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[Please direct curriculum comments to OASIS or [The Listening Post](#). For questions about LOs, use the [Discussion Board](#).]

Week overview by subject. Click the orange link to jump to that section in the Google Doc.

TBL Session 1: Neuromuscular Disease

Pre-Session Learning Objectives:

1. [Development & Regeneration of Neurons](#)
2. Neuromuscular Diseases
 - 2.1. [Basic Concepts](#)
 - 2.2. [Electrodiagnostic Tests Used in the Diagnosis of Neuromuscular Disease](#)
 - 2.3. Peripheral Neuropathies
 - 2.3.1. [Basic Concepts](#)
 - 2.3.2. [Mononeuropathies](#)
 - 2.3.3. [Common or Emergent Polyneuropathies](#)
 - 2.4. Myopathies
 - 2.4.1. [Basic Concepts](#)
 - 2.4.2. [Muscular Dystrophies](#)
 - 2.4.3. [Metabolic, Mitochondrial, Drug-Induced and Inflammatory Myopathies](#)

TBL Session 2: Applied Skeletal Muscle Physiology

1. Skeletal Muscle Fiber Types & Adaptation
 - 1.1. [Skeletal Muscle Metabolism - Basic Concepts](#)
 - 1.2. [Skeletal Muscle Fiber Types & Energy Metabolism](#)

TBL Session 3: [Clinical Anatomy of the Upper Extremity](#)

CA 44-111 is on Week 26 Google Doc (see the link above)

Week Schedule with links. Blue links go to outside resources.

MONDAY SIM: Health Literacy

MONDAY Patient: Athlete

MONDAY [TBL Session 1: Neuromuscular Disease](#)

TUESDAY Group B: Lab - Flexor Forearm, Wrist & Thumb / Group A: Independent Learning

WEDNESDAY Group A: Lab - Flexor Forearm, Wrist, Thumb, Extensor Forearm & Deep Hand / Group B: Independent Learning

WEDNESDAY Group B: Lab - Extensor Forearm & Deep Hand [11am]

THURSDAY Independent Learning (formerly TBL Session 2: Applied Skeletal Muscle Physiology)

FRIDAY [TBL Session 3: Clinical Anatomy of the Upper Extremity](#) [8:30am]

FRIDAY Patient Wrap-up

FRIDAY Practice Practical Exam (Formative Assessment) [1-5pm]

[Lower Extremity Self-Study](#)

[Lower Extremity Practice Questions](#)

TBL Session 1: Neuromuscular Disease

Pre-Session Learning Objectives:

1. Development & Regeneration of Neurons

(“Neuron Development & Regeneration” [handout](#) and online lecture)

NM162. List the major events in the development of the mature nervous system

1. Neural plate induction: ectodermal cells are signaled to become neural progenitor cells.
2. Cellular proliferation & pattern formation: neural progenitors proliferate & follow developmental programs based on location, e.g., cranial neural plate, trunk neural plate, neural crest cells.
3. Determination: neural progenitors are specified to become neurons, glia, ependyma or, in the case of neural crest cells, some other cell type (e.g. melanocytes).
4. Cellular specification & differentiation: neural progenitors differentiate into specific types of neurons, glia and other cells.
5. Morphogenesis & circuit development: newly “born” neurons project axons and dendrites; specific connections between neurons and between neurons and their effector organs or sensory receptors in the periphery are formed.
6. Circuit refinement & myelination: initial connections are adjusted and refined through interactions among the components; unused circuits are eliminated; speed of nerve conduction is increased through myelination.

NM163. Identify the tissue origin of adult neural stem cells.

- Ectoderm: originate from **radial glial cells** from neural cell progenitors within neuroepithelium
- A small number of adult neural stem cells persist in few distinct regions of brain

NM164. Describe the significance of the growth cone to neuron development and regeneration.

Growth cone: a sheetlike expansion of the tip of an elongating axon.

- “sniffs out” chemical signals (axon guidance factors) that allow the proper synaptic connections to be made.
 - Well known tropic factor = ‘netrin’
- use filopodia to pull the axons forward and help neurons reach their synaptic targets.

NM165. Define “neurotrophins” and describe their significance in circuit development and refinement, and in botulism poisoning.

- Neurotrophins (or neurotrophic factors) are growth factors expressed by neurons and target tissues (e.g. muscle), they:
 - 1) Signal neurons to divide, grow, or survive
 - 2) match #’s of neurons to target space
 - 3) regulate the degree of innervation at synapse
 - 4) modulate the growth and shape of axons and dendrites
- Neurotrophic Factors and Botulism: The terminal ends of motor neuron axons respond to botulism poisoning by sprouting a number of small branches (terminal sprouts) which forms many new synapse with the denervated (affected) muscles. The denervated muscle is thought to express trophic factors that lead to this ‘sprouting.’ Once the muscle has recovered the new synapses regress

NM166. Compare the timing and cells involved in the myelination of neurons in the peripheral and central nervous systems.

- PNS: myelination of axons by Schwann cells occurs in the 2nd-5th months of gestation (some axons remain unmyelinated)
 - Schwann cell (neurolemmocyte) wraps around the axon such that its nucleus and cytoplasm end up in the outside layer. The inner portion is the myelin sheath. The outer nucleated cytoplasmic layer of the neurolemmocyte, is the neurolemma (sheath of Schwann).
- CNS: myelination of axons by oligodendrocytes begins during the third trimester (week 28 and on) and continues through adolescence (fastest during infancy).

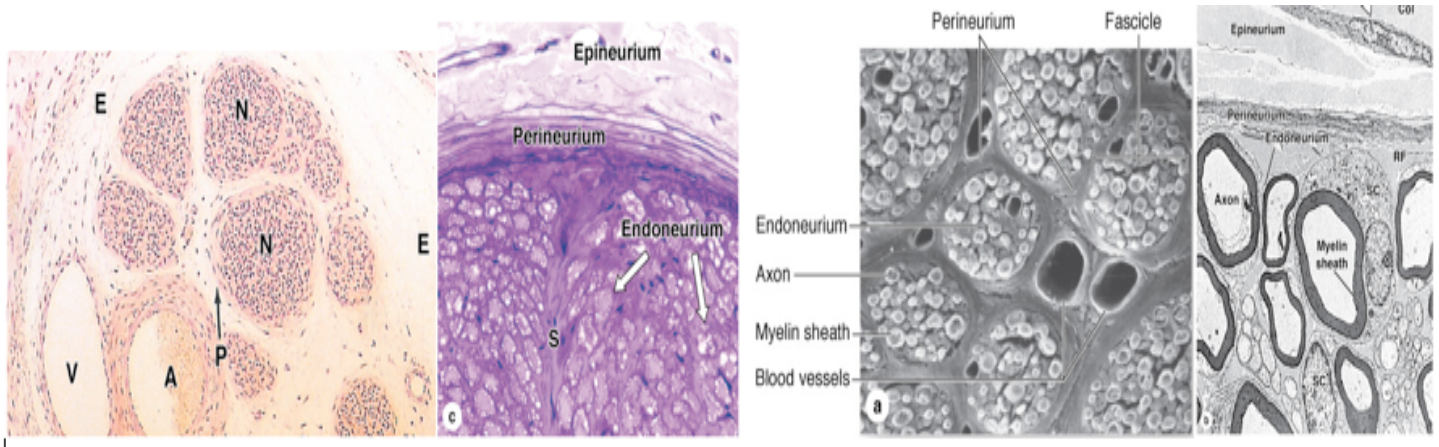
NM167. Describe the plantar reflex and compare its expected responses in infants and adults. Describe the “Babinski sign”.

plantar reflex--flexion of toes in response to deep stroking of foot’s lateral sole and base of the big toe. Slight fanning of the lateral toes and dorsiflexion of the great toe (the Babinski sign) is normal in children under age 4, but indicates CNS injury in adults.

- ‘+’ babinski after 4yo = CNS upper motor neuron injury

NM168. Describe the cross-section of a peripheral nerve and be able to identify its major features under light and scanning microscopy (see [Junquiera Figs 9-26 and 9-27](#)).

- **Endoneurium:** fine connective tissue sleeve that **surrounds individual axons & Schwann cells**, groups of these axons are bundled to form fascicles; (En) surround capillaries & is continuous with external lamina produced by Schwann cells
- **Perineurium:** **surrounds each fascicle**; consists of unusual epithelial-like fibroblast cells which are all joined at peripheries by tight junctions to form a *blood-nerve barrier* that helps regulate microenvironment
- **Epineurium:** **outer layer**, consists of dense superficial region and looser deep region with large **blood vessels (A, V) and fascicles** in which nerve fibers are bundled (N)



NM169. Describe the process of Wallerian degeneration of axons and indicate under what circumstance it occurs.

When an axon is cut or crushed the segment distal to the lesion loses its communication and support from the cell body and undergoes Wallerian degeneration.

- occurs over a week
- Schwann cells lose their myelin sheath structure and begin to proliferate
- axon swells, becomes irregular in shape, fragments, and is digested by macrophages and Schwann cells

NM170. Describe the underlying basis of “jaw-winking”, crocodile tears syndrome and the incomplete recovery of nerve function following nerve injury.

Incomplete recovery:

- Lacerations and crush injuries may damage different types (motor and sensory) of axons. During regeneration, filaments from many different axons (ie sensory and motor) typically enter the same endoneurial tube, re-innervating of end organs with wrong type of neuron.
- Axon sprouts may escape epineurial sheath and tangle into a neuroma.

