Systems Pathology: Skeletal Muscle

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Chapter 1

Systems Pathology: Muscle System

About

These notes are a fairly comprehensive collection of information to complement the lectures and labs delivered in VPM 2210 and 2220, Systems Pathology I and 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/course-materials/muscle/, as a PDF on this site (icon to the left, underneath the image) or on Moodle. Please feel free to provide feedback, whether on content, style, or typos!

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Reference material

- Zachary, J. F., & McGavin, M. D. (2022). Pathologic Basis of Veterinary Disease, 7 ed. 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-base?) using the bookdown (Xie 2015), knitr (R-knitr?), and Rmarkdown (R-rmarkdown?) packages. Source material was taken from Zachary and McGavin (2022) 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.

Chapter 2

Introduction

2.1 The anatomy of muscle

The basic structural unit of muscle is the myofiber, which represents a single, long, tubular cell (Figure 2.1). 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 arrangment of myofibrils that form the striated appearance of skeletal muscle that can be appreciated under light microscopy (Figure 2.2). 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, which is surrounded by the epimysium.

Skeletal muscle is characteristically multinucleated: each myofiber has hundreds 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 (myofiber), 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

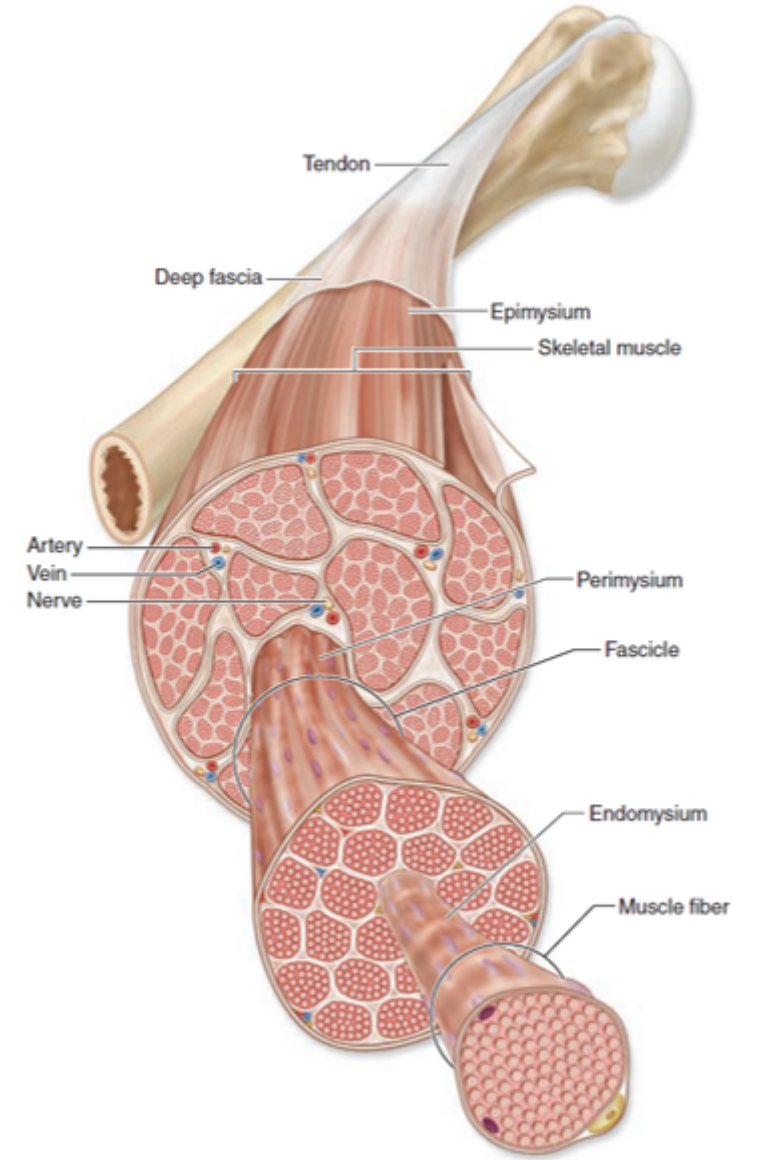

Figure 2.1: Structure and anatomy of muscle. Figure from Zachary and McGavin

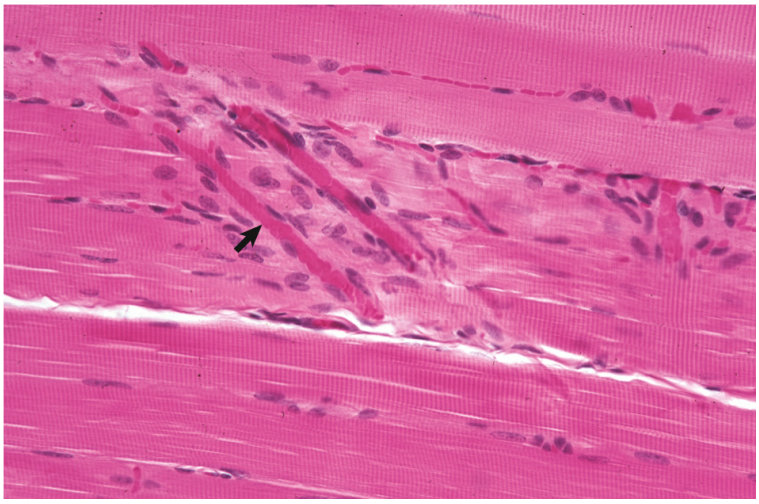

Figure 2.2: Normal skeletal muscle demonstrating striations. The arrow indicates a small capillary. Figure from Zachary and McGavin

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 2.1)). 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, and each motor neuron typically innervates multiple myofibers. The number of myofibers innervated by a neuron is dependent on the need for fine control: only 1-4 myofibers of the occular 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.

Table 2.1: Properties of different myofiber types

Fiber type	Physiologic properties	Morphologic properties	E

Type 1	Slow twitch, fatigue resistant, oxidative, aerobic, 'red'	High mitochondrial and fat content, low glycogen	M e.
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	M sp

