 2015), knitr (Xie, 2018), and Rmarkdown (Allaire et al., 2018) packages. Source material was taken from Zachary and McGavin (2016) and Maxie (2015). I gratefully acknowledge the prior course notes from Dr. Paul Hanna. Images are attributed throughout the text; unattributed images are either mine or were found in the public domain.

Learning objectives

1. one
2. two...

Chapter 1

Introduction

1.1 The anatomy of muscle

The basic structural unit of muscle is the **myofiber**, which represents a single, long, tubular cell (Figure 1.1). Within each myofiber are many tightly packed **myofibrils**, composed of actin and myosin filaments (**myofilaments**), and which form the contractile machinery of the muscle. It is the arrangement of myofibrils that form the striated appearance of skeletal muscle that is appreciated under light microscopy (Figure 1.2). The cytoplasm of a myofiber is known as the **sarcoplasm**, and the cell membrane is called the **sarcolemma**. Each myofiber is surrounded by a small amount of connective tissue called the **endomysium**. Multiple myofibers form a **fasicle** that is surrounded by another layer of connective tissue, the **perimysium**. Finally, multiple fasicles group together to form a muscle.

Skeletal muscle is characteristically multinucleated: each myofiber has 100s of nuclei scattered along its length, almost always found along the periphery of the cell. Each nucleus within a myofiber controls a specific portion of the myofiber, and each nucleus acts independently. Nuclei within muscle fibers are *terminally differentiated*, meaning they can no longer divide, thus limiting the capacity of muscle for regeneration. Having multiple nuclei within a cell provides a distinct and somewhat unique benefit: localized damage, affecting a small number of nuclei, will not necessarily kill the entire cell, and provides the myofiber with an opportunity to regenerate. We will discuss muscle regeneration in more detail in the section on Necrosis and regeneration.

Closely associated with individual myofibers are **satellite cells**. The nuclei of satellite cells are indistinguishable from myofiber nuclei under light microscopy. Satellite cells are a type of stem cell, and are important in muscle regeneration and repair.

Myofibers can be subclassified to reflect their function. The classification is based on three physiologic properties:

1. Rate of contraction (fast vs. slow)
2. Rate of fatigue (fast vs. slow)
3. Type of metabolism (oxidative, glycolytic, or mixed)

Taking these characteristics into consideration leads to three subtypes: Type 1, Type 2a, and Type 2b (Table 1.1). Note that muscles are rarely, if ever, composed of a single subtype: they are a mixture of the different subtypes, though one type often predominates.

A basic review of the innervation of muscles is also worthwhile. Every myofiber is innervated by a motor neuron, though each motor neuron typically innervates several myofibers. The number of myofibers innervated by a neuron is dependent on the need for fine control: only 1-4 myofibers of the ocular muscles, for example, are innervated by a single neuron, compared to the quadriceps where 150 or more myofibers may be innervated by a single neuron.

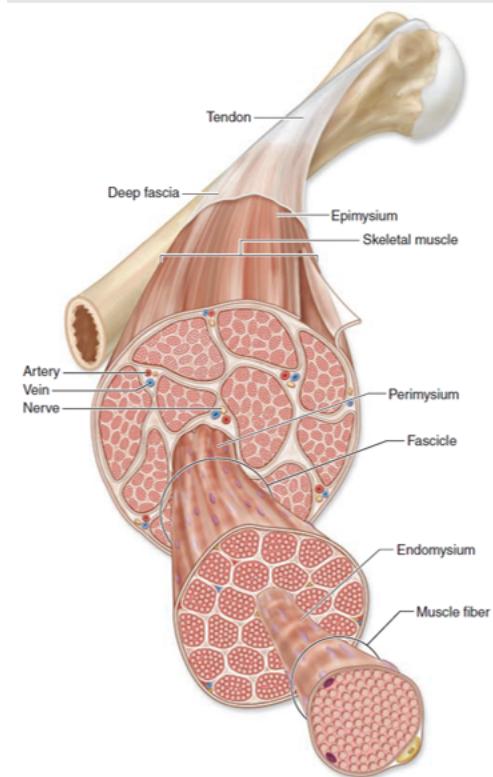


Figure 1.1: Structure and anatomy of muscle

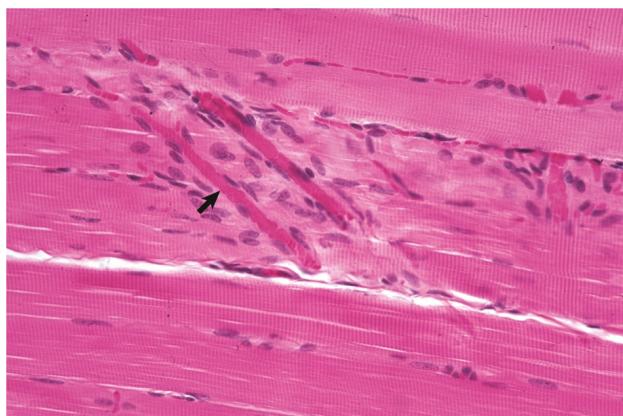


Figure 1.2: Normal skeletal muscle demonstrating striations. The arrow indicates a small capillary.

Table 1.1: Properties of different myofiber types

Fiber type	Physiologic properties	Morphologic properties	Examples
Type 1	slow twitch, fatigue resistant, oxidative, aerobic, 'red'	High mitochondrial and fat content, low glycogen	Muscles involved in prolonged activity, e.g. postural muscles, diaphragm
Type 2a	Fast twitch, oxidative, glycolytic, fatigue resistant	Intermediate mitochondria, fat, and glycogen content	
Type 2b	Fast twitch, fatigue sensitive, glycolytic, 'white'	Low mitochondrial and fat content, high glycogen	Muscles involved in athletic acitvity, e.g. sprinting

1.2 The function of muscle

The contraction of muscle is a complex, orchestrated process in which myofilaments (the components of myofibrils) undergo a conformational change. The contraction of muscle is initiated at the **motor end plate** by the release of acetylcholine from a motor neuron into the neuromuscular junction. This depolarizes the myofiber, resulting in the release of **calcium** from the sarcoplasmic reticulum. It is the binding of calcium to the myofilament troponin that results in the contraction of the sarcomere. In order for muscle to then relax, calcium must be pumped back into the sarcoplasmic reticulum in an ATP-dependent process. The importance of ATP is highlighted by a common and well-known change encountered at post-mortem: **rigor mortis**. Muscles retain the ability to contract immediately after death, but as ATP is consumed, and not replaced, relaxation cannot occur. This leads to the hard, contracted, and immobile carcass characteristic of rigor mortis. Eventually, relaxation occurs due to breakdown of muscle either from autolysis or putrefaction (bacterial decomposition).

1.3 Response of muscle to injury

Skeletal muscle can undergo a fairly limited range of changes in response to environmental and physiologic stimuli. Muscle can shrink (atrophy), get bigger (hypertrophy), or die (necrosis). Under certain circumstances, muscles that have been only mildly injured can regenerate. The reaction of muscle to injury tends to proceed in a fairly stereotypic fashion regardless of the inciting cause, making it difficult to determine the underlying etiology from gross or histopathological examination alone. Thus, **it is important to provide a good clinical history** when submitting a case with suspected muscle injury. Supplementary tests (special stains, culture, etc.) are also often necessary to obtain a definitive diagnosis.

1.3.1 Atrophy

Atrophy simply refers to the reduction in volume of muscle or myofiber, and provided the cause can be corrected, is usually reversible.