• **“Jaw-winking”:** jaw’s motor axons are misdirected to muscles that control eyelid movement

• **Crocodile tears Syndrome:** misdirection of parasympathetic fibers of salivary gland to lacrimal gland instead – so gustatolacrimal reflex causes patients to cry when eating or drinking

NM171. Define the following terms that describe nerve injuries and indicate the expected recovery associated with each: *neuropraxia, axonotmesis, neurontmesis*.

Neuropraxia: transient sustained pressure causes temporary interference with nerve function without degeneration (e.x. Saturday night palsy). Recovery is fast and complete.

Axonotmesis: axons are damaged, but the connective tissue and Schwann cells remain intact (i.e. crush and ischemic injuries) Regeneration is still possible.

Neurontmesis: complete severance of nerve, including myelin and connective sheaths. No regeneration without surgery.

2. Neuromuscular Diseases

2.1. Basic Concepts

(Robbins and Cotran Ch 27, "[General Reactions of the Motor Unit](#)")

NM172. Identify the two targets of injury in peripheral neuropathies. Define *myopathy*.

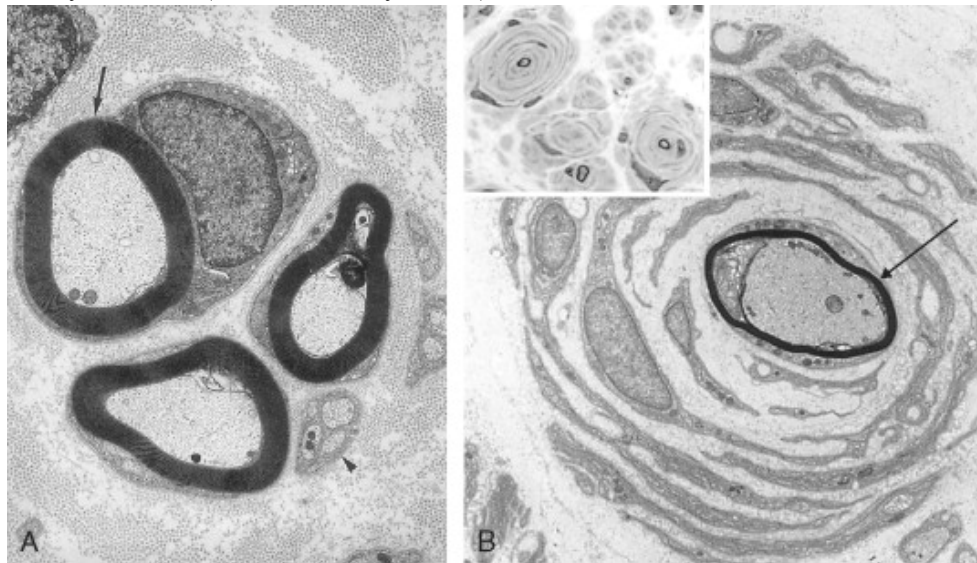
Schwann cell -- segmental demyelination

Neuron/axon -- axonal degeneration

Myopathy -- pathology caused by muscle fiber primary abnormality

NM173. Compare the appearance in cross-section of normal and regenerated myelin sheaths. Describe the appearance of the "onion bulb" and identify the specific circumstance in which this structure develops.

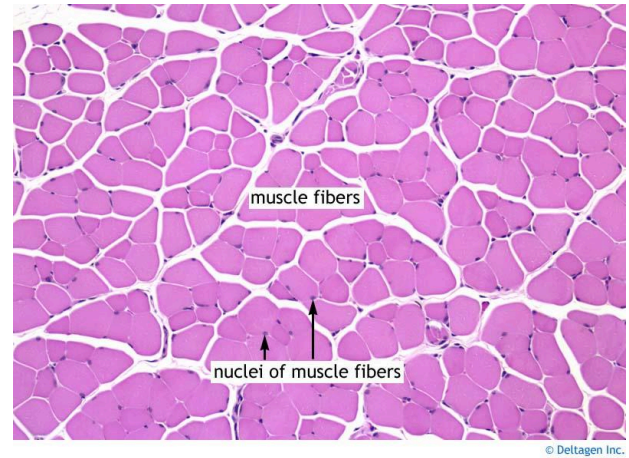
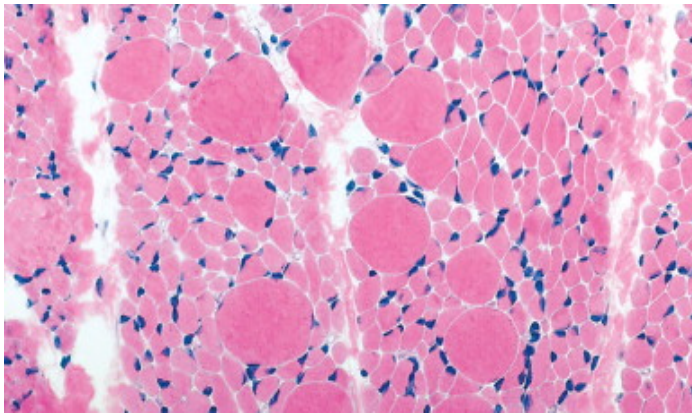
- Regenerated myelin sheaths are thinner (the image on the left is normal) and shorter; several are required to bridge demyelinated area.
- After multiple regenerations, multiple tiers of Schwann cell processes accumulate-->"onion bulb" (right image) with thin myelin layer at the center.
- May result from segmental demyelination from Schwann cell dysfunction (hereditary motor/sensory neuropathy) or damage to the myelin sheath (Guillain-Barré syndrome)



NM174. Describe the changes that occur within skeletal muscle cells as a consequence of denervation (denervation atrophy). Be able to recognize a denervated muscle on the basis of its histological cross-sectional anatomy (see also Robbins and Cotran "[Denervation Atrophy](#)"; Fig. 27-8).

Denervation:

- muscle atrophy
- myosin & actin break down
- myofibril resorption
- cells viable, but shrunk with triangular ("angulated") shape
- cytoskeleton reorganization possible --> rounded zone of disorganized myofibers in the center of the muscle fiber.



Left: Spinal muscular atrophy with groups of round atrophic muscle fibers, or panfascicular atrophy, resulting from denervation atrophy. This is what occurs in infants. In adults, the cells are not round, but triangular.
 Right: Normal image

NM175. Define “fiber type grouping” as it applies to the reinnervation of skeletal muscle cells. Discuss the effect that fiber type grouping has on the typical checkerboard appearance of normal muscle in cross-section.

When muscle fibers atrophy and are reinnervated, the nerve contacting an adjacent fiber extends new segments into the denervated myocytes. Since the adjacent unaffected fibers are typically of a different type, the result is that one fiber type starts to cluster around the affected cells. Thus the checkerboard pattern is lost as myocytes of the same type become clustered.

Long version: Reinnervation of the atrophic muscle fibers within an injured motor unit occurs when the axons belonging to an unaffected neighboring motor unit extend sprouts to reinnervate the denervated myocytes and incorporate them into the healthy motor unit. The number of muscle fibers within the healthy motor unit can thus be increased.

Since muscle fiber type is determined by the innervating neuron, the newly adopted reinnervated fibers assume the fiber type of their neighboring new siblings. The result of reinnervation is the loss of the checkerboard pattern and the occurrence of a patch of contiguous myocytes having the same histochemical type (type grouping).

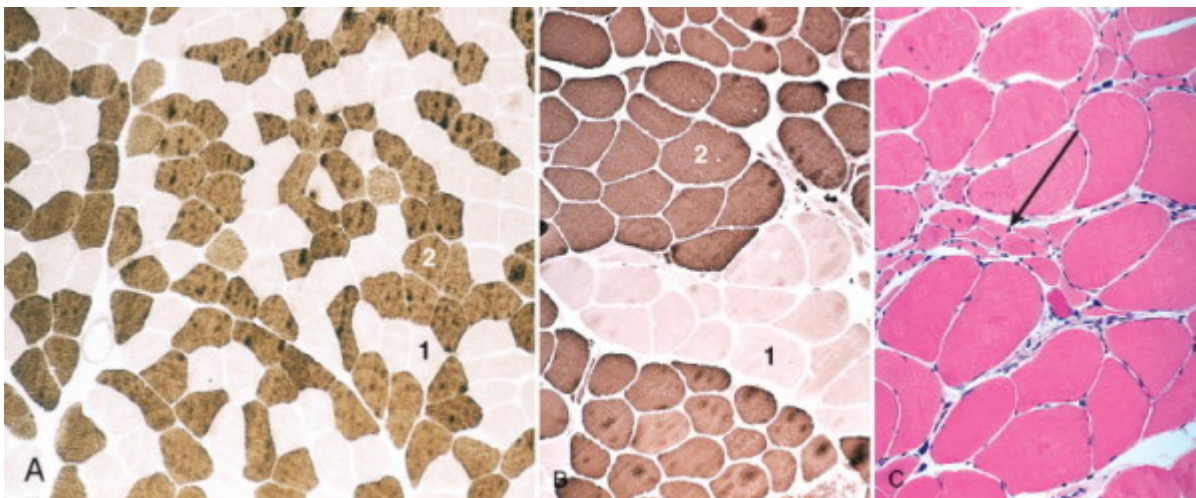


FIGURE 27-4 A, ATPase histochemical staining, at pH 9.4, of normal muscle showing checkerboard distribution of intermingled type 1 (light) and type 2 (dark) fibers. B, In contrast, fibers of both histochemical types are grouped together after reinnervation of muscle. C, A cluster of atrophic fibers (group atrophy) in the center (arrow).