2.2 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 (recall from physiology that the sarcomere is the functional unit of contraction). 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 in muscle relaxation 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 of the carcass occurs due to breakdown of muscle either from autolysis or putrefaction (bacterial decomposition).

2.3 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 specific circumstances, muscles that have been only mildly injured can regenerate. The reaction of muscle to injury tends to proceed in a fairly sterotypic fashion regardless of the inciting cause, making it difficult to determine the underlying etiology from gross or histopathological exmaination 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 helpful (and occasionally necessary) in obtaining a definitive diagnosis.

2.3.1 Atrophy

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

2.3.1.1 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. Motor neurons release trophic factors at the motor end plate, which are critical in maintaining normal myofiber mass. 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 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.

2.3.1.2 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). Disuse atrophy occurs more gradually then 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 unreliable. Unlike dennervation atrophy, usually all myofibers within a muscle group are affected by disuse atrophy, and thus there is no compensatory hyertrophy.

2.3.1.3 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 used as a source of nutrients. Nutritional muscle atrophy is usually accompanied by fat loss.

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. The term “chachectic” refers to animals with muscle atrophy secondary to illness or disease, in spite of the provision of adequate nutrition.

2.3.1.4 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.

2.3.2 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.

2.3.3 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 moderate to severe cases. Necrotic muscle is typically pale pink to white, and may appear streaked and slightly gritty if mineralization has occurred (for example, in selenium and vitamin E deficiency)(Figure 2.3)). Necrotic muscle can alternatively appear deeply red, if hemorrhage has occurred concurrently.

The outcome of muscle damage and necrosis is dependent on its severity. A structure known as the basal lamina plays an important role. 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. If the basal lamina remains intact, and the damage only affects a small portion of the myofiber, then muscle can regenerate. These two criteria (intact basal lamina, focal area of damage) determine whether or not a muscle will regenerate or undergo fibrosis.