1.3.1.1 Denervation atrophy

Denervation atrophy is caused by the loss of a nerve that innervates a myofiber. It is rapid, severe, relatively common, and can result in the loss of more than half of the affected muscle mass in a matter of weeks. The maintenance of a normal myofiber diameter is reliant in part on an intact associated nerve, which generates

trophic factors. Loss of a nerve leads to loss of the trophic factors, resulting in atrophy. Interestingly, atrophy is not due to the lack of contractile activity: paralytic disorders such as Botulism that affect the neuromuscular junction do not lead to atrophy. Denervation atrophy tends to affect both type 1 and 2 myofibers. Because only myofibers innervated by the specifically affected neuron undergo atrophy, the remaining myofibers within a fascicle may undergo hypertrophy to compensate.

Examples of disorders caused by denervation atrophy include [Equine laryngeal hemiplegia], [“Sweeney”], and [Radial nerve paralysis].

1.3.1.2 Disuse atrophy

Decreased contractile activity of a muscle for any reason leads to disuse atrophy. Common causes include lameness/pain or limb immobilization (e.g. cast), and occurs more gradually than denervation atrophy. Disuse atrophy preferentially leads to atrophy of type 2 fibers, however, this is somewhat inconsistent, thus relying solely on type 2 atrophy to distinguish this from denervation atrophy is risky. Unlike denervation atrophy, usually all myofibers within a muscle group are affected by disuse atrophy, and thus there is no compensatory hypertrophy.

1.3.1.3 Nutritional (malnutrition or cachexia) atrophy

Failure to supply the required level of dietary nutrients to maintain normal muscle mass causes nutritional atrophy. It is a gradual form of muscle loss and tends to be generalized, though in the dog, loss of the temporal, back, and thigh muscles is most prominent. Muscle proteins undergo continuous turnover, and in states of starvation, are be used as a source of nutrients. Cachectic animals with chronic illness or neoplasia lose muscle mass due to increased circulating levels of **tumour necrosis factor** (TNF, also known as “cachectin”), which increases myofiber catabolism. Type 2 fibers are preferentially affected.

1.3.1.4 Atrophy of endocrine disease

Atrophy of endocrine disease is most commonly noted in companion animals. In dogs, **hypothyroidism** leads to altered metabolism of carbohydrates and loss of energy, leading to atrophy. In canine **hyperadrenocorticism**, atrophy is caused by increased catabolism and inhibited synthesis of muscle proteins. Type 2 fibers are preferentially affected. in cats, **hyperthyroidism** can lead to muscle atrophy, with non-specific myofiber damage occasionally observed.

1.3.2 Hypertrophy

Hypertrophy refers to grossly enlarged muscles, or to histologically enlarged myofibers. It does *not* refer to an increase in number of myofibers. It can be the result of physiologic stimulation or pathologic processes. Physiologic hypertrophy is generally the result of increased workload on the muscle. Pathologic hypertrophy occurs in response to a number of conditions. Compensatory hypertrophy of unaffected myofibers can occur in a background of neuropathic atrophy.

1.3.3 Necrosis and regeneration

Myofiber necrosis is a non-specific finding that accompanies a variety of different diseases and conditions. Grossly, necrosis of muscle is usually only appreciated in severe cases. Necrotic muscle is typically pale to white, and may appear streaked and slightly gritty if mineralization has occurred (for example, in Selenium and vitamin E deficiency)(Figure 1.3). Necrotic muscle can alternatively appear deeply red, if hemorrhage has occurred concurrently.

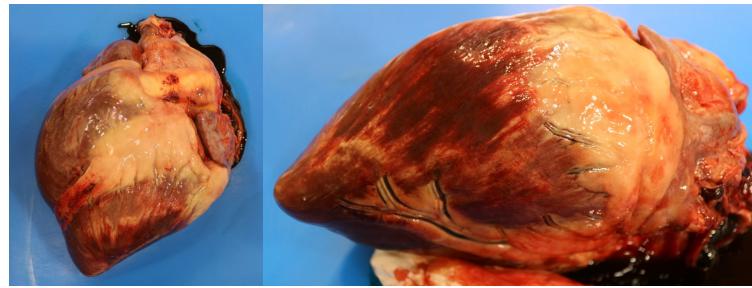


Figure 1.3: Necrosis of the myocardium. Pale white streaks bordered by hemorrhage are visible throughout the ventricle. Photo: C. Martin

The outcome of muscle necrosis is dependent on its severity. If the basal lamina remains intact, and the damage only affects a small portion of the myofiber, then muscle can regenerate. The basal lamina is a thin layer of extracellular matrix that keeps satellite cells closely associated to the myofiber, and just importantly, keeps fibroblasts out. Although myofiber nuclei themselves cannot divide, recall that each myofiber is accompanied by **satellite cells**, which can divide and differentiate into myofibers, **and are critical components of muscle regeneration**. The steps in muscle regeneration are fairly straightforward:

1. Segmental necrosis
2. Invasion of the sarcoplasm by circulating monocytes, which differentiate into macrophages.
 - i) Macrophages phagocytose cellular debris, “cleaning” up the sarcoplasm.
3. Satellite cells enter the sarcoplasm and migrate towards the center of the myofiber.
4. Satellite cells divide and form a tube (“myotube”) which produces sarcoplasm.
 - i) The myotube extends to the edges of the damaged myofiber.
 - ii) The myotube expands, though is still narrower than the unaffected myofiber.
 - iii) A row of nuclei appear in the center of the regenerating myofiber, and sarcomeres begin to form.

Note that if the basal lamina has been destroyed, or if the damage affects a large area, then regeneration does *not* occur, and instead the muscle repairs itself via fibrosis (scarring).

Segmental necrosis and regeneration occur following a variety of insults, most commonly metabolic, nutritional (e.g. Selenium and vitamin E deficiency, toxic (e.g. Ionophore toxicity)). Determining the etiology of the damage can therefore be quite difficult. It is helpful to observe the temporal pattern of the damage: are all muscle fibers at the same stage of necrosis or regeneration, suggesting a single, massive insult? Or is there a range of changes, with some fibers showing early stages of necrosis, and others at the end of regeneration, which suggests an on-going injury? These temporal changes are known as **monophasic** (occurring at one point) or **polyphasic** (an on-going process). These can be further classified by the commonly used distribution modifiers: focal, locally extensive, multifocal, or diffuse, to help narrow down the etiology. For example, a focal, monophasic injury is more likely to be traumatic in origin than metabolic, while a multifocal, polyphasic injury could be due to the on-going lack of a nutritional requirement, as seen in Selenium and vitamin E deficiency.

1.4 Gross evaluation of muscle

Although important, the gross examination of muscles during a necropsy can be underwhelming, and if muscular disease is suspected, samples of muscle should *always* be submitted for histopathology, regardless of appearance. During a gross examination of a carcass, muscles should be evaluated for changes in size, texture, and colour. Muscles can be bigger (hypertrophied) or, more commonly, smaller (atrophied), or

normal. Difficulty in assessing the normal size of muscles for different species and breeds can be aided by comparing with normal animals, or, if unilateral disease is present, with the contralateral side.

Changes in the colour of muscle are common, are often artifactual, and are dependent on blood perfusion, age, and species. Possible colour changes, along with potential causes, are listed below.