2.2. Electrodiagnostic Tests Used in the Diagnosis of Neuromuscular Disease

(Adams and Victor's [Neurology Ch 45](#), display [entire chapter](#) and read screen “pages” 7-9 and 12-20 only) **This group of LOs are awful. I honestly think most of the LOs for the Monday TBL are very poorly written. Not at all the “straightforward, 2 sentence” answers MAM claimed will be the norm. Yikes! We really need to start summarizing.**

Nah, just this section... yeah I agree not too bad except for this section

NM176. Identify the properties of peripheral nerve function reflected in each of the following measures obtained from nerve conduction studies: conduction velocity, amplitude.

<http://www.accessmedicine.com/content.aspx?aID=3641135>

SNAP = Sensory Nerve Action Potential, the electrical impulse that carries information along a sensory nerve

CMAP = Compound Muscle Action Potential, a group of simultaneous action potentials from several nerve fibers in the same area usually evoked by stimulation of the supplying motor nerve and are recorded as one multi-peaked summated action potential

Conduction velocity = maximal velocity of action potentials in fastest nerve fibers. (Normal values have been established.); measure of myelination

Amplitude of evoked CMAP = a measure of the sum of action potentials of all individual muscle fibers stimulated (and of the innervated volume of muscle) - measure of axonal degeneration

NM177. Compare the conduction velocities and amplitudes expected in axonal and demyelinating peripheral neuropathies.

Longer version: Disease processes that preferentially injure the fast peripheral nerve fibers reduce the maximal conduction velocity because the remaining thinner fibers conduct more slowly. In most neuropathies, all of the axons are affected either by a fairly uniform "dying-back" phenomenon or by wallerian degeneration, and nerve conduction velocities are less informative. This is true, for example, in typical alcoholic-nutritional, carcinomatous, uremic, diabetic, and other metabolic neuropathies, in which conduction velocities range from the low-normal range to mildly slowed. In these "axonal neuropathies," the motor and sensory nerve amplitudes are diminished.

By contrast, demyelinating neuropathies of the acute (Guillain-Barré) and chronic types, such as chronic inflammatory, metachromatic leukodystrophy, and the common type of Charcot-Marie-Tooth disease, show marked slowing of conduction and, in the case of the acquired demyelinating diseases, there is also dispersion of the motor action potential and a highly characteristic conduction block.

Demyelinating lesions affecting the large, fast-conducting fibers are detected by the finding of differential slowing among various caliber fibers that causes a dispersal of the CMAP response. Reduction in motor and sensory amplitudes is a more specific and sensitive indicator of axonal loss than is slowing of conduction velocity or prolongation of distal latencies. Conversely, prolonged distal latencies and slowed motor conduction velocities, as well as conduction blocks and dispersed responses, are the hallmarks of demyelinating lesions.

TL;DR:(what does this mean?) (TL means "too long" and DR means "didn't read"; you use it after you post something on a forum so people can get the bottom line without reading everything, then they can go back to what you wrote if they need clarification)

Axonal PN

- Amplitude down because fewer axons = fewer fibers responding = smaller AP
- Conduction velocity usually remains normal (range from low-normal range to mildly slowed)
- Affects both motor and sensory nerve amplitudes

Demyelinating PN

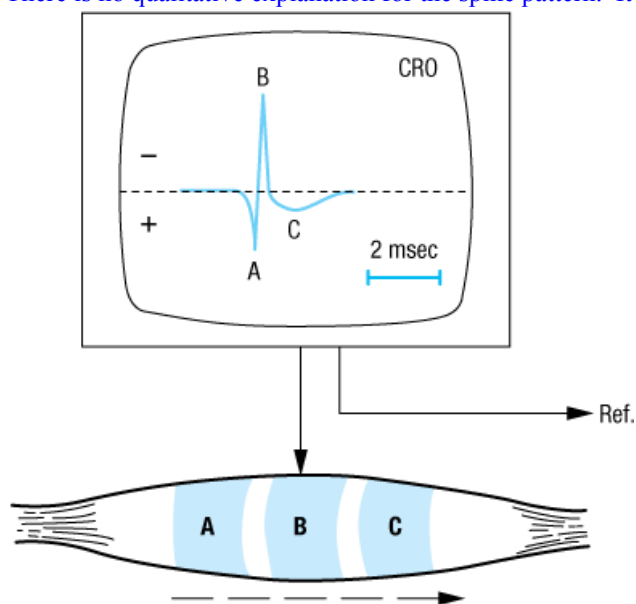
- Conduction velocity down b/c loss of myelin
- Amplitude measurements down but vary (multifocal/conduction block vs. uniform disease, uniform slowing)
- Slowed motor conduction as well as conduction blocks

NM178. Identify the property recorded in electromyography (EMG). Draw a typical triphasic motor unit potential as recorded in EMG.

Needle Examination of Muscle or electromyography detects NMJ failure by recording the electrical activity of various muscles generated by contraction.

Typical triphasic motor unit potential ("MUP") = Figure 45-5 (below).

There is no qualitative explanation for the spike pattern. It's just a pattern to memorize.



Source: Ropper AH, Samuels MA: *Adams & Victor's Principles of Neurology* 9th Edition: <http://www.accessmedicine.com>

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NM179. Define *fasciculations* (fasciculation potentials) and describe their typical presentation. Identify the pathological and normal conditions that produce fasciculations.

Fasciculation = the spontaneous or involuntary contraction of an entire motor unit, causing contraction of a group of muscle fibers

Presentation:

- contractions may cause a visible dimpling or twitching under the skin
- large distal fasciculations can briefly displace a finger or toe

Normal conditions:

- occasional FPs (fasciculation potentials) in the calves, hands, and periocular or paranasal muscles occur in many normal persons
- can be almost constant for days or weeks on end, or even for years in some individuals, without weakness or wasting ("benign fasciculations")
- Shivering induced by low temperature and twitchings associated with low serum calcium levels are other forms of fasciculatory activity.

Pathological conditions:

- FPs occur with great frequency in chronic, slowly advancing, destructive diseases of the anterior horn cells, such as ALS (aka Lou Gehrig's disease) and progressive spinal muscular atrophy.
- often seen in early stages of poliomyelitis but only occasionally in the chronic phase of the disease, perhaps because the affected cells die rapidly. When anterior horn cells degenerate once again in older individuals who had had poliomyelitis (postpolio syndrome), fasciculations may return.
- Occasionally seen in one muscle as a result of a compressive anterior root lesion, such as those caused by a protruded IV disc. Large numbers of axons may be affected in this case, with the result that the fasciculations (or even cramps) may be even more prominent than with disease of anterior horn cells but they are restricted to the territory of innervation of the root or nerve.
- FPs in lesser numbers are also observed with chronic nerve entrapments, e.g., ulnar neuropathy at the elbow and other peripheral nerve lesions and some polyneuropathies.

Fasciculation potentials are evidence of motor nerve fiber irritability. Thus, the combination of fibrillations and fasciculations indicates active denervation combined with more chronic reinnervation of muscle.

NM180. Compare the amplitude, duration and shape of the MUPs expected in cases of denervation/reinnervation, and in primary myopathies.

Denervation/reinnervation:

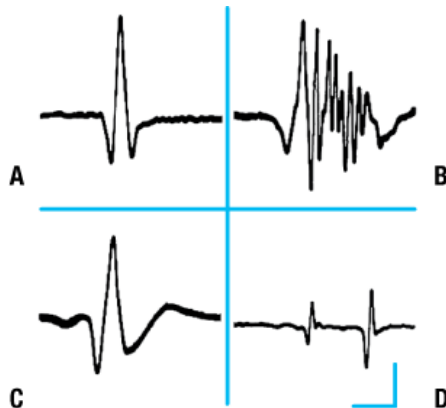
- Increased amplitude
- Long duration (>15 ms)
- Sometimes polyphasic

This happens because the motor unit now innervates far more muscle fibers than it previously did. You therefore get a stronger response.

Primary myopathies:

- Decreased amplitude
- Shorter duration
- Sometimes polyphasic (due to fragmentation into single-fiber potentials)

The motor unit no longer innervates as many functional muscle fibers. You therefore get a weaker response and a shorter duration.



Source: Ropper AH, Samuels MA: *Adams & Victor's Principles of Neurology* 9th Edition: <http://www.accessmedicine.com>

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(Left) Single voluntary motor unit potentials.

- A. Normal.
- B. Prolonged polyphasic potential seen with reinnervation.
- C. "Giant unit"—normally shaped but of much greater amplitude than normal.
- D. Brief, low-amplitude "myopathic" units.

2.3. Peripheral Neuropathies

2.3.1. Basic Concepts (Harrison's Online Chapter 379 "[Approach to the patient...](#)")

NM181. Identify the natural history of the symptoms of peripheral neuropathy.

The initial symptoms of peripheral neuropathy are often intermittent, and examination can be normal. In most situations, sensory symptoms precede motor symptoms.

Small-fiber neuropathies often present with dysesthesias and paresthesias, terms used interchangeably to describe unpleasant, unusual, or abnormal sensations such as burning or cutting pain, electric shock-like sensations, tingling, pins and needles, formication (feeling of insects crawling on your skin), prickly feelings such as a limb falling asleep, or cramp-like sensations.

Large-fiber neuropathies can present as numbness, tingling, or a gait disturbance (sensory ataxia). In most cases, the abnormal sensation originates in the toes and feet and ascends proximally to the legs in a stocking distribution. Only when the sensation reaches the level of the knee or thigh do symptoms appear in the hands, producing a length-dependent, or stocking-glove, pattern. Paresthesias that begin in one hand suggest an entrapment neuropathy such as carpal tunnel syndrome.