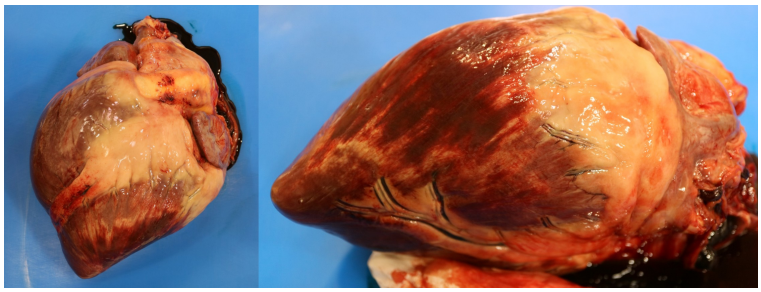

Figure 2.3: Necrosis of the myocardium. Pale white streaks bordered by hemorrhage are visible throughout the ventricle. Photo: C. Martin

Although myofiber nuclei themselves cannot divide, recall that each myofiber is accompanied by satellite cells (a type of stem cell), which can divide and differentiate into myofibers, and are critical components of muscle regeneration. The steps in muscle regeneration are fairly straightforward:

1. Segmental injury or 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 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]), or 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 (occuring at one point) or polyphasic (an on-going proceess). These can be further classified by the commonly used distribution modifiers: focal, locally extensive, multifocal, or diffuse,

to help narrrow 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].

2.4 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 @ref(fig:heart-necrosis)).
- Dark red:
  - Congestion or hemorrhage
  - Hemorrhagic necrosis
  - Inflammation
  - Hypostatic congestion (i.e. blood pooling due to gravity, a common artifact found during postmortem 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.

2.5 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, staples, or sutures, prior to placing the sample in formalin (Figure 2.4). As a general rule, a muscle biopsy should not exceed ~ 1 cm in diameter (with myofibers running lengthwise).

Note: if submitting a sample of muscle with sharps in the container, make sure to notify the pathologist on the submission form.

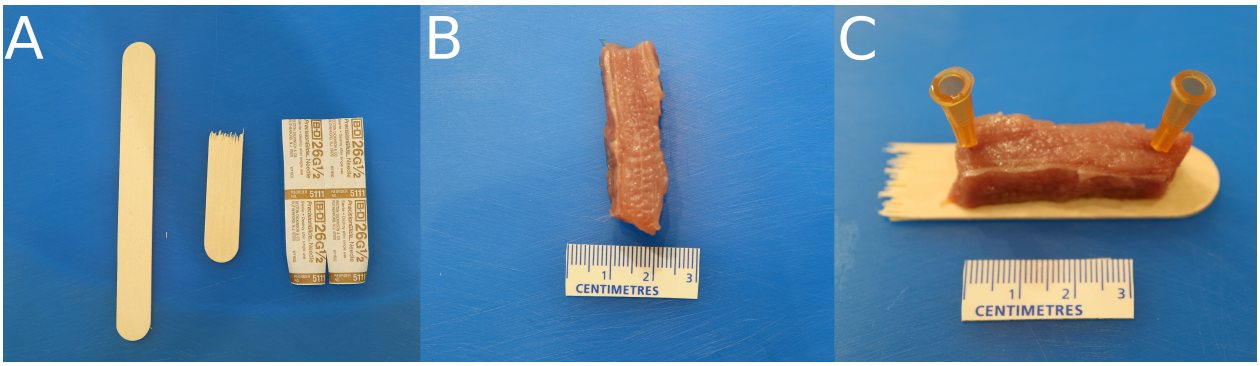

Figure 2.4: Appropriate technique for submitting muscle biopsies. A. Supplies that are readily available in most veterinary practices: a tongue depressor, broken to the appropriate size, and two small gauge needles. B. The diameter of a muscle biopsy should not exceed approximately 1 cm. C. Affix the biopsy to the tongue depressor using the two needles, staples, or sutures. Only a small amount of force is required to secure the muscle to the wood.

Chapter 3

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 do not necessarily mean that the parents are also affected.

3.1 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 at the motor end plate that are critical to the health of skeletal muscle . Conditions that primarily affect the motor neurons, therefore, can have significant effects on skeletal muscle.

3.1.1 Arthrogryposis

Arthrogryposis refers to the abnormal angulature 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.

3.2 Muscular defects

3.2.1 Splayleg

Splayleg is an odd condition that occurrs only in neonatal piglets (Figure 3.1). 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 3.1: Piglet affected by splayleg.

3.2.2 Muscular hyperplasia

Recall that normal muscle cannot undergo hyperplasia: increase in muscle size is usually a function of hypertrophy. However, myofiber hyperplasia is the hallmark of a defective protein known as myostatin. Myostatin is a protein produced and released by myofibers and normally 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 3.2) and White. The condition is also seen in Whippet dogs ("bully" Whippets). Muscular hyperplasia is most pronounced in the thighs, rumps, loins, and shoulders.