- Pale muscles:
 - Normal in young animals
 - Common in anemic animals
 - Can be due to necrosis (ischemic)
 - Denervation
 - If streaking observed, usually due to necrosis and mineralization (e.g. Figure 1.3).
- Dark red:
 - Congestion or hemorrhage
 - Hemorrhagic necrosis
 - Inflammation
 - Hypostatic congestion (i.e. blood pooling due to gravity, a common artifact found during post-mortem examinations)
- Green:
 - Putrefaction (rot)
 - Eosinophilic inflammation (rare – see Sarcocystosis)

The texture of diseased muscle can range from soft to hard (mineralized). Soft muscle can be indicative of necrosis, or potentially fat infiltration.

1.5 Biopsy techniques

As noted above, a biopsy of muscle should always accompany any suspected muscular disease. Muscle is highly susceptible to artifact, but proper preparation of the sample can help in ensuring a diagnostic sample. Muscle retains the ability to contract after biopsy/death, and this contraction can result in artifactual histological changes that mimic true pathological changes. These changes, noted as *contraction band artifact*, can be prevented relatively easily: shortly after removal, secure the muscle to a rigid surface prior to fixation. A simple and manageable technique whether in the field or clinic is to place a strip of muscle along a tongue depressor, and anchor it into place using two needles (FIGURE XXX GET PICTURE), prior to placing the sample in formalin. As a general rule, a muscle biopsy should not exceed ~ 1 cm in diameter (with myofibers running lengthwise).

Chapter 2

Congenital and inherited myopathies

This is a large group of conditions, and several are commonly seen in veterinary species. Congenital conditions tend to be evident at, or soon after, birth, but are *not* necessarily inherited. Inherited conditions indicate an underlying genetic etiology, but does not necessarily imply that the parents are also affected.

2.1 Primary central nervous system conditions

Muscles of the developing embryo require normal innervation in order to develop properly. Lack of normal innervation can lead to atrophy or replacement with fibrous connective tissue. Recall that motor neurons release trophic factors critical to the health of skeletal muscle at the motor end plate. Conditions that primarily affect the motor neurons, therefore, can have significant effects on skeletal muscle.

2.1.1 Arthrogryposis

Arthrogryposis refers to the abnormal angulation of the limbs (*arthro*: joint; *gryposis*: abnormal curvature). As you might expect, this condition is evident immediately at birth, and can affect one or more limbs in a multitude of different ways: they may be rotated, curved backwards or forwards, or abducted. The curve of the vertebral column may be affected as well: scoliosis (*lateral* deviation), kyphosis (*dorsal* deviation), or torticollis (twisted neck) are not uncommon. Muscle mass is reduced.

The causes of arthrogryposis are varied but are often unclear. There is a distinct association with **dysraphism** – the arrest or delayed closure of the neural tube (e.g. spina bifida) – and arthrogryposis. Other causes include toxins (e.g. wild lupine) and a variety of viruses, including the Orthobunyaviruses (Schmallenberg, Cache Valley, and Akabane viruses), bluetongue virus, and border disease virus.

2.2 Muscular defects

2.2.1 Splayleg

Splayleg is an odd condition that occurs only in neonatal piglets (Figure 2.1). Piglets are born unable to adduct their limbs (particularly the hindlimbs) and are often found in a characteristic “splayed” position. The cause is unknown, but is thought to be associated with immature skeletal muscle present at the time of birth. Importantly, the condition is *transient*: all animals make a full recovery within 1, or at most 2, weeks. While affected, however, the animals are at risk of accidental injury and may become malnourished due to difficulty in nursing.



Figure 2.1: Piglet affected by splayleg

2.2.2 Muscular hyperplasia

Myostatin is a protein produced and released by myofibers that *inhibits* muscle growth. Genetic defects in the myostatin gene, resulting in dysfunctional myostatin, result in hyperplasia of skeletal muscle, known as “double muscling”. As this is *hyperplasia*, muscles have increased numbers of structurally normal myofibers. This trait has been selected for in several beef breeds, including Belgian blue (Figure 2.2) and White. The condition is also seen in Whippet dogs (“bully” Whippets). Muscular hyperplasia is most pronounced in the thighs, rumps, loins, and shoulders.

2.2.3 Steatosis

Steatosis of muscles refers simply to the replacement of myofibers by adipocytes, usually following damage or denervation. It is generally considered an incidental finding at necropsy, but does sometimes raises concern at meat inspection.

2.2.4 Congenital diaphragmatic clefts

Abnormal closure of the developmentally complex diaphragm can result in congenital diaphragmatic hernias. They have been reported most frequently in the dog and rabbit.



Figure 2.2: Two Belgian Blue cattle showing marked muscular hyperplasia of the rump.

2.3 Muscular dystrophies

Muscular dystrophies (as defined in the human literature) are **inherited** conditions characterized by **progressive myopathy with necrosis and regeneration of myofibers**. Be aware that the term dystrophy is commonly misused in veterinary medicine, and only a few true dystrophies have been described, notably in the dog, cat, and sheep. These conditions typically manifest in young animals and progressively worsen as the animal ages. The canine and feline X-linked dystrophies are analogous to Duchenne and Becker muscular dystrophies of humans. Both are related to a mutation in the gene encoding dystrophin, a cytoskeletal protein. The pathogenesis of muscle damage in both conditions is poorly understood.

2.3.1 X-linked dystrophies of dogs and cats

The X-linked dystrophies of dogs and cats share several similarities and a few key differences, summarized below in Table 2.1. Both conditions affect the dystrophin protein, whose exact function is still somewhat uncertain. Because affected gene is found on the X chromosome, *males* are overrepresented. Note that the level of detail presented here is beyond what you would be expected to know on an exam.

2.3.2 Ovine muscular dystrophy

Unlike the X-linked dystrophies of dogs and cats, ovine muscular dystrophy is an **autosomal recessive** condition that affects males and females equally. The condition is still common in Merino sheep in Australia, with 1-2% of animals showing signs of the disease. Clinical signs include a lack of normal growth, abnormal gait, and/or stiffness. Most animals will show clinical signs by 1 year of age, and be severely affected by 2-3 years old. If left unattended at pasture, severely affected animals are so weak that they die of starvation.

Gross changes include emaciation and replacement of muscles with adipose tissue. Histologically there are characteristic amphophilic sarcoplasmic masses and large, vesicular nuclei.

2.4 Metabolic myopathies

Metabolic abnormalities are typically inherited, and abnormal metabolism can lead to abnormal function of muscle. There are a large number of metabolic diseases. Some affect enzymes present in multiple organs,

Table 2.1: Comparison of canine and feline X-linked dystrophy

	Canine	Feline
Breed predisposition	Golden retrievers, described in many others	Mixed breeds
Sex predisposition	Male	Male
Effect on muscle	Atrophy	Hypertrophy
Clinical signs	Progressive muscular weakness, abnormal gait, regurgitation	Stiff gait with 'bunny hopping', difficulty jumping, regurgitation. May be subtle.
Serum biochemistry	Increased CK, AST	Increased CK, AST
Gross findings	Severe cases: marked degeneration with pale white streaks of the diaphragm and strap muscles	Marked thickening of the esophagus and contraction of the diaphragm. Muscle is often pale, and there may be pale streaks in the myocardium.
Histologic findings	Myofiber atrophy, necrosis, regeneration	Marked variation in myofiber size including marked hypertrophy. Necrosis and regeneration are present.
Endomysial fibrosis	May be marked	Mild
Cardiac changes	Subepicardial necrosis, mineralization, and fibrosis leading to CHF	Necrosis and mineralization with fibrosis that typically does NOT result in clinical symptoms.

including skeletal muscle, while others affect enzymes or isoenzymes solely in muscle. The defects are often related to issues in **processing or storing of glycogen**. Examples include glycogen storage disease type II in dogs, glycogen storage disease type IV in Norwegian Forest cats and horses. These are relatively uncommon and will not be discussed further, but more information can be found in the reference textbooks.

