NORMAL SKELETAL MUSCLE:

- muscle cell = myocyte = muscle fiber = myofiber.
- embryologically skeletal muscles are derived from paraxial mesoderm:
  - muscles of the back, body wall & limbs are derived from the myotome (ie part of mesodermal somites) & muscles of the head are from cranial paraxial mesoderm that migrates into the branchial arches.
  - the mesoderm differentiates into myoblasts → align and fuse together to make longer, multinucleated tubes called myotubes → myotubes synthesize myofilament proteins (begin to see cross striations on LM) → continued differentiation to form functional myofilaments and nuclei displaced against the sarcolemma.
- the organization of muscle from gross to microscopic is as follows:
  i) a muscle seen grossly is surrounded by dense fibrous connective tissue which consists of external deep fascia that blends internally with the epimysium.
  ii) thin septa from the epimysium, extend into the muscle and divide it into fascicles (groups) of myofibers; this is called the perimysium.
  iii) individual myofibers are surrounded by endomysium which consists of a external basal lamina produced by the myofibers and some extracellular matrix from fibroblasts.
  iv) a major role of this connective tissue arrangement is to transfer the mechanical force of the contracting muscle cells, because individual myofibers rarely extend the entire length of the muscle.
- skeletal myofibers are non-branching, elongate, cylindrical, multi-nucleated cells (100-300 nuclei/cell) which can range from 1 mm to ~10 cm’s in length and 10-100 μm in diameter.
- the multiple nuclei of the myofibers are arranged at the periphery of the cell beneath the sarcolemma.
- the saroplasm (myofiber cytoplasm) contains abundant myofibrils (~ 60% of volume; which are long cylindrical filamentous bundles, 0.5 to 1 um in diameter, which lie parallel to the long axis of the cell), sarcoplasmic (endoplasmic) reticulum, glycogen +/- fat droplets, mitochondria and lysosomes.
- the sarcoplasmic reticulum has a special configuration, which along with the T-tubules (invaginations of the sarcolemma) allow for rapid simultaneous release of Ca\(^{2+}\) throughout the myofiber, for uniform contraction.

- myofibrils:
  - regular repeating subunits (sarcomeres) of myofibrils gives the distinct striation pattern of the myofiber.
  - a sarcomere, the structural/functional unit of the myofibril, is composed of myofilaments (thick and thin types) which align precisely to form A bands and I bands.
  - thin myofilaments consist of actin, tropomyosin & troponin; thick myofilaments consist of myosin.
  - A bands (anisotropic = birefringent in polarized light) are wider and darker than the lighter and narrower I bands (isotropic = don’t alter polarized light)
  - Z lines (discs) found in the middle of I bands, define the length of a sarcomere (ie from Z line to Z line).
**muscle contraction** is initiated by a motor nerve impulse to the myocyte → acetylcholine released into the neuromuscular junction → depolarization of the sarcolemma which rapidly moves into the T-tubules → rapid release of Ca\(^{2+}\) from sarcoplasmic reticulum into sarcoplasm (via DHP-ryanodyne receptors) → Ca\(^{2+}\) binds to troponin → moves tropomyosin on the actin to expose binding sites for myosin heads → myosin heads attach to binding sites on actin and pivot, moving the thin filaments toward the center of the sarcomere (shortening the sarcomere) → when the impulse stops, Ca\(^{2+}\) is pumped back into the sarcoplasmic reticulum and tropomyosin recovers the active binding sites and filaments passively slide back to their relaxed state.

**satellite cells** (= myosatellite cells = resting myoblasts)
- are adult myocyte stem (progenitor) cells, which in practical terms, are the main cell involved in muscle regeneration / repair, ie proliferate and produce new myofibers following muscle injury.
  (note, experimentally hematopoietic and mesenchymal stem cells have also been shown to be capable of participating in muscle regeneration, however their contribution in practical terms, remains unclear)
- on light microscopy they appear only as nuclei, indistinguishable from myofiber nuclei, because they have a minimal amount of cytoplasm; however on EM, they lie between the sarcolemma of the myofiber and the basal lamina / endomysium.
- in mature muscle about 3-5% of the myofiber nuclei are satellite cells, in young animals they can be up to 30% and in old animals as little few as 1%.

**Types of Myofibers**
- classified into 2 main types based on three major physiologic features:
  ① rates of contraction (slow or fast)
  ② rates of fatigue (fatigue resistant or fatigue sensitive)
  ③ types of metabolism (oxidative, glycolytic, or intermediate)
  - Type 1 fibers (red muscle)
    - slow twitch (ie slow contracting) and fatigue resistance; eg common in postural muscles, diaphragm.
    - energy derived mostly from oxidative (aerobic) metabolism; so have a high concentration of mitochondria and myoglobin (oxygen-binding protein found in muscle, related to hemoglobin).
  - Type 2 fibers (white muscle)
    - fast twitch (ie fast contracting) and fatigue sensitive (due to accumulation of lactic acid); common in athletic muscles, eg sprinting muscles.
    - energy derived mostly from glycolytic (anaerobic) metabolism; so have a high concentration of glycogen and relatively few mitochondria and lower concentration of myoglobin.
    - in many species Type 2 fibers can be further divided into Type 2a and Type 2b.
    - Type 2a (intermediate, oxidative-glycolytic) fibers, are fast contracting, but fatigue resistant; utilize both oxidative metabolism and anaerobic glycolysis to produce energy; have intermediate amounts of mitochondria / myoglobin / glycogen.
    - Type 2b (glycolytic) fibers are as described above for classic type 2 fiber, ie fast contracting but fatigue sensitive due to rapid accumulation of lactic acid.
- the proportion and distribution of Type 1 and 2 fibers, varies among muscles, species and gender; eg postural muscles are typically rich in Type 1 fibers; dogs have no Type 2b fibers; etc.
- in some species the predominance of one fiber type in specific muscles makes it possible to differentiate them grossly, eg chicken breast muscle (white meat/mostly type 2) vs leg muscle (dark meat/mostly type 1).
• innervation of myofibers
  • all myofibers innervated from the branches of a single motor neuron (called a “motor unit”) are of the same
    fiber type & an action potential on the motor neuron causes all these myofibers to contract simultaneously.
  • muscles which require fine motor control (eg eye movement) have motor units with only a few myofibers,
    while motor units of muscles which generate large forces (eg thigh muscles) may have hundreds or thousands
    of myofibers.