Motor symptoms usually have a later onset than sensory symptoms. In long-standing inherited neuropathies, patients may present with isolated weakness of the feet without sensory symptoms; the ankle jerk, the most distal deep tendon reflex, is invariably absent. When confronted with a length-dependent pattern of sensory symptoms, the diagnosis of a peripheral neuropathy is not difficult. However, in cases with pure motor weakness or wasting, localization may be difficult, and in such cases the presence of distal weakness is helpful in differentiating a peripheral neuropathy from muscle or neuromuscular junction disorders, which

typically present with proximal weakness. Motor neuron disease can also present with distal weakness and wasting; however, the findings are not in the distribution of an individual nerve.

NM182. Distinguish the following peripheral nerve distributions: polyneuropathy, mononeuropathy, multiple mononeuropathy.

- Polyneuropathy: symmetric dysfunction of the peripheral nerves
- Mononeuropathy: involves a single peripheral nerve
- Multiple mononeuropathy involves multiple individual peripheral nerves

NM183. Distinguish the sensorimotor symptoms characteristic of axonal and demyelinating peripheral neuropathies. Describe the development and anatomical representation of the stocking-glove pattern of sensory loss.

- Sensorimotor symptoms
 - Axonal
 - most follow a length-dependent (stocking-glove) pattern with sensory (small fiber more so than large) symptoms and signs predominating over motor manifestations
 - distal reflexes absent
 - demyelinating
 - affect motor and sensory fibers equally (large fibers more than small fibers)
 - more generalized areflexia or hyporeflexia
- Stocking glove pattern
 - Length-dependent pattern of sensory loss in axonal neuropathies
 - Abnormal sensation originates in the toes and feet and ascends proximally to the legs; only when the sensation reaches the level of the knee or thigh do symptoms appear in the hands

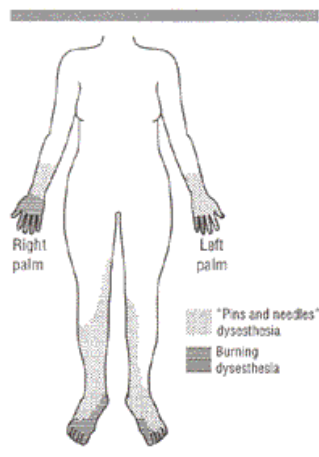


FIGURE 1. PAINFUL PERIPHERAL NEUROPATHY, SHOWING "STOCKING-GLOVE" PATTERN ON LOWER LEGS AND ARMS, AND THE CHARACTERISTIC BURNING PAIN DISTALLY AND "PINS AND NEEDLES" PROXIMALLY

Note. From *Pain: Clinical Manual* (p. 577) by M. McCaffery and C. Pasero, 1999, St. Louis, MO: Mosby. Copyright 1999 by Mosby, Inc. Reprinted by permission.

2.3.2. Mononeuropathies
(Harrison's Online Chapter 379 screen "[Mononeuropathes](#)")

NM184. List the common causes of mononeuropathies. Describe Tinel's and Phalen's signs.

Mononeuropathy refers to disease or damage of a single nerve.

The most common causes are compression, entrapment, and trauma. Extrinsic compression usually occurs when a limb is maintained in a fixed position that produces sustained pressure on the nerve. The neuropathy is often reversible if the position is changed. Intrinsic factors such as arthritis, fluid retention (pregnancy), amyloid, tumors, and diabetes mellitus may make nerves at entrapment sites more susceptible to injury. Often both extrinsic and intrinsic factors contribute to neuropathy, e.g., an anatomically narrowed region coupled with repetitive activity, poor posture or position.

Since most entrapped nerves contain both motor and sensory fibers, both types of symptoms occur, usually in the distribution of the affected nerve. Sensory symptoms may include numbness, pins and needles, tingling, prickling, burning, or electric shock sensations.

Reflexes are generally unaffected since most entrapped nerves are distal to the deep tendon reflexes typically examined.

Percussion of the nerve at the affected site may induce paresthesias (Tinel's sign); however, this may also occur in normal individuals and is not a reliable sign. Placing the limb in a posture known to **aggravate the compression may accentuate symptoms (e.g., Phalen's sign evoked by flexing the wrist for carpal tunnel syndrome).**

NM185. Identify the prognosis and treatment of acute mononeuropathies. Identify when surgical treatment should be considered.

EDx studies confirm the clinical diagnosis and provide information about location, severity, and prognosis. Focal demyelination is detected as a focally reduced nerve conduction velocity along the length of the sensory and/or motor fibers. Wallerian degeneration is reflected in a reduction of distal amplitudes and as denervation potentials. The latter is associated with a relatively poor prognosis for recovery.

Treatment for acute and subacute compressive neuropathies consists of identifying and removing extrinsic contributors and the use of splints to avoid further compression. In patients with chronic compressive neuropathies, exacerbating factors should be identified and treated before surgical correction is considered. The use of splints, a change of work habits to avoid activities or movements that precipitate the neuropathy, or anti-inflammatory medication for tenosynovitis may be helpful.

Surgical treatment may be required for management of chronic compressive neuropathies when conservative measures have failed and the site of entrapment is clearly delineated.

2.3.3. Common or Emergent Polyneuropathies

(Robbins and Cotran Ch 27, "[Diseases of Peripheral Nerve](#)" – see appropriate sections only) **Would anyone be willing to summarize these? This is the summary.**

NM186. Describe Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP - Guillain-Barré Syndrome) in terms of etiology, pathogenesis, dominant histomorphologic features, and primary clinical findings.

AIDP – Guillain-Barré Syndrome:

Etiology: peripheral neuropathy disease; **acute-onset immune-mediated demyelinating neuropathy.** ~2/3 of cases are **preceded by an acute, influenza-like illness** from which the affected individual has recovered by the time the neuropathy becomes symptomatic. Infections with *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, and *Mycoplasma pneumoniae*, or prior vaccination, are associated with Guillain-Barré syndrome. No consistent demonstration of an infectious agent, and an immunological reaction is generally favored as the underlying cause.

Pathogenesis: **T cell-mediated immune response** to a peripheral nerve myelin protein (**cross-reactivity with Ag from microbes discussed above?**) accompanied by **segmental demyelination induced by activated macrophages.** Lymphocytes from individuals with Guillain-Barré syndrome produce demyelination. Circulating Abs may also play a part, and plasmapheresis can be an effective treatment.

Dominant histomorphologic features: **inflammation of peripheral nerve**, manifested as perivenular and endoneurial infiltration by lymphocytes, macs, and a few plasma cells. Inflammatory foci and demyelination are widely distributed throughout the PNS with variable intensity. The **most intense inflammatory reaction is often localized in spinal and cranial motor roots and the adjacent parts of the spinal and cranial nerves. Segmental demyelination affecting peripheral nerves is the primary lesion, but damage to axons is also characteristic**, particularly in severe cases. Early effect on myelin sheaths → cytoplasmic processes of macs penetrate the basement membrane of Schwann cells, particularly near the nodes of Ranvier, and extend between the myelin lamellae, stripping away the myelin sheath from the axon. Remnants of the myelin sheath are engulfed by the macs; remyelination follows the demyelination (**onion bulb appearance**)

Primary clinical findings: **weakness in distal limbs then ascending paralysis. Deep tendon reflexes disappear early;** sensory involvement can often be detected, but is less troublesome than weakness. Nerve conduction velocity is slowed because of the multifocal destruction of myelin segments involving many axons within a nerve. **CSF protein is elevated due to inflammation and altered permeability of the microcirculation within the spinal roots as they traverse the subarachnoid space.** Inflammatory cells are contained within the roots, however, and there is **little to no CSF pleocytosis** (elevated WBC in CSF). Many pt's spend weeks in hospital ICU's before recovering normal function. Mortality rate has fallen from 25% but is still considerable; 2-5% die of respiratory paralysis, autonomic instability, cardiac arrest, or complications of treatment. Up to 20% of hospitalized patients have long-term disability.

NM187. Compare AIDP with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) in terms of clinical course and primary clinical findings.

CIDP:

Clinical course and findings: **relapses and remissions over a period of several years**, rather than the acute course of Guillain-Barré syndrome. **Often a symmetric, mixed sensorimotor polyneuropathy**, although some pt's have predominantly sensory or motor impairment. Clinical **remissions may occur with steroid treatment and plasmapheresis**. Biopsies of sural nerves show evidence of **recurrent demyelination and remyelination** associated with well-developed **onion bulb structures**.

NM188. With respect to the following infectious polyneuropathies, for each identify its etiology and typical symptoms: AIDS-associated distal symmetric polyneuropathy, Lyme disease-associated neuropathy, herpes zoster (see [Harrison's Online Ch 379](#) for AIDS and Lyme-associated neuropathies).

<u>Infectious Polyneuropathy Disease</u>	<u>Etiology</u>	<u>Typical Symptoms</u>
AIDS-associated distal symmetric polyneuropathy	worse HIV infection, older age, nutritional deficiencies, and toxic exposures are risk factors Length-dependent axonal degeneration of sensory fibers; both large myelinated and unmyelinated fibers are lost	- Painful burning, tingling, and numbness in the feet. - bilateral, gradual in onset, and worse at night - distal loss of pin and temperature sensation - absent or decreased ankle jerk. -Weakness either undetected or confined to intrinsic foot muscles. -Inflammatory infiltrates of lymphocytes and activated macrophages and reduced numbers of DRG neurons
Lyme disease-associated neuropathy	Infection with <i>Borrelia burgdorferi</i> , with or without associated meningitis.	--Subacute cranial neuropathy (especially VII) - radiculitis is dysesthetic (impaired sensitivity to touch) or painful; variable in distribution. - CSF pleocytosis with intrathecal production of <i>B. burgdorferi</i> Ab's is typical. -Most patients improve either spontaneously or after IV ceftriaxone treatment. - In the chronic phase, a mild, chronic distal polyneuropathy (sensory more than motor), however, the CSF is normal and the association may be coincidental
Herpes zoster (VZV)	latent infection from chicken pox persists in the sensory ganglia of CNS; reactivation factors are not fully understood, perhaps though decreased cell-mediated immunity	- painful, vesicular skin eruption (<i>shingles</i>), most frequently thoracic or trigeminal dermatomes. -Neuronal destruction/loss + abundant mononuclear inflammatory infiltrates - regional necrosis w/ hemorrhage -axonal degeneration after death of sensory neurons. -Focal destruction of large motor neurons of anterior horns or cranial nerve motor nuclei may be seen at the corresponding levels.