Figure 3.2: Two Belgian Blue cattle showing marked muscular hyperplasia of the rump.

3.2.3 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 sometimes raises concern at meat inspection.

3.2.4 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.

3.3 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 analagous 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.

3.3.1 X-linked dystrophies of dogs and cats

The X-linked dystrophies of dogs and cats share several similarities and a few key diferences, summarized below in Table 3.1. 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.

Table 3.1: Comparison of canine and feline X-linked dystrophy

	Canine	Feline
Breed predisposition	Golden retrievers, but also 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.

3.3.2 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.

3.4 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, 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. Many of these conditions are rare and relatively breed specific (for example, include glycogen storage disease type II in dogs and glycogen storage disease type IV in Norwegian Forest cats and horses). These uncommon conditions will not be discussed further here, but more information can be found in the reference textbooks. Instead, we will focus on a common metabolic myopathy of horses known as polysaccharide storage myopathy.

3.4.1 Equine polysaccharide storage myopathy (PSSM)

Equine polysaccharide storage myopathy (PSSM) is seen with some frequency in horses. Although Quarter horses, Warmbloods, and Draft horses are overrepresented, PSSM has been

reported in almost all breeds. As it's name suggest, 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, but not all cases of PSSM are caused by this mutation.

The pathogenesis of PSSM is still poorly defined, but is characterized by the abnormal accumulation of glycogen in myofibers, predominantly of the type 2 variety. A specific abnormality explaining abnormal utilization of intracytoplasmic glycogen has yet to be found, but a metabolic defect is still suspected.

Horses with PSSM present with a variety of clinical signs. Unexplained pelvic limb lameness is the most common finding. Horses may also have a stiff gait, sore back, muscle cramping, and/or muscle weakness. Some horses may present with recurrent episodes of [exertional rhabdomyolysis][Equine exertional rhabdomyolysis]. Some horses with the condition may be subclinically affected. Horses with PSSM are at increased risk of suffering from [postanesthetic myopathy][Postanesthetic myopathy of horses].

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 predominanlty of type 2 fibers: the semimembranosus, semitendinosus, and gluteals, for example. Biopsies of the semimebranosus and semitendinosus muscles are good choices for the diagnosis of PSSM. In cases of sudden death, the diaphragm should be carefully examined, as severe myonecrosis may have occurred. Along with microscopic evidence of polyphasic, multifocal necrosis, myofibers contain notable intrasarcoplasmic, PAS-positive inclusions (Figure 3.3).

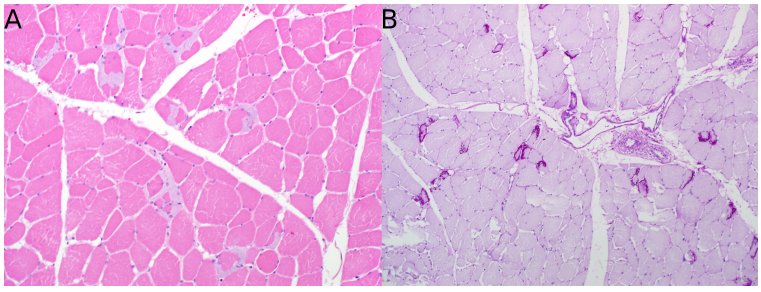

Figure 3.3: Photomicrograph of muscle from a horse with PSSM. A) Multiple myofibers show distinct amphophilic material, particularly along the periphery of the myofiber. H&E B) The material stains positive with PAS (bright magenta). PAS.

3.5 Malignant hyperthermia

Though clasically thought of as a disease of pigs, malignant hyperthermia is better thought of as a syndrome that predominantly occurs in swine, but which also affects dogs and horses. The underlying issue is a defect in 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 excess Ca^{2+} release, prolonged contraction, hypercontraction, and hyperthermia.

3.5.1 Porcine stress syndrome

Malignant hyperthermia is best characterized in pigs, and is also known as porcine stress syndrome (PSS). It is the cause of pale, soft, and exudative pork that is sometimes encountered at slaughter. 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 attritutable to heart failure, including pulmonary edema, hydrothorax, and hepatic congestion, may occur if the animal survives the acute episode. Histologically, multifocal, monophasic necrosis is present, and edema separates myofibers in animals that have suffered from hyperthermia.