EXAMINATION OF MUSCLES
1) Gross examination
  • check color (pale, red or dark), volume (normal, increased or reduced) and texture (normal, firm or soft).
  • compare muscles with those of the opposite side (if unaffected) or with animals of the same age and breed.
  • make several slices into the muscles to look for internal lesions.

2) Histopathologic examination
  • most muscular diseases require microscopic examination of muscle.
  • put small (1 x 1 x 3 cm) slices of muscle from several sites (both normal and affected) in formalin; note, good
    fixation requires a 10:1 formalin to tissue volume ratio.
  • submit tissues along with gross description of the muscle lesions (eg lesion size or % affected, color, etc)

3) Postmortem changes
  • be aware that artifacts are common, eg pallor due to exsanguination, livor mortis, rigor mortis.
    a) Rigor mortis
      • a postmortem contraction of skeletal muscles which results in the fixation of joints (note, all muscles affected,
        so causes rigidity of joints); generally starts in the jaws and trunk and follows to the extremities.
      • generally starts ~ 2-4 hours after death, and persists for 24 to 48 hours, after which it dissipates.
      • pathogenesis: after death, circulation of blood/O2 ceases → muscle cells resort to anaerobic glycolysis →
        glycogen stores run out & ATP becomes depleted (ATP needed to maintain muscle relaxation by keeping Ca2+
        in sarcoplasmic reticulum) → Ca2+ floods into sarcoplasm → muscles contract (rigor) further depleting ATP →
        rigor mortis gradually dissipates with autolysis of structural and functional muscle proteins.
      • presence and intensity of rigor mortis depend on several factors such as body condition / glycogen stores; eg
        occurs very rapidly in animals that die when glycogen stores are low (after exercise or if animal emaciated),
        rigor mortis is also accelerated by warmer ambient temperatures and delayed at cooler temperatures.

DISTURBANCES OF GROWTH AND POSTMORTEM ALTERATIONS
1) Muscle Atrophy
  • muscular atrophy refers to the reduction in muscle volume mass, which can be generalized or localized.
  • in most cases it is due to decreased myofiber diameters (rather than cell loss), ie a loss of myofibrils and other
    organelles (eg ER, mitochondria, etc) due to increased catabolism (via proteosomes / autophagy).
  • it is reversible providing the source of injury is removed in a relatively short time interval.
  • histologically, there is a reduction in myofiber diameters with an unchanged amount of connective tissue.
  • types of muscle atrophy include:
a) Denervation atrophy
- myofibers that lose tonic stimulation due to nerve damage undergo atrophy.
- muscles become rapidly and severely atrophic; eg >50% of muscle mass can be lost in a few weeks.
- characterized histologically by atrophy of usually both type 1 and 2 myofibers.
- examples of denervation atrophy include:
  ① Laryngeal hemiplegia in horses (“roarers”) due to axonal degeneration of left recurrent laryngeal nerve.
    - current hypothesis suggests it is a ‘dying-back’ neuropathy caused by the inability of the cell bodies in
      the nucleus ambiguus to maintain the integrity of long motor neurons.
  ② Suprascapular nerve damage causing atrophy of the supraspinatus / infrasinatus muscles in horses.
    - nerve damage can be by sudden trauma (eg horses colliding with stall doors, trees, etc) or chronic low-
      grade trauma (eg poor fitting collars in work horses; “Sweeney” was a common collar type).
  ③ Radial or brachial nerve trauma / paralysis causing muscle atrophy in dogs or horses.
  ④ Equine motor neuron disease (symmetric muscle atrophy) vs Equine protozoal myeloencephalitis
      (asymmetric muscle atrophy).

b) Disuse atrophy
- innervation is intact (ie tonic stimulation) but there is reduced movement because of pain, bone fracture,
  ankylosis, limb immobilization (eg cast), etc.
- lesions are localized to affected groups of muscles and atrophy of type 2 fibers often predominates.