2.4.1 Equine polysaccharide storage myopathy (PSSM)

Equine polysaccharide storage myopathy (PSSM) is seen not uncommonly in horses. Although Quarter horses, Warmbloods, and Draft horses are overrepresented, PSSM has been reported in almost all breeds. As its name suggests, PSSM is a glycogen storage myopathy. It is an inherited, autosomal dominant disease with variable clinical expression. One form of the disease has been linked to a mutation in the glycogen synthase I gene, for which a genetic test is now available.

Horses with PSSM present with recurrent exertional rhabdomyolysis, become progressively weak, and may show muscle atrophy. Some horses with the condition may be subclinically affected. Gross findings may range from normal musculature to muscles with pale, white, necrotic streaks. When present, lesions tend to be most notable in muscles composed predominantly of type 2 fibers: the semimembranosus, semitendinosus, and gluteals, for example. In cases of sudden death, the diaphragm should be carefully examined, as severe myonecrosis may have occurred. Histologically, muscles demonstrate notable intrasarcoplasmic, PAS-positive inclusions (Figure 2.3).

2.5 Malignant hyperthermia

Though classically thought of as a disease of pigs, malignant hyperthermia is better thought of as a syndrome that predominantly occurs in swine, but also affects dogs and horses. The underlying issue is a defect in

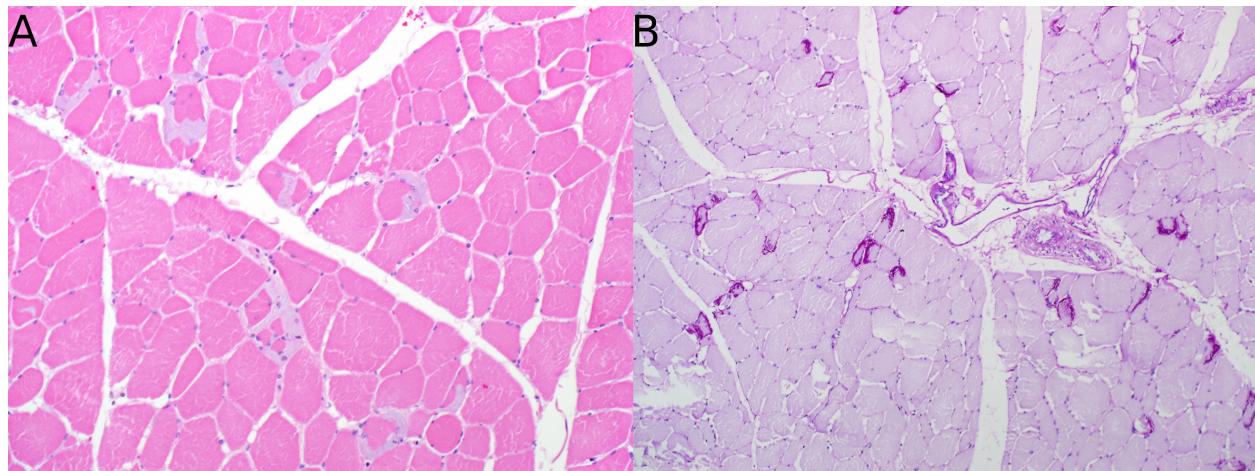


Figure 2.3: Photomicrograph of muscle from a horse with PSSM. A) Multiple myofibers show distinct amphophilic material, particularly along the periphery of the myofiber. H&E B) The material stains positive with PAS (bright magenta). PAS.

the *RYR1* gene, which encodes the ryanodine receptor, a calcium channel present within the sarcoplasmic reticulum. Defective ryanodine receptors are responsible for the release of Ca^{2+} during contraction. Defective ryanodine receptors stay open for longer, leading to prolonged contraction, hypercontraction, and hyperthermia.

2.5.1 Porcine stress syndrome

Malignant hyperthermia is best characterized in pigs, and is also known as porcine stress syndrome (PSS) and is the cause of pale, soft, and exudative pork. A single nucleotide polymorphism in the *RYR1* gene of pigs is the cause. It is estimated that between 2-30 % of pure-bred pigs are susceptible to PSS.

Pigs may be unaffected or subclinical. Stressful events (such as fighting or transport), or halothane anesthesia, however, can trigger severe episodes in which pigs display intense limb and torso rigidity, hyperthermia, tachycardia, dyspnea, metabolic acidosis, and rapid death. Gross lesions are related to the increased body temperature: classically pale, soft, exudative muscle (meat). Lesions attributable to heart failure, including pulmonary edema, hydrothorax, and hepatic congestion, may also be present. Histologically, multifocal, monophasic necrosis is present, and edema separates myofibers in animals that have suffered from hyperthermia.

2.6 Congenital myasthenia gravis

Myasthenia gravis is a neuromuscular disorder characterized by decreased availability of acetylcholine (Ach) receptors on the myofiber membrane. In congenital myasthenia gravis, decreased Ach-R availability is due to an inherent defect in the receptor. In Acquired myasthenia gravis, circulating autoantibodies bind to and block the binding of Ach to their receptor. The acquired form is much more common than it's congenital counterpart.

In dogs, congenital myasthenia gravis is autosomal recessive. Puppies develop exercise-induced collapse by 5-16 weeks of age, depending on breed. Regurgitation secondary to megaesophagus is a common problem. Antibodies against Ach-R cannot be demonstrated.

The disorder is even less common in cats, which may seem normal at birth, but by approximately 4-5 months of age show signs of episodic weakness. Megaesophagus is *not* a feature. The condition remains poorly characterized.

2.7 Myotonic and spastic syndromes

Myotonia is the temporary inability of muscles to relax. It can be acquired or inherited; in veterinary species, the inherited form is most common. Three are a variety of myotonias in dogs, cats, and goats that will not be covered here; more information can be found in the reference textbooks.

2.7.1 Hyperkalemic periodic paralysis (HYPP)

Only horses descended from the Quarter Horse stallion “Impressive” are at risk for HYPP. The condition presents differently depending on whether the animal is a heterozygote or homozygote. Homozygote foals characteristically suffer from laryngospasm, which can generate a distinctive inspiratory noise. They may develop dysphagia and become emaciated during their first 2 years. The larynx may collapse with exercise. Heterozygotes are less severely affected, and often appear normal but suffer from transient attacks of paralysis, muscle fasciculations and spasms, inspiratory stridor, and may collapse. Sudden death may occur in the most severe cases.

The underlying cause is a defect in Na^+ channels causing excess influx of Na^+ and efflux of K^+ from myofibers. This alters the membrane potential of myofibers and leads to increased action potentials. There are no gross or histologic lesions; diagnosis is based on clinical history, signs, and DNA testing.

Chapter 3

Circulatory disturbances

Due to the high demand for oxygen and nutrient, skeletal muscle is a relatively well vascularized tissue (as you will find out when you cut a muscle belly during surgery!). This makes it somewhat resistant to vascular injury, as there is substantial collateral circulation: each myofiber is supplied by 3-12 capillaries. Thus, for the most part, ischemic damage to muscle is due to pressure over *large* surfaces of the body. Thromboembolic occlusion of a large vessel, most commonly seen at the aortoiliac junction in cats (and horses), can also lead to ischemic necrosis of large areas of muscle.