3.6 Congenital myasthenia gravis

Myasthenia gravis is a neuromuscular disorder characterized by decreased availability of acetylcholine (Ach) receptors (Ach-R) on the myofiber membrane. Lack of the receptor leads to decreased Ach binding, fewer depolarizations, and weaker muscle contractions. In congenital myasthenia gravis, decreased Ach-R availability is due to an inherent defect in the receptor. In [acquired myasthenia gravis][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 clinical finding. 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.

3.7 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. There 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.

3.7.1 Hyperkalemic periodic paralysis (HYPP)

Only horses descended from the Quarter Horse stallion "Impressive" are at risk for HYPP. Affected animals have very well defined musculature, a desireable trait, which has led to the propogation of the condition in the quarter horse breed.

The pathogenesis of the condition is poorly understood. 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 and prolonged action potentials, and excess contractile activity.

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. Homozygotes typically do not survive beyond 2 years of age.

Heterozygotes are less severely affected, and often appear normal but suffer from transient attacks of muscle fasiculations and spams (myotonia), inspiratory stridor, protrusion of the third eyelid, and sometimes followed by acute paralytic collapse. Sudden death may occur in the most severe cases.

There are no gross or histologic lesions; diagnosis is based on ancestry, clinical history, signs, and DNA testing. Despite the name, hyperkalemia is not a consistent finding.

Chapter 4

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.

4.1 Compartment syndrome

Compartment syndrome occurs most commonly in chickens (and humans). As discussed in the [review of muscule anatomy][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 muscle is contained by the breastbone on one side, and a relatively rigid outer sheath on the other, forming an inelastic or fixed “compartment”. When a chicken participates in short, vigorous exercise (wing flapping), there is a significant increase intramuscular vascular pressure that collapses veins and decreases 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.

4.2 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.

4.3 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 comorbities, especially [PSSM][Equine polysaccharide storage myopathy (PSSM)] and [HYPP][Hyperkalemic periodic paralysis (HYPP)].

Chapter 5

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 [bacterial infection][Suppurative myositis] or [tetanus][Tetanus], may result.

Chapter 6

Nutritional myopathies

6.1 Selenium and vitamin E deficiency

Deficiency in selenium, and to a lesser extend, vitanim 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 degrades over time, and feed that was originally properly formulated may wind up being low in vitamin E if stored for prolonged periods.

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 find-

ing, 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 multifocal, polyphasic necrosis with regeneration. The damage tends not to affect the basal lamina or satellite cells, so skeletal (not cardiac) 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.

Chapter 7

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.

7.1 Ionophore toxicity

Ionophore antibiotics are commonly found in the feed of livestock and are used as growth promoters. Horses are particularly susceptible to ionophore toxicity, requiring only low concentrations of the drug to cause severe damage, 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 sings 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 7.1; 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.