c) Atrophy of malnutrition / cachexia / senility
- a distinct type of progressive muscle atrophy occurs in malnutrition, excess protein loss (eg parasitism,
  protein-losing enteropathy or glomerulopathy, etc), cachexia (eg cancer or chronic disease) and senility.
- note, 1 to 5% of muscle protein is turned over each day (dismantled / reconstructed).
- in malnutrition:
  - muscle becomes the source of nutrients (ie muscle protein mobilized for energy use); atrophy can start
    within 24 hours following starvation & is more pronounced in animals with few fat reserves.
  - tonic stimulus and movement is intact; lesions are generalized but essential muscles (eg diaphragm,
    tongue) are less affected, ie type 2 fibers affected more than type 1.
- in cachexia
  - cachexia = muscle wasting, weight loss, general debility that can occur during a chronic disease, even
    when normal or increased amounts of energy are consumed.
  - occurs most commonly with certain neoplasms and chronic inflammatory diseases (eg tuberculosis).
  - associated with production of cytokines (eg TNF =“cachectin”) by the tumor cells or macrophages.

d) Atrophy of endocrine disease
- neuromuscular weakness and muscle atrophy can be seen in some endocrine disorders, eg hypothyroidism and
  hyperadrenocorticism.

2) Muscle Hypertrophy
- the response of muscle to increased demand; either physiologic in response to an increased workload or
  compensatory in unaffected myofibers adjacent to weak / dysfunctioning myofibers due to myopathic or
  neuropathic disorders; also note that muscular hypertrophy can be enhanced by anabolic steroid drugs.
- see an increase in the size but not in the number of muscle fibers.
- diameter of hypertrophic myofibers is increased due to formation of additional new myofilaments / organelles.
DEGENERATION AND REPAIR OF MUSCLE

1) Muscle Degeneration and Necrosis (rhabdomyolysis)
   - degeneration is a common sequel to myofiber injury regardless of its cause (toxic, metabolic, traumatic, etc).
   - myofiber degeneration can be reversible, however, if the injury progresses beyond the “point of no return,”
     degeneration becomes irreversible and necrosis will follow.
   - muscle degeneration can only be detected grossly in severe lesions; degenerate muscle typically appears pale
     (note, don’t mistake degeneration with pale muscles of veal calves, anemia, exsanguination, fat in tongue, etc).
   - calcification of degenerate myofibers is common in many muscle disease (eg WMD); if calcification is extensive
     and severe, the muscles can show chalky white foci or streaks.
   - red discoloration may be present when degenerated muscle coexists with hemorrhage or with sudden and
     extensive release of myoglobin into the interstitium/ECF when myofibers undergo necrosis (ie rhabdomyolysis)
   - other discolorations of muscle are occasionally found and are usually incidental, eg black discoloration is seen in
     melanosis (rare) and brown / tan discoloration occasionally seen in old cattle with lipofuscinosis.
   - Histopathology:
     - changes indicative of muscle degeneration / necrosis include vacuolation and loss of striations followed by
       swelling (one or more segments), hypereosinophilic glassy appearance (so-called hyaline or Zenker's
       degeneration/necrosis), +/- calcification and finally segmental rupture of fibers and formation of retraction
       caps (ie concavities at the free ends of ruptured myofiber fragments).
     - calcified myofibers have a granular, bluish appearance on H&E staining; special stains such as Von Kossa (in
       which calcium stains black) are used to conclusively demonstrate calcium in affected tissues.

2) Regeneration and repair of muscle
   - skeletal muscle has a remarkable ability to regenerate, providing the lesion is segmental and the basal lamina /
     endomysium and satellite cells remain intact.
   - the integrity of the basal lamina / endomysium (ie “sarcolemmal tube”) is critical to providing an effective
     scaffold for regeneration; note, the intact BL keeps satellite cells, myonuclei and myoblasts inside, keeps
     fibroblasts outside, but allows easy entry and exit of phagocytes.
   - macrophages and to lesser extent neutrophils clean cell debris within 12-24 hours of necrosis.
   - satellite cells initially round-up within hours of damage and prepare for mitotic division.
   - myoblasts (from proliferating satellite cells) fuse within the sarcolemmal tube and produces new sarcomeres;
     these eventually unite (bridge) with remaining viable segments of the original myofiber.
   - if sarcolemmal tubes are disrupted (trauma, infarction, infection), partial regeneration can occur but is generally
     impaired by fibrosis (scarring).

CONGENITAL AND INHERITED MUSCLE DEFECTS
   - there are a wide variety of congenital and/or hereditary muscle conditions in animals.

1) Primary CNS conditions
   - neuroectodermal defects affecting the innervation of individual myotomes and muscles that form from them, can
     result in abnormal muscle development.
a) Arthrogryposis (congenital articular rigidity)
- arthrogryposis (= crooked joint) is found most commonly in aborted fetuses and stillborns.
- it can be caused by myogenic or neurogenic disorders, but lack of innervation during gestation causing muscular hypoplasia, with resultant shortening of the muscles, is by far the most common cause.
- the neurologic defects are usually related to failure of neural tube closure (dysraphism/myeloschisis), +/- spina bifida; but can also occur with other cord defects (eg syringomyelia, hydromyelia).
- these CNS defects can be genetic/hereditary, but can also be associated with in utero exposure to toxins (eg wild lupine) or in utero viral infections (eg bluetongue, border disease, Schmallenberg virus, etc).