3.1 Compartment syndrome

Compartment syndrome occurs most commonly in chickens and humans. As discussed in the section on The anatomy of muscle, muscles are covered by various layers of connective tissue. Some muscles – the supracoracoid muscles in chickens, for example – are surrounded by inelastic tissues. In the case of the supracoracoid, the breastbone on one side, and a relatively rigid outer sheath on the other encases the muscle in a fixed “compartment”. In the case of the chicken, short, vigorous exercise (wing flapping) is enough to increase intramuscular pressure significantly, collapsing veins and decreasing venous outflow. On top of this, muscle contraction can increase the diameter of myofibers by 20%, and in a restricted compartment, this contributes to further venous collapse. Increased muscular activity also increases arterial blood flow. The net result is increased arterial flow with decreased venous outflow leading to ischemic necrosis, all caused by a muscle held captive by rigid surrounding tissues. Damage to vessels subsequent to the necrosis can lead to interstitial edema, further increasing tissue pressure, and exacerbating the condition. Treatment (generally for humans) can involve a fasciotomy to relieve the pressure.

3.2 Downer syndrome

Downer syndrome refers to ischemic myopathy caused by long periods of recumbency, leading to undue pressure on the dependent muscles. Size and weight of the animal are important factors: larger, well muscled animals are more prone to this syndrome than are thin animals. Cows are most frequently affected, while cats seem to be exempt.

The pathogenesis is more complicated than initially meets the eye. The increased pressure on muscles caused by prolonged recumbency initially collapses veins, causing congestion and ischemia. Eventually arteries are affected as well, further contributing to the ischemic damage. If and when the animal changes positions and relieves the pressure, arteries are the first to recover, and the increased arterial pressure in the face of decreased venous outflow leads to edema, which itself can cause increased pressure and decreased venous outflow, further compounding the problem. Reperfusion injury also likely contributes to muscle damage.

3.3 Postanesthetic myopathy of horses

Horses that undergo prolonged anesthesia are prone to ischemic myopathy, especially if inadequate padding is used. Pressure on the muscle capillaries, caused by the weight of the horse, exceeds the pressure of perfusion, resulting in ischemia. The muscles affected depend on the position of the horse. Predisposing factors include intraoperative hypotension and the presence of comorbidities, especially Equine polysaccharide storage myopathy (PSSM) and Hyperkalemic periodic paralysis (HYPP).

Chapter 4

Physical injuries

Traumatic injuries to muscle include lacerations, penetrating wounds, tears, and strains are common in domestic species. Their pathogenesis is straightforward, and the outcome depends on the severity of the trauma.

A muscle rupture can occur following violent exercise or trauma. The muscle forms a bulge at the end opposite of the rupture. The most commonly ruptured muscle is the diaphragm, particularly after traumatic injury (e.g. hit by car). Healing is usually by fibrosis, as the damage is usually too extensive for regeneration to occur.

A muscle strain is the overextension of muscles resulting in myofiber disruption, particularly at the junction with tendons. Severity varies, and healing is by fibrosis.

The physical consequences of penetrating wounds are self-explanatory, but you should also be aware that secondary complications, such as Suppurative myositis or Tetanus, may result.

Chapter 5

Toxic myopathies

Skeletal muscle is a highly vascular and metabolically active tissue and is therefore somewhat susceptible to a variety of toxins. The most commonly encountered toxins in veterinary species are ionophore antibiotics and plant associated toxins. Livestock and horses are most frequently affected.

5.1 Ionophore toxicity

Ionophore antibiotics are commonly found in the feed of livestock and are used as growth promoters. Horses are particularly susceptible to low concentrations of ionophores, and may be exposed either through errors at feed mills, or by consuming feed formulated for other species. Monensin is the most frequently implicated ionophore. Ionophores affect membrane permeability to electrolytes, and results in calcium overload and subsequent death of skeletal and cardiac muscle. Affected horses may show signs of colic, lethargy, stiffness, and/or weakness. Lesions are often seen within 48 hours. The heart is often most severely affected, showing pale, white to tan, often streaked areas of necrosis (Figure 5.1); other muscles may show similar changes, though to a lesser degree. Horses usually only require one dose to become severely affected, and therefore show acute, multifocal, monophasic muscle injury.

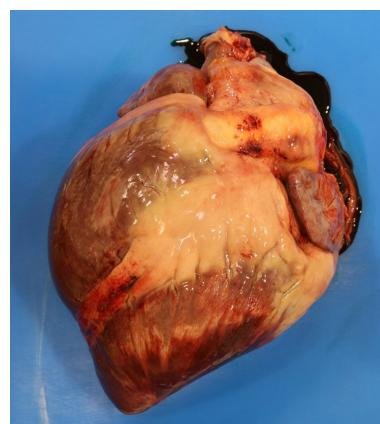


Figure 5.1: Equine heart demonstrating marked myocardial necrosis, manifesting as pale white streaks across the ventricle. Photo: C. Martin



Figure 5.2: Left: A coffee senna plant. Photo by Jee and Rani Nature Photography (License: CC BY-SA 4.0, <https://commons.wikimedia.org/w/index.php?curid=9452256>). Right: Box elder (Manitoba) maple seeds.

5.2 Plant toxicities

Gossypol from cottonseeds (*Gossypium* spp.), senna or coffee senna plant (*Senna occidentalis*, formerly *Cassia occidentalis* or *C. obtusifolia*), or coyotillo (*Karawinskia humboldtiana*) are the most common sources of plant toxin-induced myopathy (Figure 5.2). The latter two produces a rapidly progressing disease characterized by a swaying, stumbling gait followed by recumbency, myoglobinuria, and elevated CK. Mortality is high. Gross lesions include ill-defined pallor of many muscles, that under light microscopy demonstrate multifocal, monophasic myonecrosis. Cattle, horses and pigs are particularly affected.

Gossypol toxicity occurs mostly in pigs. Cottonseed, the source of gossypol, is added to swine feed as a protein supplement, and toxicity occurs when excess cottonseed (> 10 % of feed) is consumed. Lesions take weeks to 1 month to appear, and include skeletal and cardiac myonecrosis.

5.2.1 Seasonal pasture myopathy of horses

Ingestion of box elder and/or sycamore maple tree seeds containing hypoglycin A causes seasonal pasture myopathy of horses. This disease is characterized by rhabdomyolysis and myoglobinuria, typically occurs in the fall, and can be fatal. Gross findings are non-specific, typically consisting of pale, necrotic muscles affecting multiple different muscles.

Chapter 6

Degenerative/necrotizing myopathies

Although degeneration and necrosis are a feature of a number of different myopathies, this section describes myopathies that *do not have a congenital, nutritional, toxic, or infectious etiology*.

6.1 Exertional myopathies

An exertional myopathy is defined as myofiber damage occurring as the direct result of exercise.

6.1.1 Equine exertional rhabdomyolysis

Synonyms: blackwater, Monday morning disease, set fast, paralytic myoglobinuria, azoturia

This condition is often worse in heavy, draft breeds as compared to light breeds, and female horses are predisposed. The pathogenesis of the condition is not completely known. The current accepted theory is that muscle damage is most often due to underlying metabolic abnormalities, possibly a post-exercise hypokalemia, and not management factors. Interestingly, although diet is not considered to be the underlying cause of exertional rhabdomyolysis, virtually all horses suffering from the condition respond favourably to a diet high in fat and fiber and low in starches.