7.2 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

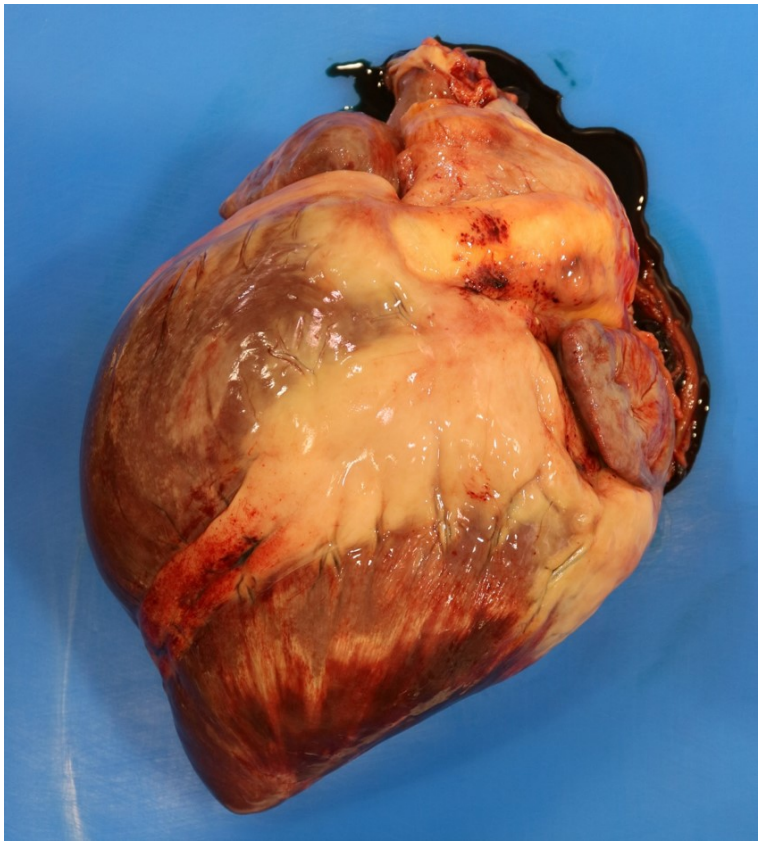

Figure 7.1: Equine heart demonstrating marked myocardial necrosis, manifesting as pale white streaks across the ventricle. Photo: C. Martin

@ref(fig:plants)). The latter two produce 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.

7.2.1 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.

Figure 7.2: 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.

Chapter 8

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.

8.1 Exertional myopathies

An exertional myopathy is defined as myofiber damage occuring as the direct result of exercise. Note that both [PSSM][Equine polysaccharide storage myopathy (PSSM)] and [equine malignant hyperthermia][Malignant hyperthermia] are induced by exercise, and can thus be considered exertional myopathies. These notes are organized primarily by underlyign etiology, rather than inciting cause, and thus these conditions are often found elsewhere in these notes, despite their relationship to exercise. They are included elsewhere.

8.1.1 Equine exertional rhabdomyolysis

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

These synonyms broadly refer to the clinical syndrome of exhibited by horses that experience muscle injury (necrosis, degeneration) following exercise. As noted above, several have already been discussed. Here we will discuss equine recurrent exertional rhabdomyolosis.

8.1.1.1 Equine recurrent exertional rhabdomyolosis

This condition is primarily noted in young, excitable, Standardbred or Thoroughbred fillies. It presents as acute onset of muscle pain, secondary to degeneration and necrosis, often 15-30 minutes into submaximal exercise. Between episodes of muscle pain horses are typically asymptomatic. The cause is poorly described, but is believed to be the result of unknown genetic abnormality concurrent with environmental factors leading to an abnormality in intracellular calcium regulation. Gross and histologic findings are typical of rhabdomylosis and are not specific for RER.

Risk factors (beyond breed and temperment) have been identified. They include diets high in grain, a parent with the condition, and increased periods of rest between exercise.

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

8.1.2 Canine exertional rhabdyomyolysis

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.

8.1.3 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 9

Myopathies associated with serum electrolyte imbalance

9.1 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, atlerted glycogen metabolism, and ischemia from hypokalemia-induced vasocontriction. 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 diaphram – and these are recommended for sampling at autopsy if the disease is suspected.

9.2 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 10

Immune-mediate myopathies

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

A difficulty when evaluating immune-mediate 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-mediate myopathies, the invasion of intact myofibers by mononuclear leukocytes is characteristic.

10.1 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.

10.2 Polymyositis of dogs

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

10.3 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][Congenital myasthenia gravis]. Acquired myasthenia gravis is caused by antibodies against the acetylcholine receptors located at the motor end plate (Figure 10.1). 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. Lack of Ach-R in turn reduces the ability of the myofiber to depolarize, resulting in the clinical signs noted below. 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.