2) Metabolic myopathies
- abnormal skeletal muscle metabolism typically result in reduced muscle cell energy production.
- are mostly due to mitochondrial dysfunction or inherited defects of glycogen or fatty acid metabolism.
- a variety of these syndromes have been described in dogs, cats, cattle and horses, eg:
  a) Equine Polysaccharide Storage Myopathy
- a glycogen storage myopathy seen in many horse breeds (esp draft, warm blood and Quarter horses)
- autosomal dominant with variable clinical expression; some forms are associated with single nucleotide polymorphisms of the glycogen synthase 1 gene (GYS1) that result in increases in its activity.
- see range from asymptomatic (subclinical) to progressive weakness / hind limb lameness / muscle atrophy to exertional rhabdomyolysis (see below)
- Gross: normal to pale streaking of muscles or red staining due to rhabdomyolysis / myoglobin release.
- Histopathology: accumulation of PAS positive material (complex polysaccharides), and degeneration / necrosis (aka rhabdomyolysis) in type 2 fibers.

3) Malignant hyperthermia (MH)
- rare in dogs, horses & humans; common in several pig breeds (eg Landrace, Pietrain, Poland China, etc).
- can see life-threatening Porcine Stress Syndrome (PSS); also causes Pale, Soft and Exudative Pork (PSE).
- autosomal recessive mode of inheritance in pigs, associated with mutation of the ryanodine receptor gene (RYR1); note, commercial DNA testing available.
- pathogenesis relates to a defect in the sarcoplasmic reticulum calcium-release channel (ie ryanodine receptor)
  \[ \text{uncontrolled intracytoplasmic Ca}^{2+} \text{ release} \rightarrow \text{severe muscle contraction / heat production} \rightarrow \text{prolonged / excessive contraction progresses to degeneration and necrosis of fibers} \rightarrow \text{denaturation of sarcoplasmic proteins and escape into ECF leads to movement of intracellular water into the interstitium.} \]
- any type of stress such as fighting, exercise or heat can trigger PSS; can also be triggered by general anesthetic agents (especially halothane) which was once the basis for testing before DNA testing available.
- characterized clinically by severe muscle rigidity, hyperthermia, respiratory and metabolic acidosis, myoglobinemia, hyperkalemia, cardiovascular collapse and death.
- Gross Pathology:
  - muscles with higher proportions of type 2 fibres (eg longissimum, psoas; semitendinosus) are pale and are wet due to interstitial edema.
  - making several longitudinal cuts in affected muscles promotes oozing and dripping of edema fluid.
  - extra-muscular lesions include severe pulmonary edema (froth in the trachea) and accumulation of edema fluid in abdominal and thoracic cavities (consistent with acute heart failure).
- Histopathology:
  - acute myofiber degeneration / necrosis and interstitial edema of skeletal and often cardiac muscle.
4) Other Muscular defects

a) "Splayleg" (myofibrillar hypoplasia) in piglets
   - piglets are born with their hindlimbs splayed to the side.
   - the muscular form of this disease is thought to be due to delayed myofibril development; note, it is a transient defect as most affected pig appear normal within 1-2 weeks.

b) "Double muscling" (muscular hyperplasia) in cattle and dogs
   - seen in several beef breeds as an autosomal recessive trait with incomplete penetrance.
   - genetic defect is an inactivation of the myostatin gene, which negatively regulates muscle growth → see an increased number (hyperplasia) and size (hypertrophy) of otherwise normal muscle cells.

c) Muscular steatosis (aka fatty infiltration of muscle or lipomatosis)
   - seen in cattle, usually subclinical and typically only a problem at meat inspection.
   - some cases may be defective muscle development but many now thought to be adipocytes derived from intramuscular mesenchymal cells following chronic damage or denervation of muscle.

5) Muscular dystrophy  [for information only]
   - "Muscular Dystrophies" (MD’s) of humans are a heterogenous group of inherited disorders of muscle which are characterized by progressive muscle weakness and wasting, defects in muscle proteins and ongoing muscle fiber degeneration and regeneration with eventual replacement by fibrous / fatty tissue (this distinguishes dystrophies from other myopathies)
   - the 2 most common forms, ie Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are the result of mutations in the intercellular protein ‘dystrophin’ and have an X linked mode of inheritance.
   - dystrophin forms a mechanical link between the intracellular contractile proteins (via link to actin) and the extracellular connective tissue matrix (via links to transmembrane proteins)
   - Hereditary Muscular Dystrophies are not as common in domestic animals; however X-linked MD’s have been reported in dogs (eg Canine X-linked muscular dystrophy), cats (eg Feline X-linked muscular dystrophy).
   - muscle biopsies reveal swelling of the affected fibres followed by progressive and irreversible atrophy.

6) Myotonic and Spastic syndromes  [for information only]
   - myotonia is defined clinically as a temporary inability of skeletal muscle to relax; transient uncontrollable muscle tension occurs after voluntary contraction and is manifested by muscle stiffness.
   - myotonias result from muscle membrane electrical abnormalities, most often associated with ion channel defects for regulation of sodium or chloride (also called “channelopathies).
   - a variety of these myotonic syndromes are seen in domestic animals, eg
     a) Hyperkalemic periodic paralysis (HYPP)
        - an autosomal dominant muscle disorder of horses; especially Quarter horses related to “Impressive”.
        - underlying defect is a point mutation in the muscle sodium channel (DNA testing is available) leading to increased open time; see increased influx of sodium and resultant compensatory potassium efflux, hence the hyperkalemia.
        - homozygote foals develop laryngospasm and pharyngeal collapse.
        - heterozygote adults show transient paralysis / collapse (hypotonia!) following initial signs of hypertonia (eg muscle fasciculation / spasms, flashing of the third eyelid, inspirator stridor); occasional sudden deaths due to hyperkalemia.
        - spastic syndromes are associated with tightening of the muscles, causing stiff and awkward movement (eg “Scotty cramp” and “Spastic paresis of cattle”)
7) **Congenital myasthenia gravis** [for information only]