NM189. Describe Charcot-Marie-tooth (CMT1) Disease in terms of etiology, typical presentation, dominant histomorphologic features and prognosis.

Etiology: segmental trisomy of 17p11.2--> demyelinating neuropathy

presentation: **progressive atrophy below knee** in childhood to early adulthood

histomorphology: demyelination/remyelination--> onion bulbs

prognosis: progressive disease w/o loss of life expectancy

Before you think of this as simply normal life expectancy watch this: <http://www.youtube.com/watch?v=TCRbJaOGTAw>

Long version: Charcot-Marie-Tooth (CMT1):

***Etiology:** genetically heterogeneous disease; the most common subtype (HMSN IA or CMT1A) has a duplication of a large region of chromosome 17p11.2 → “segmental trisomy”. Duplicated segment includes the gene that encodes peripheral myelin protein 22 (PMP22), a transmembrane protein expressed in compacted myelin. PMP22 and a set of related proteins are involved in the compaction of myelin in the PNS. **Mutations → demyelinating neuropathies (CMT1). Mutations in another gene on chromosome 1, which codes for myelin protein zero (MPZ), produce an identical clinical phenotype (HMSN IB).** Additional pedigrees with hereditary demyelinating neuropathy show mutations in genes encoding structural proteins (connexin-32), protein degradation pathways (LITAF), and myelination induction genes (early growth response 2, EGR2).*

***Typical presentation:** usually presents in **childhood or early adulthood**. A characteristic **progressive muscular atrophy of the leg below the knee** seen in these pt's gives rise to the common clinical term peroneal muscular atrophy. Affected individuals may be asymptomatic, but when they present, it is often with symptoms such as **distal muscle weakness, atrophy of the leg below the knee, or secondary orthopedic problems of the foot** (such as pes cavus).*

***Dominant histomorphologic features:** demyelinating neuropathy; repetitive demyelination and remyelination with multiple onion bulbs, more pronounced in distal nerves than in proximal nerves. The axon is often present in the center of the onion bulb, and the myelin sheath is usually thin or absent. The redundant layers of Schwann cell hyperplasia surrounding individual axons → enlargement of involved peripheral nerves that may become palpable, which has led to the term hypertrophic neuropathy. In the longitudinal plane, the axon may show evidence of segmental demyelination. Autopsy studies of affected individuals have shown degeneration of the posterior columns of the spinal cord.*

***Prognosis:** most often autosomal dominant and slowly progressive, but the disability of sensorimotor deficits and associated orthopedic problems such as pes cavus are usually limited in severity, and a normal life span is typical.*

NM190. Describe the typical symptoms and clinical course of diabetic sensorimotor polyneuropathy (DSPN).

Diabetic sensorimotor polyneuropathy (DSPN):

Sx: any combination of distal symmetric sensory or sensorimotor neuropathy, autonomic neuropathy, and focal or multifocal asymmetric neuropathy; the **most common** peripheral neuropathy in DM2 is **distal symmetric neuropathy that involves sensory and motor nerves**.

Clinical course:

- *Distal symmetric sensory or sensorimotor neuropathy:* **decreased sensation in the distal extremities with less evident motor abnormalities**. The loss of pain sensation can result in development of **ulcers, which heal poorly** because of the diffuse vascular injury in diabetes and are a major cause of morbidity

- *Autonomic neuropathy:* affects 20-40% of DM pt's, is nearly always associated with a **distal sensorimotor neuropathy**. Diabetic autonomic neuropathy has protean manifestations, including **postural hypotension, incomplete emptying of the bladder resulting in recurrent infections, and sexual dysfunction**

- *Focal/multifocal asymmetric neuropathy:* **affects elderly adults with a long history of DM**; manifests as a disorder of single individual peripheral or cranial (oculomotor nerve) nerves (mononeuropathy), or of several individual nerves in an asymmetric distribution (multiple mononeuropathy or mononeuropathy multiplex); **involves vascular insufficiency and ischemia of the affected peripheral nerve**.

NM191. List the vitamin deficiencies that produce peripheral neuropathies. Recognize that many therapeutic drugs can

produce peripheral neuropathies.

vitamins B12 (cobalamin), B6 (pyridoxine), E (α -tocopherol), and thiamine

NM192. For each of the following conditions, identify the agent(s) or procedures (if any) used in their treatment: AIDP, CIPD, DSPN, Lyme disease, herpes zoster (see appropriate sections in Harrison's Online Chs [379](#) & [380](#)).

AIDP: begin treatment asap (each day counts, ~2 weeks after the first motor symptoms, immunotherapy is no longer effective); either high-dose IV Ig or plasmapheresis; **glucocorticoids not effective**; early-treated pt's may relapse in 2nd/3rd week – retreatment with original therapy is usually effective; very mild forms of GBS can be treated conservatively without Ig or PE; in the worsening phase of GBS most pt's require monitoring in a critical care setting, many require ventilator

CIPD: initiate treatment when progression is rapid or walking is compromised; treat with high-dose IV Ig, plasmapheresis, or glucocorticoids (except when sensory findings are absent). If all 3 treatments fail, then try immunosuppressants (azathioprine, methotrexate, cyclosporine, cyclophosphamide, rituximab)

DSPN: strict glucose control, alpha lipoic acids, and, in a select few cases, pancreas transplant. Consistent check ups to prevent unnoticed ulceration in the foot

Lyme disease: 14-28 days of IV ceftriaxone (1st choice), IV cefotaxime (2nd choice), IV penicillin G (3rd choice)

Herpes zoster: acutely – acyclovir, famciclovir, or valacyclovir are equally effective. Glucocorticoids are of unproven benefit. Treatment of postherpetic neuralgia includes tricyclic antidepressants, duloxetine, gabapentin, pregabalin, oxycodone, morphine sulfate, tramadol, lidocaine patch, and topical capsaicin.

2.4 Myopathies

2.4.1. Basic Concepts

(Harrison's Online Ch 382 "[Introduction](#)")

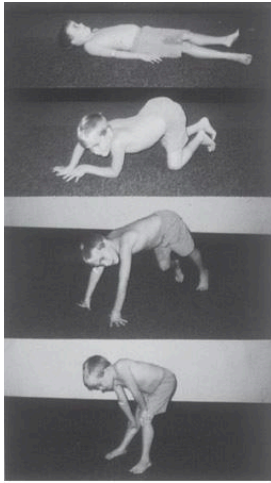
NM193. List the most common clinical findings of myopathic conditions (1) and identify how peripheral neuropathies and CNS injury findings differ in presentation (2).

Myopathy: Disorder with structural changes or functional impairment of the muscle

1. Proximal, symmetric limb weakness (arms and legs) with preserved reflexes and sensation
2. If have sensory loss, think injury to peripheral nerve or CNS rather than myopathy
Disorders of the spinal cord motor nerve cell body, NMJ, and peripheral nerve can mimic myopathies

NM194. Describe the "limb-girdle" pattern of weakness. Identify the functional impairments indicative of proximal lower limb (i.e., hip) weakness. Describe the "Gowers' Sign".

1. Limb-girdle: the proximal muscles are weaker than the distal and are symmetrically affected, and the facial muscles are spared
2. Functional impairments assoc with hip weakness: inability to walk without a waddling gait, inability to get up from the floor without climbing up the extremities (**GOWER'S SIGN**), inability to get up from a chair without using arms, lordotic posture exaggerated by standing on toes.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: <http://www.accessmedicine.com>
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NM195. Define *myalgia*.

True myalgia refers to muscle aching (localized or generalized). May be accompanied by weakness, tenderness to palpation, or swelling. May be associated with cramps, spasms, contractures, and stiff/rigid muscles. Can be drug induced.

NM196. Distinguish muscle cramps from muscle contractures in terms of underlying cause and EMG findings.

Muscle cramps:

Underlying cause: painful, involuntary, muscle contraction with a visible or palpable hardening of the muscle. Abrupt and short in duration.

EMG findings: firing of motor units, reflecting an origin from spontaneous neural discharge.

Muscle contractures: *(are these also painful?)*

Underlying cause: Continuous muscle contraction in the absence of a stimulus, such as an action potential (essentially rigor). The muscle also becomes hard but is unable to relax after the active contraction.

EMG findings: electrical silence.

to be distinguished from “contracture” which refers to a muscle that cannot be passively stretched to its proper length (fixed contracture) because of fibrosis

NM197. Define *myotonia*. Indicate how the condition is typically elicited and relate this to handshake- and grip-release.

1. myotonia: a condition of prolonged muscle contraction followed by slow muscle relaxation. Always follows muscle activation (which is usually voluntary but can be elicited by mechanical stimulation of the muscle)
2. Typically causes difficulty releasing objects after a firm grasp. Inability to release after a handshake is a common example

Good squeeze, can't let go.

NM198. Identify why serum creatine kinase (CK) levels are used preferentially to diagnosis myopathies.