Exertional rhabdomyolysis presents as a sudden onset of weakness, pain, and discomfort, sometimes with tremors or sweating, during or after periods of exercise. The exercise does not have to be overly strenuous or exhaustive. Severe cases may progress to recumbency. Type 2 glycolytic myofibers are most severely affected. Cardiac muscle is spared, and mineralization is not a feature. Grossly, affected muscles (particularly the gluteal, femoral, and lumbar muscles) may be swollen and dark red, with streaks of pale pallor present in severe cases. Histologically there is necrosis of type 2 fibers. Fibrosis and atrophy will be present in chronic cases. Myoglobinuria is a common feature, and can lead to myoglobinuric nephrosis.

There is evidence that horses with Equine polysaccharide storage myopathy (PSSM) are predisposed, but the exact mechanism is unclear.

6.1.2 Canine exertional rhabdomyolysis

As one might expect, this syndrome appears most frequently in racing dogs, namely Greyhounds and sled dogs. It is not particularly well understood, but thought that separate mechanisms cause the syndrome in sprinting versus endurance racing. In Greyhounds, clinical signs and symptoms are similar to those noted for horses, while in sled dogs may present with sudden death.

6.1.3 Capture myopathy

This is a syndrome seen both in free and captive wildlife. The stress of capture, which is usually preceeded by a chase and/or struggle in these animals, results in a combined massive release of catecholamines and overexertion that is frequently fatal. Muscles may be pale and edematous or may show pale streaks with hemorrhage. Degeneration and necrosis is frequently observed histologically. This condition is extremely important in zoological collections, and as such great care is often taken when tranquilizing or restraining animals for examination.

Chapter 7

Myopathies associated with serum electrolyte imbalance

7.1 Feline hypokalemia

Hypokalemia in cats can lead to a distinct clinical syndrome called feline hypokalemic polymyopathy. It is characterized by ventroflexion of the neck, a stiff, stilted gait, muscle pain, reluctance to walk, and weakness. Low potassium can be the result of decreased dietary intake, chronic renal disease, or in cats fed acidifying diets to control urolithiasis. The pathogenesis of muscle injury in hypokalemia is attributed to a decrease in resting membrane potential of myofibers, altered glycogen metabolism, and ischemia from hypokalemia-induced vasoconstriction. Frustratingly, lesions can be mild or absent in clinical cases. Histologic lesions are most likely to be found in **respiratory muscles – the intercostals and the diaphragm** – and these are recommended for sampling at autopsy if the disease is suspected.

7.2 Bovine hypokalemia

Rather specifically, muscle weakness has been observed in cattle being treated with isoflupredone for ketosis. The drug can cause severe hypokalemia. These animals are weak and recumbent. Acute necrosis occurs in both weight- and non-weight bearing muscles.

Chapter 8

Immune-mediated myopathies

Generally speaking, immune-mediated disease is the result of abnormal immune response against self-peptides or antigens.

A difficulty when evaluating immune-mediated disease is determining whether the immune response is the primary *cause* of muscle damage, or whether the leukocytes are simply *responding* to the damage. In the case of immune-mediated myopathies, the invasion of intact myofibers by mononuclear leukocytes is characteristic.

8.1 Masticatory myositis

This is a rare condition of dogs characterized by profound atrophy of the muscles of mastication: the masseter, temporal, and pterygoid muscles. Two conditions, atrophic myositis and eosinophilic myositis, formerly thought to be distinct entities, are now known to represent two manifestations of the single disease known as masticatory myositis.

Animals present with difficulty opening their mouth and concurrent muscle atrophy. Pain is noted upon opening the mouth, and the jaw remains difficult to open even under general anesthesia. German shepherds seem to be predisposed, but the condition affects a variety of breeds.

The root cause of masticatory myositis is a unique myosin isoform, **2M myosin**, found only in the masticatory muscles of the dog. Antibodies against 2M myosin lead to a patchy lymphocytic inflammatory response, ultimately resulting in variably severe, multifocal, polyphasic necrosis. Both T- and B-cells are present in the inflammatory response. In some cases, eosinophils are present in large numbers. Prompt treatment with corticosteroids can resolve clinical signs and lead to recovery. Untreated cases result in necrosis followed by fibrosis, which, if severe, can be devastating. A serologic test to detect antibodies against 2M myosin is available.

8.2 Polymyositis of dogs

Immune-mediated polymyositis is generalized myopathy of dogs. It can mimic masticatory myositis, and both should be considered as differential diagnoses when confronted with a dog with masticatory muscle atrophy. The condition occurs in adult dogs of a variety of breeds, though German shepherds are again overrepresented. Clinical signs are variable and include muscle atrophy, exercise intolerance, weakness, stiff gait, and pain on deep muscular palpation. Muscle atrophy may be mild to severe and is generalized. The esophagus may be affected. Dogs with immune-mediated polymyositis generally do *not* have antibodies against 2M myosin. The disease is mediated by CD8⁺ T-cells, with little to no involvement of B cells, a feature that helps differentiate this condition from masticatory myositis. Muscle necrosis multifocal and polyphasic,

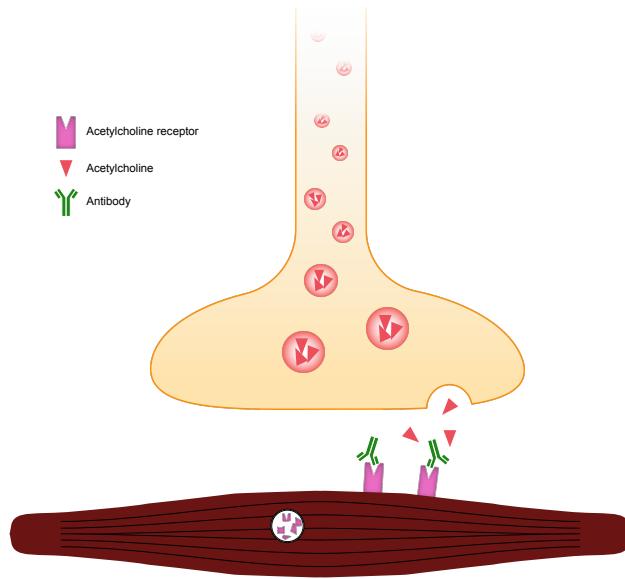


Figure 8.1: Illustration of a motor end plate affected by acquired myasthenia gravis. Note the immunoglobulin binding to the acetylcholine receptor, preventing the binding of acetylcholine, and also leading to endocytosis and decreased receptor density.

myofibers are frequently invaded by lymphocytes, and there is evidence of degeneration, regeneration, and fibrosis.

8.3 Acquired myasthenia gravis

Myasthenia gravis is a rare but important disease of dogs and cats (and humans), and two clearly defined types exist: acquired, and congenital (discussed in Congenital myasthenia gravis). Acquired myasthenia gravis is caused by antibodies against the acetylcholine receptors located at the motor end plate (Figure 8.1). Binding of antibodies to the receptors forms an immune complex that results in endocytosis, ultimately decreasing the density of acetylcholine receptors at the neuromuscular junction. In dogs, the condition has been linked to thymomas, which are thought to create an abnormal immune response leading to antibody formation. It has also been linked to hypothyroidism and various malignant neoplasms.

A variety of breeds are affected, and age of onset follows a bimodal distribution, with one peak at 3 years and another at 10. Affected dogs can present with one of three clinical syndromes:

1. Generalized: these animals have generalized weakness, suffer from exercise induced collapse, and commonly regurgitate due to megaesophagus. Aspiration pneumonia may result from regurgitation.
2. Localized: this form preferentially involves the esophageal, facial, and pharyngeal muscles, leading to megaesophagus and regurgitation, but no weakness.
3. Fulminant: rapid and sustained generalized weakness.