- an inherited disorder of dogs, cats & humans that is much less common than acquired myasthenia gravis.
- affected animals have defective neuromuscular junctions, eg decreased density of postsynaptic acetylcholine receptors, shallow secondary clefs in the end plate synaptic gutters, etc.
- affected animals can appear normal at birth with minimal muscle mass, but with postnatal growth there is progressive weakness as a consequence of insufficient functional receptors to support growing muscles.

## TRAUMATIC / CIRCULATORY DISTURBANCES OF MUSCLE

1) **Downer syndrome**

- mature animals (cows > sheep, pigs, horses) in good bodily condition are most susceptible.
- in large animals following prolonged recumbence (disease/anesthesia) → the weight of the body compresses the muscles to the point where there is inadequate vascular perfusion pressure (+/- thrombosis) → as early as 6 to 12 hours get ischemic necrosis of pectoral muscles or limb muscles that are tucked under the body.
- vicious cycle of prostration → muscle injury → edema → compression → ischemia → muscle injury → continued prostration → ....
- Gross Pathology: grossly, can see pale areas (due to ischemia / degeneration / fibrosis) &/or red areas (due to congestion / hemorrhage / myoglobin release).

2) **Compartment syndrome**

- characterized by degeneration and necrosis of muscles that are surrounded with a heavy aponeurosis (sheetlike fibrous membrane, resembling a flattened tendon, that serves as a fascia to bind muscles together).
- in animals, most commonly seen in poultry (deep pectoral myopathy - see below).
- in humans, associated with injury or certain muscles in well-conditioned athletes (eg calves, pre-tibial muscles)
- pathogenesis is based on muscular swelling / expansion occurring with injury (or in some cases just vigorous exercise) in a non-expandable compartment → vascular compression → ischemia and infarction of the muscle.

   a) **Deep pectoral myopathy**

   - frequently seen in poultry, esp heavily muscled breeds of turkeys and chickens.
   - disease is preceded by a brief but vigorous period of wing flapping (eg birds being chased) → few hours later see localized area of degeneration and necrosis in the deep breast (supracoracoid) muscle.

3) **Postanesthetic myopathy in horses**

- a degenerative myopathy seen in 3-6% horses undergoing prolonged recumbency, esp with inadequate padding.
- due to vascular occlusion from compressive pressure caused by the large weight of the animal during recumbency and/or muscle hypoxia from systemic hypotension associated with the general anesthetic.
- severity varies from muscle swelling with lameness to paresis with renal failure and shock.

4) **Muscle crush syndrome**  [for information only]

- an acute degenerative myopathy caused by severe trauma to a muscle group often with secondary myoglobin-induced acute renal tubular injury; more common in humans than other animals.
NUTRITIONAL MYOPATHY / WHITE MUSCLE DISEASE (WMD)

- in older veterinary literature it was mistakenly called muscular dystrophy or nutritional muscular dystrophy.
- WMD is associated with dietary deficiencies of selenium / Vitamin E, but it is exacerbated by other factors such as exercise, environment (eg climatic conditions), other nutrition factors and some toxicants.
- it is still a very common and economically important condition in farm animals.
- has variable morbidity and mortality, generally affecting young (few wks to few months; occasionally neonates), rapidly growing, well-conditioned sheep, cattle, pigs; less common in foals & goats; also others (eg mink).
- in pigs it may be independent or coexist with other selenium / Vitamin E deficiency diseases (eg mulberry heart disease, hepatitis dietetica).
- pathogenesis is related to the oxidation of cell membranes by free radicals (lipid peroxidation) due to inadequate amounts of free radical-scavengers, (esp selenium containing glutathione peroxidase / reductase system, +/- Vitamin E) → lipid peroxidation of membranes → influx of Ca\(^{2+}\) into sarcoplasm → hypercontraction and activation of destructive proteases → myofiber degeneration / necrosis & often dystrophic calcification.
- with cell membrane damage intracellular enzymes (eg CK, AST) leak into ECF / serum (basis of blood test)
- since muscle activity relates to the production of free radicals, muscles with higher oxidative activity (ie type 1 fibers), such as diaphragm, intercostals, tongue and heart, are more severely affected.
- Gross pathology:
  - muscle pallor reflecting degeneration and necrosis can be subtle in mild cases or inapparent in peracute cases (caution, don’t confuse with normally pale muscles of veal calves or animals with anemia, or pallor in tongue muscles due to fat).
  - in severe cases (fatal), affected muscles appear pale with chalky white areas or streaks (calcification).
  - remember to inspect the heart (LV in calves; RV in sheep) and muscles which are physiologically active (high oxidative phosphorylation / type 1 myofibers), eg diaphragm, intercostals, tongue, etc.
- Histopathology:
  - segmental degeneration / necrosis → hypereosinophilia / hypercontraction with loss of striation, myofiber fragmentation (retraction caps), calcification (often severe), proliferation of myosatellite cells (attempts to repair), and macrophages cleaning cell debris.