1. Damage to muscle causes the CK to leak from the muscle fiber into the serum. The MM isotype predominates in skeletal muscle
2. Serum CK can be elevated in normal individuals without provocation, presumably on a genetic basis, or after strenuous activity, minor trauma, a prolonged muscle cramp, or a generalized seizure.
3. Other markers may reflect liver rather than muscle function (aspartate aminotransferase, alanine aminotransferase, aldolase, lactic dehydrogenase).

NM199. Define myoglobinuria and indicate under what circumstances it occurs (Adams and Victor's [Neurology Ch 45](#), screen “pages” 7-8).

The red pigment myoglobin, responsible for much of the color of muscle, is an iron-protein compound present in the sarcoplasm of striated skeletal and cardiac fibers.

Destruction of striated muscle, regardless of the cause, liberates myoglobin, and because of its relatively small size, the molecule

filters through the glomeruli and appears in the urine, imparting to it a burgundy-red color. Because of the low renal threshold for myoglobin, excretion of the pigment is so rapid that the serum remains uncolored. In contrast, the high renal threshold for hemoglobin, colors both the serum and the urine if there is destruction of red blood corpuscles. Myoglobinuria should thus be suspected when the urine is deep red and the serum is normal in color. **It is estimated that 200 g of muscle must be destroyed to color the urine visibly.**

2.4.2. Muscular Dystrophies

(Robbins and Cotran Ch 27, "[Muscular Dystrophies](#)")

NM200. Identify the single histological feature that distinguishes dystrophies from other myopathies.

The muscular dystrophies are a heterogeneous group of inherited disorders of muscle, often beginning in childhood, that lead to progressive weakness and muscle wasting. Histologically, in advanced cases **muscle fibers undergo degeneration and are replaced by fibrofatty tissue and collagen**. This feature distinguishes dystrophies from myopathies, which also present with muscle weakness.

NM201. Describe the function of the dystrophin-glycoprotein complex of skeletal muscle fibers and identify its role in muscular dystrophy.

Dystrophin and the dystrophin-associated protein complex form an interface between the intracellular contractile apparatus and the extracellular connective tissue matrix. The role of this complex of proteins in transferring the force of contraction to connective tissue has been proposed to be the basis for the myocyte degeneration that occurs in the absence of dystrophin or various other proteins that interact with dystrophin.

Muscle biopsy specimens from individuals with DMD (Duchenne muscular dystrophy) show little or no dystrophin by both staining and western blot analysis. People with BMD (Becker muscular dystrophy), who also have mutations in the dystrophin gene, have diminished amounts of dystrophin, usually of an abnormal molecular weight, reflecting mutations that allow synthesis of an abnormal protein of smaller size

NM202. Identify the mode of inheritance and primary histopathologic findings of Duchenne and Becker muscular dystrophies.

Mode of inheritance = X-linked recessive genetic disorder. Mutation in DMD gene that encodes dystrophin.

Histopathologic abnormalities common to DMD and BMD include:

- (1) variation in fiber size (diameter) due to the presence of both small and enlarged fibers, sometimes with fiber splitting;
- (2) increased numbers of internalized nuclei (beyond the normal range of 3% to 5%);
- (3) degeneration, necrosis, and phagocytosis of muscle fibers;
- (4) regeneration of muscle fibers; and
- (5) proliferation of endomysial connective tissue

DMD cases also often show enlarged, rounded, hyaline fibers that have lost their normal cross-striations; such fibers, believed to be hypercontracted, are rare in BMD. Both type 1 and type 2 fibers are involved, and no alterations in the proportion or distribution of fiber types are evident. Histochemical reactions sometimes fail to identify distinct fiber types in DMD. In later stages **the muscles eventually become almost totally replaced by fat and connective tissue**. Cardiac involvement, when present, consists of interstitial fibrosis, which is more prominent in the subendocardium.

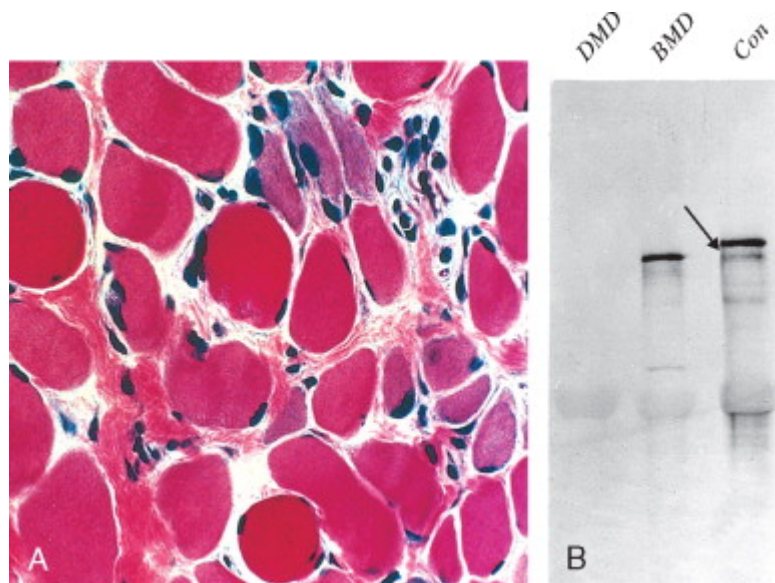


FIGURE 27-10 A, Duchenne muscular dystrophy (DMD) showing variation in muscle fiber size, increased endomysial connective tissue, and regenerating fibers (blue hue). B, Western blot showing absence of dystrophin in DMD and altered dystrophin size in Becker muscular dystrophy (BMD) compared with control (arrow) (Con).

NM203. Compare Duchenne and Becker muscular dystrophies in terms of the following variables: age of onset of symptoms, clinical course, association with cardiac disease and mental retardation, prognosis (Harrison's Online Ch 382 "[Hereditary Myopathies](#)"; Table [382-5](#)).

	Age of onset of symptoms	Clinical course	Association w/ cardiac disease and mental retardation	Prognosis
Duchenne Muscular Dystrophy (DMD)	Before 5 years	-Progressive weakness of girdle muscles - Unable to walk after age 12 - Progressive kyphoscoliosis - Respiratory failure in 2d or 3d decade	Cardiomyopathy Mental impairment	Death from respiratory insufficiency, pulmonary infection, and cardiac decompensation in late teens to mid-30s
Becker Muscular Dystrophy (BMD)	Early childhood to adult (later than DMD)	- Progressive weakness of girdle muscles - Able to walk after age 15 - Respiratory failure may develop by 4th decade	Cardiomyopathy (less common than in DMD)	Many have a nearly normal lifespan

Most data is from [Table 382-5](#).

2.4.3. Metabolic, Mitochondrial, Drug-Induced and Inflammatory Myopathies (Robbins and Cotran Ch 27, "[Diseases of Skeletal Muscle](#)" – see appropriate sections only)

NM204. Review (from MCM – "[Regulation of Glycogen Metabolism](#)") the etiology and histopathology of myophosphorylase deficiency (McArdle's disease) (see also Harrison's Online Ch 382 "[Disorders of Muscle Energy Metabolism](#)").

From the handout:

Patients with McArdle's disease (type V) lack muscle glycogen phosphorylase and accumulate glycogen, but survive reasonably; their problem is one of cramps and pain upon initiation of exercise, with no lactate formation. However, if they get over this a

"second wind" with vasodilation brings glucose and other fuels, and they can exercise. A characteristic of the disease is a high level of glycogen in the muscle. Rhabdomyolysis may lead to renal failure.

Etiology = Autosomal recessive genetic disorder. Myophosphorylase deficient.

Histopathology = High levels of glycogen. Serum CK fluctuates wildly. Lack of myophosphorylase.

NM205. Describe the etiology and histopathology of carnitine palmitoyltransferase (CPT II) deficiency. Compare McArdle's disease and CPT II deficiency in terms of serum CK levels between episodes and venous lactate levels during forearm exercise test (Harrison's Online Ch 382 "[Disorders of Muscle Energy Metabolism](#)").

Abnormalities of carnitine transport:

- blocks fatty acid oxidation --> less energy
- accumulation of lipid droplets within muscle (lipid myopathies).
- muscle pain, tightness, and myoglobinuria following prolonged exercise or exercise during fasting states.
- Concomitant cardiomyopathies and fatty liver possible

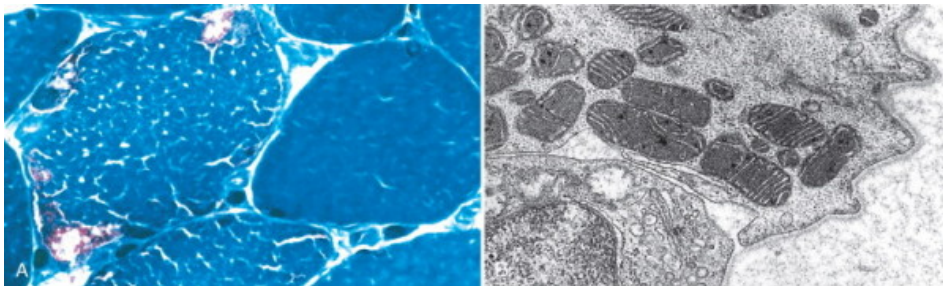
In McArdle's, the serum CK levels fluctuate widely and may be elevated even during symptom-free periods. CK levels >100 times normal are expected, accompanying myoglobinuria. An *impaired rise in venous lactate* is highly indicative McArdle's

In CPT II deficiency: Serum CK levels are typically normal between episodes. A *normal rise* (as opposed to an impaired rise) in venous lactate levels during forearm exercise distinguishes this condition from glycolytic defects, especially McArdle's.