Gross lesions of acquired myasthenia gravis are limited to disuse atrophy, megaesophagus, and possibly aspiration pneumonia or thymoma. Microscopic lesions are underwhelming, but immune complexes at the neuromuscular junction can be demonstrated using immunohistochemistry. Detection of circulating anti-acetylcholine-receptor antibodies is the (antemortem) diagnostic test of choice.

Chapter 9

Infectious myositis

9.1 Clostridial myositis

Clostridial infections are **common and important diseases of livestock**. Common causes of clostridial disease are *C. septicum*, *C. chauvoei*, *C. perfringens*, *C. novyi*, and *C. sordellii*. Occasionally more than one species can be cultured. Although the following conditions are often attributed to specific clostridial organisms, these should be considered *the most common cause*, and not necessarily the *sole* cause. Clostridial disease is caused by the release of exotoxins, leading to local damage and systemic illness. They are often fatal.

A common thread in the pathogenesis of clostridial myositis is the prerequisite for muscle with reduced oxygen tension that leads to vegetative growth of the organism and the production of damaging exotoxins. Further detail is found in the sections below.

9.1.1 Malignant edema and gas gangrene

Malignant edema and gas gangrene are two forms of clostridial myositis, occurring most commonly in the horse but also in cattle and other livestock. They share a pathogenesis and many clinical signs; it is simply the presence of gas bubbles that distinguishes gas gangrene from malignant edema. *C. septicum* is most commonly the cause of malignant edema, while *C. perfringens* is more frequently isolated from gas gangrene.

Malignant edema/gas gangrene is the result of a deep, penetrating wound, almost always from an injection, though surgical procedures (castration) may also introduce spores. Local anaerobic conditions allow organisms to proliferate and produce exotoxin that damage blood vessels, causing hemorrhage and myonecrosis. The damage is often extensive and accompanied by a serosanguineous exudate and extremely foul smell. Microscopically, hemorrhage, edema, and myonecrosis predominate. Neutrophils and bacteria are present but are infrequent. Without prompt treatment (antibiotics and fasciotomy, Figure 9.1), death occurs within 24-48 hours.

9.1.2 Blackleg

Blackleg is a **common and deadly** condition of well-conditioned, pastured cattle 9 months to 2 years old. The cause of blackleg is *C. chauvoei*. Unlike malignant edema/gas gangrene, **penetrating wounds are not a feature of blackleg**. Instead, spores are ingested from contaminated pasture, and, through as yet unknown mechanisms, cross the intestinal mucosa and spread hematogenously to various organs, including skeletal muscle. **It is only when an event creates muscle damage or leads to low muscle tension** that the disease manifests. Low oxygen tension creates the right environment for spores to germinate and for



Figure 9.1: Malignant edema in a cow resulting in marked swelling of the gluteal muscles. This cow was treated with several fasciotomy incisions to release the pressure and allow exposure to oxygen. Image courtesy of Dr. H Staempfli.

organisms to multiply and release toxin, leading to vascular necrosis, hemorrhage, and myonecrosis. Lesions are most frequently found in the muscles of the limbs, though the tongue and diaphragm are also common sites. The myocardium may also be affected. The clinical course is so rapid that clinical signs are rarely observed; animals die within 24-36 hours.

The condition derives its name from the gross appearance of muscle at necropsy, which is typically dark red to black, with or without gas bubbles. Histologically, severe myonecrosis and fragmentation are present alongside marked edema and hemorrhage.

9.1.3 Botulism

Note: Botulism and Tetanus are described here, as they are clostridial diseases, but they should be considered neuromuscular diseases. They do NOT cause a myositis!

C. botulinum is the causative agent of botulism, a neuromuscular disease leading to flaccid paralysis of skeletal muscle. Horses are particularly susceptible. In foals < 6 months of age, ingestion of *C. botulinum* spores can lead to proliferation of the organism and production of botulinum toxin. In adult horses, it is more commonly the ingestion of botulinum toxin, not the bacteria itself, that is the cause of the disease. Hay contaminated with the corpses of rodents is a common source of botulinum toxin. Botulinum toxin spreads hematogenously to the neuromuscular junction where it is taken up by the terminal axon. Botulinum toxin binds to synaptic vesicles containing acetylcholine, preventing their release, and thereby preventing the spread of action potentials, ultimately resulting in paralysis. There are no gross or histological lesions.

9.1.4 Tetanus

Like Botulism, tetanus is the result of a clostridial toxin affecting neurotransmitter release. It develops when spores of *C. tetani* are introduced into tissue by penetrating injuries. Anaerobic conditions at the site of injury prompt the spores to vegetate. Tetanus toxin is taken up by endocytosis into the axon of the nearest

Table 9.1: Most common bacterial isolates from muscle abscesses in veterinary species

Species	<i>Bacteria</i>
Cattle	<i>T. pyogenes</i>
Swine	<i>C. pseudotuberculosis, H. parasuis</i>
Sheep	<i>C. pseudotuberculosis</i>
Goats	<i>C. pseudotuberculosis</i>
Horses	<i>C. pseudotuberculosis, S. equi</i>
Cats	<i>P. multocida</i>

motor neuron and brought via retrograde transport to the neuronal cell body within the spinal cord. There the tetanus toxin is released, and is then taken up by the axon of an *inhibitory* neuron. Once within the inhibitory neuron, the toxin acts in a fashion similar to that of botulinum toxin, and interferes with the release of acetylcholine. *It is the abolishment of inhibitory signals that leads to the clinical signs associated with tetanus.* Motor neurons are under more or less constant stimulation, and the inhibitory neurons serve to counter balance this stimulation. With the removal of inhibitory constraint, all that is left is stimulation, leading to prolonged, severe muscle contraction.

Horses, guinea pigs, and humans are most susceptible to disease, while dogs and cats are relatively resistant. There are no gross or histologic lesions.

9.2 Suppurative myositis

Suppurative myositis is most commonly the result of inoculation from trauma or surgery. Occasionally, abscesses can develop in muscle through extension from nearby structures (e.g. joint or tendons), or through hematogenous spread. The most common bacterial isolates from muscle abscesses are given in Table 9.1.

Chapter 10

Parasitic myositis

Parasitic diseases of the muscle are rarely pathological to the host, but are a critical part of the lifecycle of several important parasites.

10.1 Sarcocystosis

Sarcocysts are a very common protozoan parasite found in the muscle of herbivores. They have an indirect life cycle. Carnivores are typically the definitive host, and become infected through consumption of muscle from an infected intermediate host. Most herbivorous species have their own *Sarcocystis* species (e.g. *S. bertrami* in horses, *S. cruzi* in cattle, and *S. tenella* in sheep), and sarcocysts are routinely found in the muscles of these species, almost always with little to no associated pathology. Rarely, pathology in the form of myositis can occur. Even less commonly, cattle and sheep may develop eosinophilic myositis, which is thought to be caused by the degeneration of sarcocysts and which provokes a profound – and deadly – eosinophilic myositis. This grossly presents as distinctive, well demarcated areas of green discolouration the muscle.

10.2 *Neospora caninum* and *Toxoplasma gondii*

Although more commonly associated with abortion and neurological disease, *N. caninum* and *T. gondii* both occasionally present as a disease of muscle. Puppies and kittens tends to be affected most often. The disease manifests as a myositis with lymphoplasmacytic inflammation, myonecrosis, and atrophy.