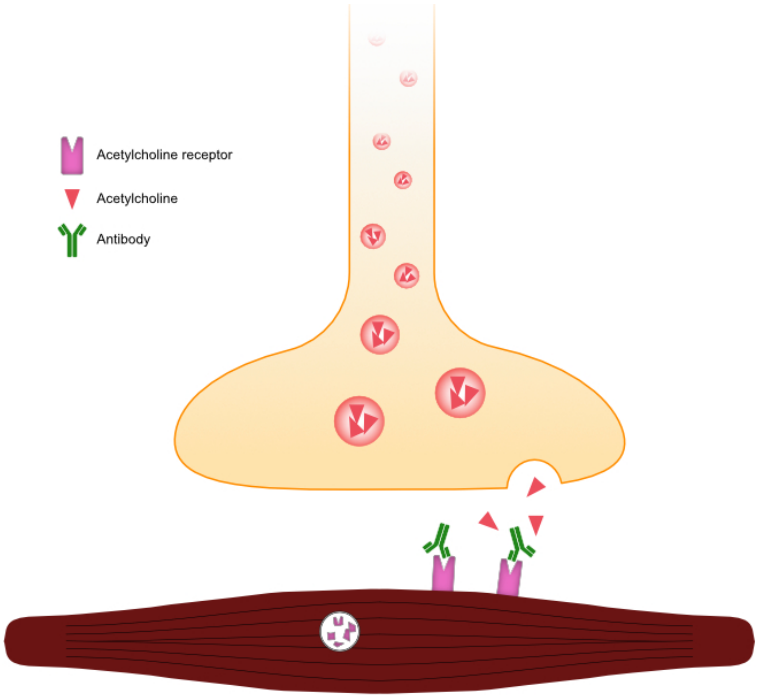

Figure 10.1: Illustration of a motor end plate affected by acquired myasthenia gravis. Note the immunoglobulin binding to the acetylcholine receptor, preventing the binding of acetylcholine, and also leading to endocytosis and decreased receptor density.

Chapter 11

Infectious myositis

11.1 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 species, 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.

11.1.1 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 isoltaed from gas gangrene.

Malignant edema/gas gangrene occurs following the introduction of spores by a deep, penetrating wound, almost always from an injection, though surgical procedures (castration) may also contribute. Local anaerobic conditions allow organisms to proliferate and produce exotoxin that damage blood vessels and myofibers, 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 Figure 11.1, death occurrs within 24-48 hours.