EXERTIONAL MYOPATHIES

- a group of diseases in which there is severe muscle degeneration / necrosis following strenuous exercise.
- lesions are mainly in major muscles with predominantly type 2 (glycolytic) fibers.
- postulated pathogenesis includes abnormal excitation-contraction coupling (altered Ca\(^{2+}\) homeostasis), altered energy metabolism, and mechanical stresses of excessive contraction → myofiber degeneration / necrosis.
- with myofiber necrosis, leakage of enzymes (eg CK & AST) and myoglobin (myoglobinemia / myoglobinuria).

1) Equine Exertional Rhabdomyolysis (= azoturia, paralytic myoglobinuria, Monday morning disease)

- a disease of typically heavy horse breeds, associated with strenuous exercise after a long resting period and a diet rich in carbohydrates (note, reduction of CHO in diet seems to help in prevention).
- clinically characterized by muscle weakness, reluctance to move, excessive sweating, myoglobinuria, and in severe cases renal failure with recumbency / death.
- currently postulated that many of these horses have an underlying abnormality of starch / sugar metabolism (see above - equine polysaccharide storage myopathy).
• Gross Pathology:
  - muscles of the extremities (gluteal/lumbar) are swollen, edematous, pale to dark areas (myoglobin staining), and the kidneys appear dark; in horses that survive, affected muscles become pale and atrophic.
• Histopathology:
  - in acute cases, see segmental degeneration and necrosis with little or no calcification and in chronic cases there is fibrosis and atrophy.
  - in severe cases, there is also toxic injury to the kidneys (ie myoglobin-induced acute renal tubular injury) which may result in death from renal failure.

2) Tying Up (= transient exertional rhabdomyolysis, setfast)
• considered to be a mild, transient form of equine exertional rhabdomyolysis; rarely see visible myoglobinuria.
• typically seen in lighter horse breeds; note, a similar syndrome has been reported in racing greyhound dogs.
• no gross lesions are seen in euthanized horses, but histologically see mild to severe muscle degeneration / necrosis (rhabdomyolysis).

3) Capture Myopathy
• an acute and often fatal myopathy of many wild mammals and birds.
• preceded by a chase / struggle or immobilization / transport → extreme overexertion, +/- catecholamine release.
• grossly may see pale edematous muscle (like PSS) or may have pale streaks and/or hemorrhagic streaks; occasional rupture of tendons.
• histologically, see degeneration / necrosis of skeletal muscle and sometimes heart muscle; +/- myoglobin-induced acute renal tubular injury.

TOXIC MYOPATHIES
• naturally occurring myopathies in domestic animals are mostly due to ingestion of ionophores and toxic plants.

1) Ionophore toxicosis
• ionophores are used in veterinary medicine as drugs / feed supplements, eg monensin (growth-promotion in ruminants, coccidiostat in birds and other animals).
• they act by altering membrane transport / permeability of electrolytes.
• at excess levels ionophores cause degeneration and necrosis of skeletal and cardiac muscle
• note, horses are extremely susceptible to muscle damage at relatively low levels compared to other species.
• Histopath: see multifocal degeneration & necrosis of muscle (both type 1 & 2 fibers) by 48 hrs after exposure.

2) Toxic plants and plant-origin toxins
• a variety of plants contain toxins that can cause degeneration and necrosis of muscle.
• eg’s: Cassia (coffee senna), Gossypium spp (cottonseed contain gossypol), Thermopsis spp (false lupine), etc.

   a) Season pasture myopathy (atypical myopathy) of horses
   • extensive rhabdomyolysis with myoglobinuria is seen in pastured horses following ingestion of seeds of box elder and sycamore maples trees (and possibly other maples) in North America and Europe.
   • seeds contain hypoglycin A which causes multiple acyl-CoA dehydrogenase deficiency (MADD); lack of these enzymes damages mitochondria / impairs lipid metabolism within skeletal and cardiac muscle cells.
IMMUNE-MEDIATED CONDITIONS

- occur when the immune system is abnormally activated resulting in tissue damage (eg antibody or cytotoxic T cells directed against muscle cells) or immune-complex deposition.

1) Masticatory myositis of dogs
- a rare immune-mediated, eosinophilic and atrophic myositis; seen in many breeds (esp G. Shepherd).
- in the early phase see repeated bouts of bilateral swelling and pain of the masseter, temporal & pterygoid muscles associated with eosinophilic myositis.
- over time see progressive destruction and atrophy / fibrosis of these muscles, ie atrophic myositis.
- the pathogenesis is believed to be due to autoantibody directed against type 2M myosin, a unique isoform of myosin found only in the muscles of mastication (note, a diagnostic test for 2M autoantibodies is available).
- Histopathology:
  - acutely see edema & extensive infiltration of eosinophils / lymphocytes in affected muscles.
  - chronically see predominately lymphocytes and plasma cells and myofibers are atrophic.

2) Polymyositis of dogs
- rare condition affecting dogs of presumed autoimmune etiology, mediated by T cells.
- all muscles affected (esp esophagus), but in some cases masticatory muscle involvement can be dominate; note however, most dogs are negative for serum antibody to 2M myosin.
- characterized by degeneration and necrosis with infiltration of mostly lymphocytes and variable numbers of eosinophils.