10.3 Trichinellosis

Trichinellosis is an important parasitic disease of animals and humans. Several species of *Trichinella* exist. The most common is *T. spiralis*. The parasite infects a multitude of species, including pigs, dogs, cats, bears, rodents, and many other wild animals. The disease in humans in North America has largely become historical due to routine meat inspection, but does still affect people, and is still present in wild carnivores. Wild animals of the arctic, such as walrus and polar bears, are an important source of food for the Inuit, and represent a particularly important risk of Trichinella. Ingestion of undercooked wild meat is perhaps the most important risk factor for human trichinellosis.

The life cycle of *Trichinella* spp. is relatively simple. Nematode larva encysted in muscle are consumed, and released by the gastric juices of the host. The liberated larva molt into adults and reproduce. The females penetrate through the intestinal crypts (the males die), and deposit larva into the lymphatics. The larva

Table 10.1: Tapeworm and cysticercus species, along with their hosts and predilection sites

<i>Tapeworm</i>	Definitive.host	<i>Cysticercus</i>	Intermediate.host	Predilection.site
<i>T. solium</i>	Human	<i>C. cellulosae</i>	Pigs (and humans)	Heart, masseter, tongue
<i>T. saginata</i>	Human	<i>C. bovis</i>	Cattle	Heart, masticatory muscles
<i>T. ovis</i>	Dogs, wild carnivores	<i>C. ovis</i>	Sheep and goats	Heart, skeletal muscle

travel through the lymphatic system and into the systemic circulation, where they then preferentially encyst into muscles, and await the next cycle. Those that do not encyst in muscle are cleared by the immune system. Through an unknown mechanism, the larva encyst prefentially in the **diaphragm, tongue, laryngeal muscles, and masseter muscles**.

The pathology caused by *Trichinella* spp. is relatively mild. A single larva will enter into a single myofiber, where it enlarges and coils. The myofiber undergoes some changes, including enlargement of the nuclei, decrease in number of myofibrils, and an increase in the thickness of the basal lamina, to become what is known as a “nurse cell”. Rarely, lymphoplasmacytic inflammation is present. Larva can live in an encysted form for over 20 years, and *T. nativa*, the species found in northern animals, resists freezing.

In humans, clinical signs and symptom related to trichinellosis include fever, myalgia, facial edema, rash, and occasionally chronic diarrhea.

10.4 Cysticercosis

The taxonomy and nomenclature of the tapeworms is confusing and frustrating. Adult taenids are classified separately from their intermediate form, the cysticerci. *Cysticercosis is the result of consumption of taenid eggs, not the consumption of cysticerci*. It is the pathology related to the development of cysticerci in the muscle, and is still an important disease in developing countries.

Like many parasites, the life cycle of tapeworms revolves around a predator-prey dynamic. Predators are the definitive host of the adult tapeworm and are infected through consumption of larval stages in the flesh of the prey. Larva of tapeworms go through several developmental cycles, one of which is a cysticercus, in the intermediate host. In some tapeworm species, the cysticercus has a predilection site for skeletal muscle; it is those species that interest us here, and which are described in Table 10.1.

The pathology in intermediate hosts is fairly minimal. Cysticerci form grossly visible cysts (1-2 cm) containing clear fluid and a larva. These may elicit a mild lymphoplasmacytic and eosinophilic inflammatory response. Dead larva become heavily calcified.

Chapter 11

Neoplasms of muscle

Primary neoplasms of the striated muscle are rare in veterinary species. Although usually found in muscle, they can arise in unexpected locations devoid of striated muscle, such as the bladder.

11.1 Rhabdomyoma

As its name suggests, a rhabdomyoma is a benign tumour of striated muscle. It is seen most frequently in the hearts of pigs, particularly the red wattle breed and are typically incidental findings. They often present grossly as circumscribed, smooth-surfaced, nodular masses embedded in the myocardium. A similar neoplasm occasionally arises on the larynx of dogs. Laryngeal rhabdomyomas may cause respiratory difficulty or altered bark. They are typically minimally invasive and tend not to metastasize.

11.2 Rhabdomyosarcoma

These are the malignant counterparts to rhabdomyomas. They are most common in the dog. Counterintuitively, they occur more frequently at sites that normally lack skeletal muscle versus those that don't. There are a variety of subtypes, however, whether there is any prognostic significance to differentiating them is uncertain. They all tend to be locally invasive and metastatic. Prognosis is poor for all subtypes. Grossly, the tumours appear as pale, white to tan, firm masses, often with areas of necrosis. The botryoid ("cluster of grapes") subtype occurs in the bladder as a polypoid mass. The histologic appearance of these tumours is quite variable, though occasionally elongated, variably striated, myotube-like cells known as "strap cells" are present, which is suggestive of rhabdomyosarcoma. Immunohistochemistry is usually required to definitively diagnose these tumours.

11.3 Non-muscle primary tumours of muscle

Granular cell tumours occur in the tongue of dogs and cats. They are composed of densely packed round cells with PAS positive granules. The supporting mesenchyme of muscle can occasionally produce a (usually) malignant neoplasm. Hemangiosarcomas can arise in the muscles of dogs and horses, and aspiration of these large, intramuscular masses typically only reveals hemorrhage. Like their splenic cousins, they metastasize frequently.

11.4 Secondary tumours

Muscles are occasionally infiltrated by local neoplasms. Infiltrative lipomas are characterized by relatively well differentiated adipocytes crawling and invading through myofibers. They are highly invasive and require excision. Other neoplasms, such as subcutaneous mast cell tumours, lymphoma, hemangiosarcomas, and soft tissue sarcomas can invade into muscle. Metastasis to muscle is uncommon but does occur.

Chapter 12

Nutritional myopathies

12.1 Selenium and vitamin E deficiency

Deficiency in selenium, and to a lesser extend, vitamin E, is a **very important** disease of young cattle, sheep, swine, and horses. Neonatal animals are particularly susceptible, as they rely on stores accumulated *in utero*, which may be sub-optimal. The disease is rarely seen in carnivores. This disease is also colloquially known as **white muscle disease**. Selenium and vitamin E levels in animals are directly related to dietary intake, it is thus important that animals are fed well balanced rations. Complicating matters, vitamin E is often low, in part due to degradation when stored for prolonged periods of time.

Selenium and vitamin E are components of antioxidants that play important roles in the control of free radicals and oxidative damage. Recall that a free radical is a molecule with an unpaired electron, and as such are highly reactive and have enormous potential to damage cell and mitochondrial membranes (lipid peroxidation). Antioxidants are protective against free radicals: vitamin E directly scavenges free radicals, while selenium is a component of an enzyme, glutathione peroxidase, that reduces free radicals.

When levels of selenium and/or vitamin E are low, free radical damage accumulates, particularly in skeletal and cardiac muscle. The high oxygen requirement and contractile activity of these two tissues renders them particularly susceptible to oxidative damage. Free radical damage to cell and organelle membranes contributes to a loss of ionic gradient and increased sarcoplasmic Ca^{2+} concentrations, leading to hypercontraction, myofiber necrosis, and potentially mineralization.

Grossly, the necrotic muscle appears **white**, though, if you recall, this is a *non-specific* finding, and could be the result of a number of etiologies. When performing a necropsy, pay close attention to muscles that tend to be the most active: the heart (particularly the left ventricle of calves, right ventricle of sheep, the tongue, diaphragm, and intercostal muscles). Histologically, there is *multiphasic necrosis with regeneration*. The damage tends not to affect the basal lamina or satellite cells, so myofibers are able to regenerate and recover, depending on the severity of the damage. Although regeneration is possible, it is not infrequent for animals to die or be euthanized due to this condition.

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