NM206. Identify the symptoms and histopathologic findings characteristic of mitochondrial myopathies. Explain why these conditions are sometimes classified as mitochondrial encephalomyopathies. Recognize ragged red fibers in a histological section and explain their significance.

mitochondrial myopathies:

- caused by mutations in both nuclear and mitochondrial genes
- diseases that involve the mtDNA show maternal inheritance (only the oocyte contributes mitochondria to the embryo).
- mtDNA mutates more than nuclear DNA.
- present in young adulthood
- classified as mitochondrial encephalomyopathies because of proximal muscle weakness (**limb-girdle pattern?**), severe involvement of the extraocular muscles (external ophthalmoplegia), other neurologic symptoms, lactic acidosis, and cardiomyopathy,



The most consistent pathologic finding in skeletal muscle is aggregates of abnormal mitochondria that are demonstrable only by special techniques. These occur under the sarcolemma in early stages, but with severe involvement, they may extend throughout the fiber. Since they are also associated with distortion of the myofibrils, the muscle fiber contour becomes irregular on cross-section, and the descriptive term ragged red fibers has been applied to them (Fig. 27-12A) (Left).

NM207. Identify the mode of inheritance of myoclonic epilepsy with ragged red fibers (MERRF), mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), and Kearns-Sayre syndrome.

PLEASE let's try to be concise:

- MERRF: maternal pattern (point mutations in mtDNA)
- MELAS: maternal pattern (point mutations in mtDNA)
- Kearns-Sayre syndrome: spontaneous (deletions or duplications of mtDNA)

Note on Kearns-Sayre: mtDNA deletions are presumed to arise spontaneously in ovum or zygote.

NM208. Identify the two therapeutic agents that commonly cause myopathy. List the clinical features typical of chronic steroid myopathy (Harrison's Online Ch 382 "[Drug-Induced Myopathies](#)").

glucocorticoids, statins, and chloroquine

Sx in short:

- proximal or generalized weakness
- type 2 muscle atrophy
- loss of myosin and ATPase

Long version:

*Glucocorticoid myopathy occurs with chronic treatment or as "acute quadriplegic" myopathy secondary to high-dose, IV glucocorticoids. Chronic administration produces **proximal weakness** accompanied by cushingoid manifestations, which can be quite debilitating; the chronic use of prednisone at a daily dose of 30 mg/d is most often associated with toxicity. Patients taking fluorinated glucocorticoids (triamcinolone, betamethasone, dexamethasone) appear to be at especially high risk for myopathy.*

Patients receiving high-dose, IV glucocorticoids for status asthmaticus, chronic obstructive pulmonary disease, or other indications may develop severe generalized weakness. Involvement of the diaphragm and intercostal muscles causes respiratory failure and requires ventilatory support. In this setting, the use of glucocorticoids in combination with nondepolarizing neuromuscular blocking agents to further decrease airway resistance is particularly likely to lead to this complication.

*In chronic steroid myopathy the serum CK is usually normal. Serum potassium may be low. **The muscle biopsy in chronic cases shows preferential type 2 muscle fiber atrophy**; this is not reflected in the EMG, which is usually normal. In acute cases with quadriplegic myopathy the muscle biopsy is abnormal, showing a distinctive loss of thick filaments (myosin) by electron microscopy. By light microscopy there is focal loss of ATPase staining in central or paracentral areas of the muscle fiber. Calpain stains show diffusely reactive atrophic fibers. Withdrawal of glucocorticoids will improve the chronic myopathy. In acute quadriplegic myopathy, recovery is slow. Patients require supportive care and rehabilitation.*

NM209. Distinguish the following inflammatory myopathies in terms of age of onset, clinical presentation and histopathologic findings: dermatomyositis, polymyositis and inclusion body myositis.

see: <http://accessmedicine.com/content.aspx?aid=2907992>

	Age of onset	Clinical presentation	Histopathologic findings
Dermatomyositis	Adult and Juvenile Juvenile: also abdominal pain and GI involvement. Mucosal ulceration, hemorrhage, perforation from vasculopathy. Calcinosis in 1/3 of youths	-- rash takes the form of a lilac or heliotrope discoloration of the upper eyelids associated with periorbital edema -- Often scaling erythema or dusky red patches over knuckles, elbows, and knees (Groton lesions). -- slow onset, bilateral muscle weakness, myalgias, proximal muscles affected 1st --1/3 have dysphagia -- often interstitial lung disease, vasculitis, and myocarditis --Higher risk of visceral cancers.	--inflammatory around small blood vessels and in perimysial connective tissue. -- perifascicular atrophy: atrophic fibers are particularly prominent at the periphery of fascicles; diagnostic -- reduced intramuscular capillaries from vascular endothelial injury and fibrosis. --Necrotic muscle fibers and regeneration throughout the fascicle
Polymyositis	Adulthood	--symmetric proximal muscle involvement. -- lack of cutaneous involvement -- inflammatory involvement of heart,	-- inflammatory cells in the endomysium. -- lymphoid cells surround and invade healthy muscle fibers --necrotic and regenerating muscle fibers

		lungs, and blood vessels.	throughout the fascicle, without the perifascicular atrophy --no evidence of vascular injury
Inclusion Body Myositis	--Typically after 50+ yrs. --mostly sporadic, but familial cases possible	--begins with the involvement of distal muscles , esp. knee extensors (quadriceps) and wrist& finger flexors -- weakness may be asymmetric.	--diagnosis: rimmed vacuoles in myocytes, highlighted by basophilic granules at their periphery. --vacuolated fibers with amyloid deposits that stain with Congo red. --Under the electron microscope, tubular and filamentous inclusions (β -amyloid or hyperphosphorylated tau) in cytoplasm and nucleus. --inflammatory cell infiltrate like in polymyositis.

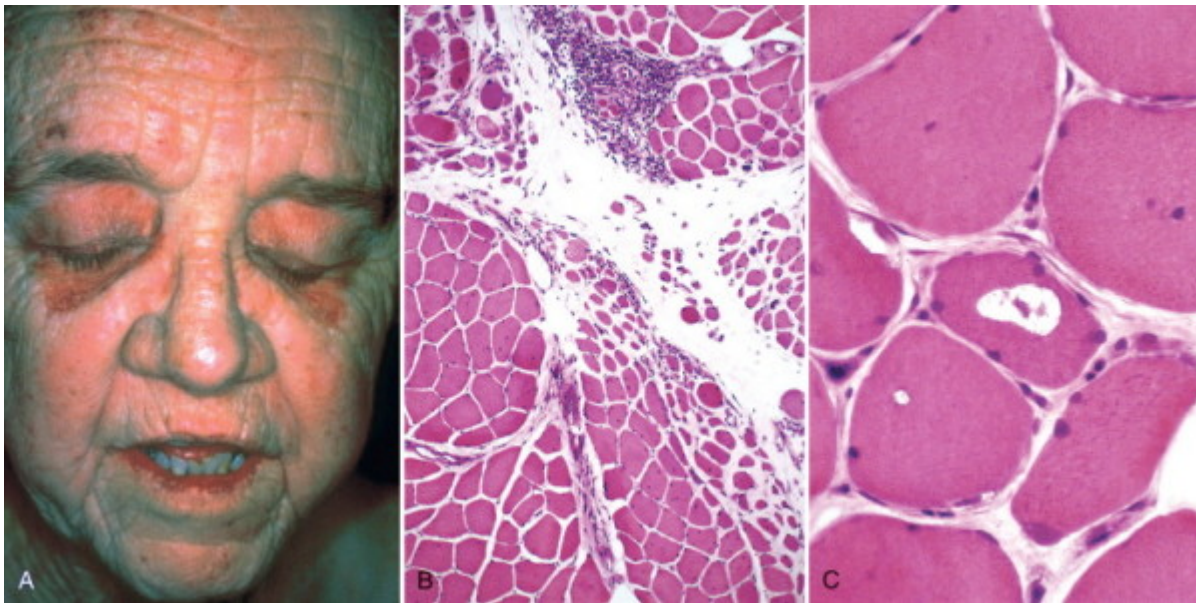


FIGURE 27-13 A, Dermatomyositis. Note the heliotrope rash affecting the eyelids. B, Dermatomyositis. The histologic appearance of muscle shows perifascicular atrophy of muscle fibers and inflammation. C, Inclusion body myositis showing a vacuole within a myocyte.

1. Skeletal Muscle Fiber Types & Adaptation

1.1. Skeletal Muscle Metabolism - Basic Concepts

(Review from appropriate handouts in MCM or BRS Biochemistry, Molecular Biology & Genetics)

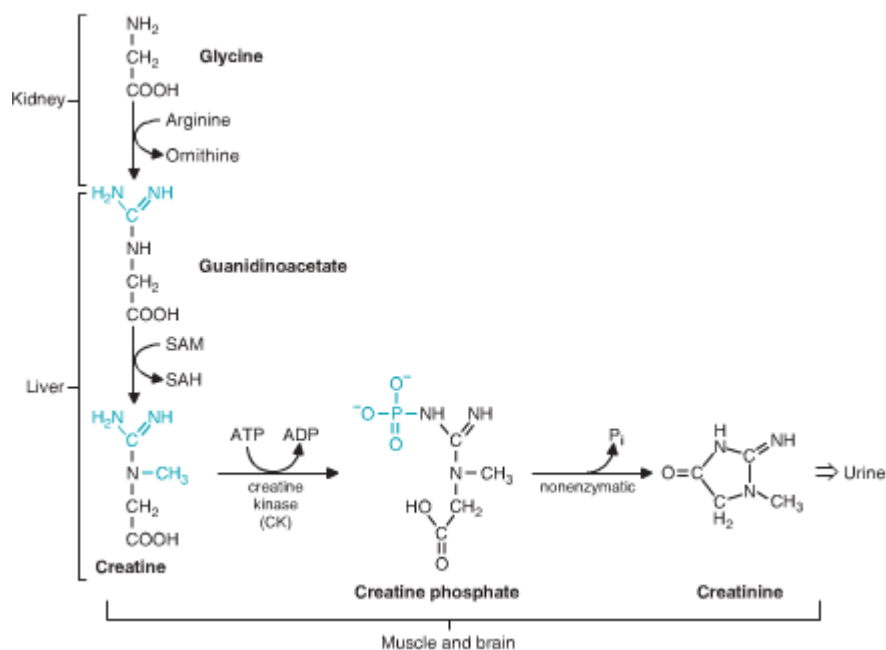
NM210. Review creatine synthesis in the body and its activation by creatine (phospho)kinase in muscle.