3) Acquired myasthenia gravis
- myasthenia gravis is a rare but important disease of human beings, dogs and cats.
- a disease of the neuromuscular junction which causes weakness and severe muscular fatigue, often following mild exercise (eg exercise-induced collapse).
- the two major forms are congenital / hereditary (see previous) and acquired (ie animals develop antibodies against motor end plate acetylcholine receptors which results in reduction in the density of ACh receptors).
- some dogs and cats with acquired myasthenia gravis have thymomas → abnormal thymic function / failure to remove self-recognizing clones, also associations with hypothyroidism and some paraneoplastic syndromes.
- in dogs megaesophagus, dysphagia, and aspiration pneumonia are common complications; in cats see generalized weakness.
- see dramatic improvement in clinical signs following administration of anti-cholinesterase drugs (neostigmine).
- histopathology see muscle atrophy (disuse type) and immune complexes can be detected at NM junctions.

4) Dermatomyositis [for information only]
- a familial disease of dogs (esp Collies & Shelties) that is presumed immune-mediated (pathogenesis unknown)
- clinically characterized by waxing / waning dermatitis (face, tip of tail, bony prominence) and myositis (predominately masticatory muscles and muscles of extremities below stifle/elbow)

INFECTIOUS MYOSITIS

- muscle is generally an inhospitable site for most bacteria; exceptions are *Clostridial spp & Histophilus somni*.
- also only a few viral agents (eg foot-and-mouth disease in calves, blue tongue in sheep) cause muscle lesions.
1) Blackleg (Black quarter, emphysematous gangrene)

- an acute fatal emphysematous myositis of ruminants caused by *Clostridium chauvoei* and characterized by the activation of latent spores in muscle.
- The pathogenesis is complex:
  - step 1 - soil-containing spores → ingestion by host → spores from GIT go to liver and muscle (latent).
  - step 2 - muscle injury/hemorrhage → changes local environment (low O₂ tension) → germination of spores in the muscle → exotoxins → edema/myonecrosis → emphysema → generalized toxaemia → death (24 hrs)
- Gross Pathology:
  - generally affects large muscle masses, esp pectoral and pelvic regions; but can affect any striated muscle, eg tongue, heart or diaphragm; note lesions may be small and escape detection.
  - affected muscle is red-black, with gas (emphysema), crepitation on palpation and has “rancid butter” smell.
  - peripheral to the lesion, there is a mild interstitial and subcutaneous edema (gelatinous fluid).
  - fibrin tags are typically found on the epicardial and pleural surfaces.
  - other lesions include widespread serosal hemorrhages, severe pulmonary edema and rapid post-mortem bloating.
- Histopathology:
  - histologic lesions are somewhat disappointing, when compared to the magnitude of gross lesions.
  - in affected muscle see segmental degeneration / necrosis, edema, occasional neutrophils (most destroyed by diffusing toxins) and emphysema; bacteria are often sparse.
  - for laboratory diagnosis, submit formalin-fixed tissues for histopathology and fresh tissues for anaerobic culture and fluorescent antibody testing (a confirmatory test).

2) Malignant edema and gas gangrene

- an acute often fatal infection caused by wound infection with *Clostridium septicum, Cl. perfringens, Cl. novyi, Cl. sordelli* and *Cl. chauvoei* alone or in combination; their spores are commonly present in soil and feces.
- generally affects ruminants, horses and swine; carnivores are only sporadically affected.
- route of entry of these anaerobic, highly toxigenic, opportunistic organisms is always through a wound.
- note, not all wounds contaminated with these organisms result in malignant edema / gas gangrene since optimal conditions are required, ie deep wounds with low oxygen tension.
- affected areas are cold on palpation (in live animals!) and can be crepitant (due to emphysema); animals show generalized signs of toxemia, and finally prostration / death.
- Gross Pathology:
  - locally extensive lesions of mainly the connective tissues (subQ & fascia); characterized by severe edema (“malignant edema”), variable emphysema (“gas gangrene”), hemorrhage & discoloration of overlying skin.
- Histopathology:
  - predominately edema and cellulitis with minimal myositis; definitive diagnosis requires FA testing.

**Overall (subjective) differences between Blackleg and Malignant Edema / Gas Gangrene**

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<th>Cellulitis</th>
<th>Edema</th>
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PARASITIC MYOSITIS

- several important parasites encyst in and/or cause myositis in domestic animals.
- note, Toxoplasma, Neosporosis & Trypanosoma will be covered in other systems (nervous, cardiovascular, etc).

1) Trichinellosis (Trichinosis)
- Trichinella spp infection is an important zoonotic disease; rare in USA and Canada (except in the Arctic).
- many animals can be hosts (eg humans, pigs, dogs, cats, many wild canids / felids, bears, rats / mice, etc);
  infections acquired through consumption of incomplete cooked meat, esp pork, bears, or aquatic mammals.
- adults reside in the small intestinal mucosa, larvae migrate from the intestine to encyst in muscle tissue
- some predilection for active muscles, eg tongue, masseter, laryngeal, diaphragm & intercostals and eye.
- after initial larval invasion of myofiber there is mild focal inflammation, esp lymphoplasmacytic & eosinophils.
- after cyst formation there is only a minimal host response and therefore it is difficult to see them grossly without
  the help of a trichinoscope (ie microscopic with compression apparatus to make squash preps of muscle tissue)
- larvae remain viable for years, or die and become calcified (small visible white nodules).