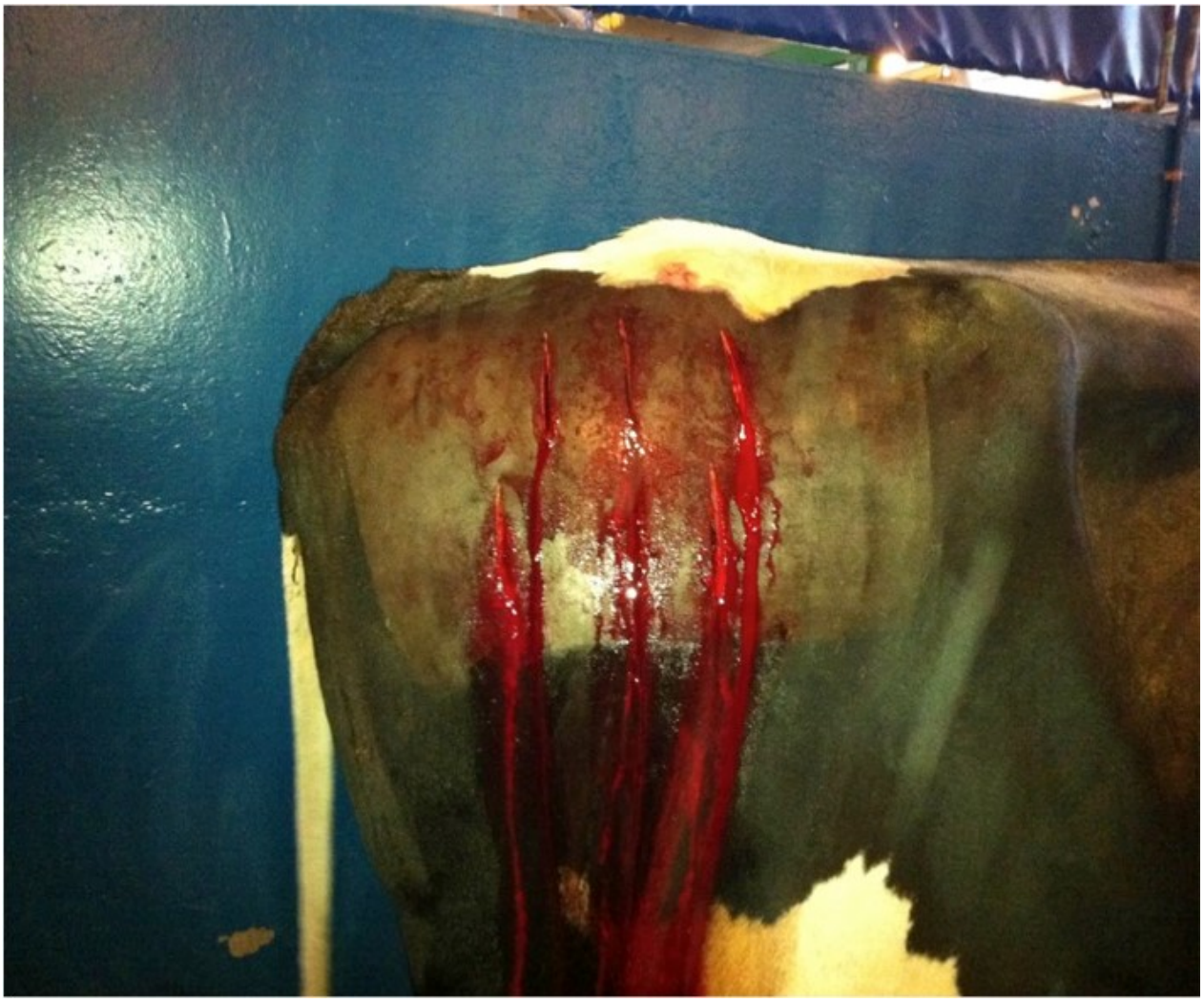

Figure 11.1: Malignant edema in a cow resulting in marked swelling of the gluteal muscles. This cow was treated with several fasciotomy incisions to release the pressure and allow exposure to oxygen. Image courtesy of Dr. H Staempfli, OVC.

11.1.2 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. chauveoi. 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 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.

11.1.3 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 susceptibe. 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 synpatic 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.

11.1.4 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 motor neuron and brought via retrograde transport to the neuronal cell body within the spinal cord. There the tetanus toxis 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 asso-

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

11.2 Suppurative myositis

Suppurative myositis is most commonly the result of innoculation 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 11.1.

Table 11.1: Most common bacterial isolates from muscle abscesses in veterinary species

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

Chapter 12

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.

12.1 Rhabdomyoma

As it's 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. They are typically incidental findings. They present grossly as circumscribed, smooth-surfaced, nodular masses embedded in the myocardium. A similar neoplasm occasionally arises on the larynx of dogs. Laryngeal rhadomyomas may cause respiratory difficulty or altered bark. They are typically minimally invasive and tend not to metastasize.

12.2 Rhabdomyosarcoma

These are the malignant counterparts to rhadomyomas. 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 rhadomyosarcoma. Immunohistochemistry is usually required to definitively diagnose these tumours.

12.3 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.

12.4 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 13

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. Generally speaking, the most important aspect of parasitic diseases of muscles in animals is their threat to human health.

13.1 Sarcocystosis

Sarcocysts are a very common protozoan parasite found in the muscle of herbivores. They have an in 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 theses 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.

13.2 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.

13.3 Trichinellosis

> **!** Important
>
> Trichinellosis is a REPORTABLE 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 the penetrate through the intestinal crypts (the males die), and deposit larva into the lymphatics. The larva 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.

Trichinellosis is zoonotic. In humans, clinical signs and symptosm related to trichinellosis include fever, myalgia, facial edema, rash, and occasionally chronic diarrhea.

13.4 Cysticercosis

> **!** Important
>
> Cysticercosis is a REPORTABLE DISEASE.

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 teanid 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 13.1.

Table 13.1: Tapeworm and cysticercus species, along with their hosts and predilection sites

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

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, but otherwise do not harm the host. Dead larva become heavily calcified.

Occasionally, cysticerci can infect in an unusual intermediate host and form cysts in devastating anatomic locations. Consider the life cycle of T.solium and C. cellulosae. Adult tapeworms living in the definitive host, humans, pass eggs or proglottids in their feces, which are

normally taken up by pigs, in which cysticerci form in muscle. Occasionally, however, humans can also come ingest the eggs, in which case the cysticerci develop not just in muscle, but also in brain and eyes, with devastating consequence. This condition can be devastating and is still prevalent in areas of high poverty and poor sanitation.

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