Glycine + Arginine → Guanidinoacetate (+ ornithine) in KIDNEY

- Driven by the conversion of arginine into ornithine
- Inhibited by creatine

Guanidinoacetate + SAM → Creatine (+SAH) in LIVER

Creatine + ATP → Creatine phosphate (+ADP; via CK) → Creatinine (+P_i) in MUSCLE & BRAIN (to rapidly regenerate ATP from ADP)



<http://www.med-ed.virginia.edu/CourseSites/display.cfm?keyID=2037&click=0&Content=http%3A%2F%2Fwww.med-ed.virginia.edu%2Fpublic%2FCourseSitesDocs%2FMolecularCellularMedicine%2Fhandouts%2Frestricted%2Foriginal%2FHND.7.1.4.mayoSDL.pdf>

NM211. Review the sources of glucose used by muscle during exercise and how this relates to the enzyme defects underlying glycogen storage diseases that affect skeletal muscle function.

Muscle glycogen and blood glucose (from liver glycogen) are the glucose sources for muscle use during exercise (Cori cycle also plays a role). With glycogen storage defects, no glycogen available for muscle function.

Sources of Glucose

- Glycogenolysis
- Ingested glucose
- Gluconeogenesis (rarely)

Enzyme Defects

- Lack of **glucose 6-phosphatase** precludes conversion of glucose 6-phosphate to glucose in glycogenolysis or gluconeogenesis (**von Gierke's Disease**)
- Defects in **muscle phosphorylase** prevent the breakdown of glycogen to glucose (**McArdle's Disease**)

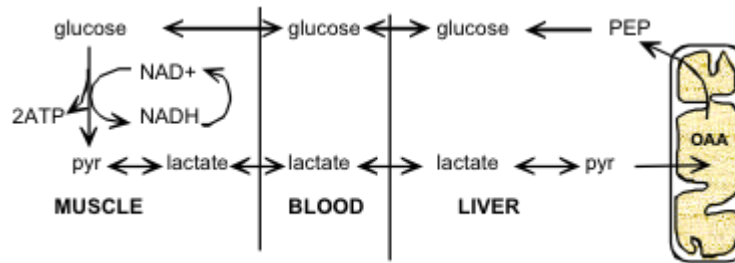
NM212. *Review the fates of NADH, in shuttles and lactate formation, during aerobic and anaerobic glycolysis.*

In the conversion of Glyceraldehyde-3-P → 1,3-bisphosphoglycerate, NAD⁺ removes 2 e⁻s and 2H⁺s from G-3-P and forms NADH. After aerobic glycolysis, the NADH is reoxidized to NAD⁺ by the ETC (ETC is in mitochondria so NADH is transported there via the glycerol-phosphate or malate-aspartate shuttle). This conversion → 4 or 6ATP/glucose. After anaerobic glycolysis, the NADH is used as a reducing agent to reduce pyruvate → lactate (which regenerates NAD⁺ to be used again)

NM213. *Review the role of the Cori cycle during anaerobic muscle metabolism.*

Muscles produce lactate via anaerobic glycolysis, which goes to liver and converts to glucose, which goes back to muscles and is converted to lactate again.

The muscle gets 2 ATP out of the deal and sends the products back to the liver; the liver requires 6 ATP to turn those products back into glucose, which it then sends back to the muscle. Thus, Cori Cycle = unsustainable for long periods.



1.2. Skeletal Muscle Fiber Types & Energy Metabolism

(Online article: **Skeletal muscle: Energy metabolism, fiber types, fatigue and adaptability.** *Experimental Cell Research*, **Volume 316, Issue 18**, pp. 3093-3099)

NM214. *Identify the two principle means of anaerobic muscle metabolism and indicate the type of physical activity in which these forms of energy metabolism are used.*

- degradation of **phosphocreatine (PCr)**
- breakdown of **muscle glycogen** to lactate and hydrogen ions
- type of physical activity: faster and therefore dominate during **high-intensity** physical activity of short duration

NM215. *Identify the type of physical activity in which aerobic pathways of energy production are utilized. Identify the principal substrates used in these pathways and their tissue source.*

- **carbs & lipids** during prolonged sub-maximal exercise
- carbs are mostly from muscle glycogen but **extracellular blood glucose** use increases w/exercise duration and short-term maximal exercise
- free fatty acids are derived from TAGs stored in muscle and adipose tissue (highest contribution to aerobic ATP production is at exercise with ~60% maximal oxygen uptake, contribution decreases at higher exercise intensities)

NM216. *Discuss the role of reactive oxygen species (ROS) in aerobic muscle metabolism.*

- **ROS** induce contraction-mediated **glucose uptake** via signaling involving **AMPK** (AMP-dependent protein kinase)
- ROS production is increased throughout periods of sub-maximal exercise, where extracellular glucose makes a significant contribution to aerobic ATP productions

NM217. *List the four types of skeletal muscle fiber types that occur in mammals and identify those found in human muscles.*

- Type I, IIa, IIx, and IIb
- **Type IIb is not found in humans. Correct me if I'm wrong, but type IIx is sometimes referred to as IIb which is way confusing**

NM218. *Relate skeletal muscle fiber types to rate of cross-bridge cycling and speed of contraction, and to energy needs and means of energy metabolism.*

Type I: slowest cross bridge cycling (and speed of contraction); consume least amount of energy (SERCA2 pumps w/less dense distribution); generally higher oxidative capacity

Type IIa: intermediate cross bridge cycling (and speed of contraction); consume intermediate amount of energy

Type IIb/x: fastest cross bridge cycling (and speed of contraction); consume most amount of energy (SERCA1 pumps w/dense distribution); generally lower oxidative capacity

NM219. *Define fatigue as it relates to skeletal muscle function. Identify which muscle fiber types are more resistant to fatigue.*

Fatigue = a **reversible activity-induced decline in performance** (muscle contraction), highly dependent on the capacity of the aerobic metabolic system. Accordingly, slow oxidative muscle fibers are markedly more fatigue resistant than fast glycolytic fibers under normal conditions.

NM220. *Distinguish central and peripheral fatigue. Identify how the properties of skeletal muscle contraction are affected by peripheral fatigue.*

-Central fatigue: each alpha-motor neuron activates a number of muscle fibers (together they represent the “motor unit”); all muscle fibers in a motor unit are of the same type (hence metabolically matched to fit discharge properties of their alpha-motor neuron); fatigue may occur as a consequence of **impaired alpha-motor neuron activation** (central fatigue). Central fatigue is of greater importance during prolonged low-intensity activities, where metabolic changes within muscle cells are likely to be limited, whereas intramuscular factors dominate during activities of higher intensity.

-Peripheral fatigue: relates to factors within the **muscle** that cause impaired contractile function during strenuous exercise. Reduced ability of cross-bridges to generate force and decreased myofibrillar Ca^{2+} sensitivity (initially) and decreased SR Ca^{2+} release (later) decreased isometric force production. Reduced shortening speed, altered force-velocity relationship, and slowed relaxation all play parts as well. High lactate and Pi levels in muscle occur as well.

NM221. *Discuss the roles of lactic acidosis and inorganic phosphate ions in peripheral fatigue.*

-Acidosis: acidosis of the magnitude observed in severely fatigued muscle fibers has little impact on force production, contractile speed, and rate of fatigue development. Despite the fact that acidosis is not a major cause of fatigue, blood lactate is easy to measure and can serve as a good indicator of the extent of anaerobic metabolism used by muscles during exercise.

- Pi : anaerobic metabolism includes the **breakdown of phosphocreatine**, which --> an increase in Pi , which subsequently --> decreased force production and myofibrillar Ca^{2+} sensitivity (by reducing the # of force generating cross bridges). In addition, Pi might enter the SR during fatigue --> Ca^{2+} - Pi solubility product being exceeded (precipitation of CaPi and decreased free Ca^{2+} available for release).

NM222. *Distinguish resistance training and endurance training in terms of the repetition and force of muscle contractions.*

Identify the effects of these training regimes on the characteristics of skeletal muscle fibers.

-Resistance (strength): involves relatively few high-force contractions; results in an **increase in muscle fiber cross-sectional area** and hence larger force production due to an increased number of parallel myofibrils.

-Endurance: consists of repeated low-force contractions; has beneficial effects on most aspects of skeletal muscle energy metabolism. Endurance training stimulates **mitochondrial biogenesis** and **increased oxidative capacity** and increased fatigue resistance, enhances glucose uptake and insulin sensitivity, increases FA metabolism which leads to better-preserved glycogen stores during prolonged exercise, and stimulates angiogenesis and capillary formation which results in improved oxygen delivery to mitochondria.