2) Cysticercosis
- another important zoonotic disease prevalent in many developing countries; occasionally in Canada and USA.
- cysticercus is the larval stage of a taenia (tapeworm) with indirect life-cycle; the adult stage (tapeworm) resides
  in the intestine of definitive hosts (carnivores) while the larval stage (cysticercus) resides in the viscera / muscle
  of an intermediate host / prey species (eg pigs and cattle).
- the cysticerci of some tapeworms have a predilection for skeletal muscle and myocardium; eg’s
  - Taenia saginata is a tapeworm of primarily humans with the cysticerci (Cysticercus bovis) mostly in muscles
    of cattle (preference for heart and masticatory muscles).
  - Taenia solium is a tapeworm of primarily humans with cysticerci (Cysticercus cellulosae) found mainly in
    the heart and skeletal muscles of domestic or wild pigs.
  - Taenia ovis is a tapeworm of primarily dogs and wild carnivores with cysticerci (Cysticercus ovis) found
    mainly in the heart and skeletal muscles of sheep and goats.
- cysticercosis in humans implies fecal/oral contamination involving the ingestion of taenia eggs (not from
  ingestion of cysticerci which would result in tapeworm infestation).
- in some hosts, including humans, the cysticercus may reside in sites other than muscle, ie connective tissue,
  viscera, brain; in the brain it is called neurocysticercosis (which may or may not cause neurological signs).
- Gross Pathology:
  - cysticerci form large visible cysts (1-2 cm) which generally contain a clear fluid and larvae.
- Histopathology:
  - encysted cysticerci in myofibres have a minimal inflammatory response, ie few lymphocytes & eosinophils.
  - dead larvae generally become extensively calcified.

3) Sarcocystosis (Sarcosporidiosis)
- an important protozoal disease affecting primarily herbivores and pigs.
- parasite has an indirect life-cycle where carnivores (dogs, cats, humans) are definitive hosts and herbivores, pigs
  and birds are the intermediate hosts.
- sarcocystosis is so common that most herbivores have sarcocystis cysts in their musculature, however in most
  cases these protozoa cause no inflammatory response (see below for exceptions).
- although muscle cysts are generally subclinical and incidental, sarcocystosis is considered important primarily
  because it can cause abortion.
Gross and microscopic pathology:
- in most cases there is no inflammatory reaction to the cysts and in most species they are to small to be visible grossly (note, some large sarcocysts of birds and sheep can be seen grossly).
- in a small percentage of cattle and swine the cysts rupture, with resulting focal necrosis and eosinophilic granuloma formation; these can be seen grossly at slaughter in skeletal and heart muscle as yellow-green foci, a few mm in diameter.
- also, a small percentage of cattle at slaughter have locally extensive green discoloration of muscles; microscopically see severe eosinophilic myositis; thought to be reaction to sarcocysts.

NEOPLASTIC DISEASES OF MUSCLE
- spontaneous tumors of striated muscles are rare in veterinary medicine.
- striated muscle neoplasia occurs most frequently in the heart and skeletal muscles, also seen sporadically in non-muscular sites (eg kidney, urinary bladder and lung); ie likely from pluripotential mesenchymal stem cells.
- muscle tumor cell morphology varies from mononuclear round cells resembling myoblasts to spindloid cells to multinucleate cells resembling myotubes.
- neoplasia can also arise from supporting mesenchymal tissues of muscle; eg, adipose cells (lipoma/-sarcoma), fibrous connective tissue (fibroma/-sarcoma), vascular cells (hemangioma/-sarcoma) or nerves (neurofibroma).
- can also see infiltration and/or metastasis of tumor cells from other sites, eg lymphoma, hemangiosarcoma.

1) Rhabdomyoma
- a benign and often congenital tumor (hamartoma?) of striated muscle; most frequently found in pigs.
- most (up to 66%) originate in the heart (see cardiovascular system); occasionally seen in larynx of dogs.
- Gross Pathology:
  - in the laryngeal region, often protrude into lumen causing dyspnea, stridor &/or altered bark.
  - in the heart these tumors are found in the myocardium; can be pedunculated.
- Histopathology:
  - neoplastic cells have characteristic cross-striation resembling skeletal muscle.

2) Rhabdomyosarcoma
- most common in the cow, sheep, dog and horse.
- the malignant counterpart of the rhabdomyoma; frequent metastasis to lung, spleen, lymph nodes and kidneys.
- metaplastic rhabdomyosarcomas arising from sites with no striated muscle are seen sporadically (eg kidney & urinary bladder); thought to arise from pluripotential mesenchymal stem cells.
- Gross pathology
  - the tumors are often poorly encapsulated spherical nodules formed by pale fleshy tissue.
- Histopathology:
  - extremely variable, with or without striation; may have tumor giant cells.
  - in the most anaplastic tumors it is necessary to do immunohistochemistry, ie:
    - desmin and muscle actin expressed early in muscle differentiation (but also found in smooth muscle).
    - myoglobin and sarcomeric actin are specific for skeletal muscle; but often expressed in only well differentiated cells.
    - myoD and myogenin are myogenic regulatory factors that are specific for skeletal muscle and are best able to confirm poorly differentiated rhabdomyosarcomas.