Diseases of Skeletal Muscle

APPROVED

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Chapter 27 R&C

A patient that presents with muscle weakness can have any of these:

1. Neurogenic atrophy

Primary to the nerve, secondary to the muscle

2. Muscular dystrophies
3. “Congenital” myopathies
4. Metabolic myopathies
5. Inflammatory myopathies
6. Toxic myopathies
7. Diseases of the neuromuscular junction

2-6 are primary to the muscle

Normal muscle architecture

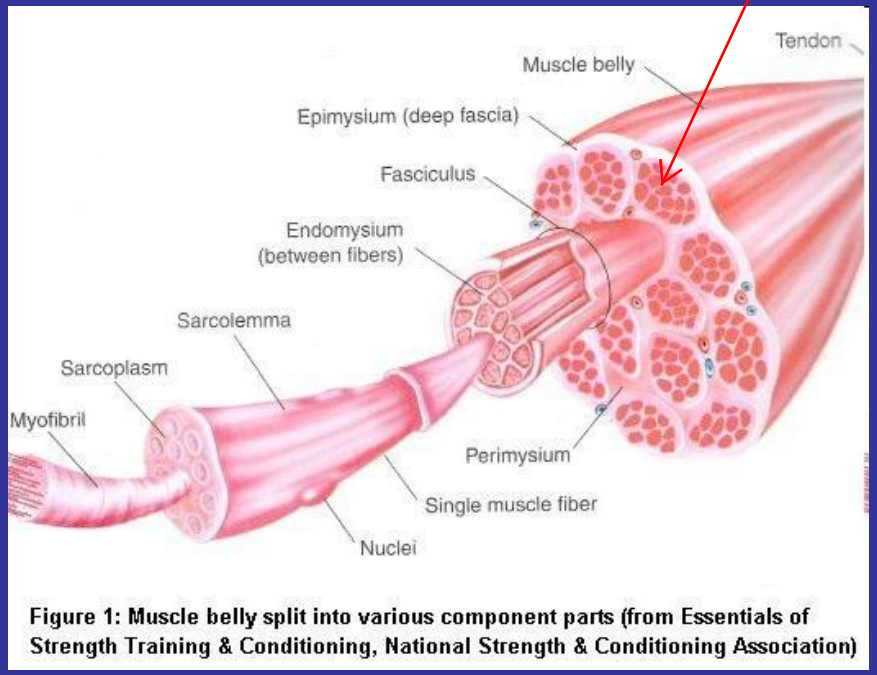
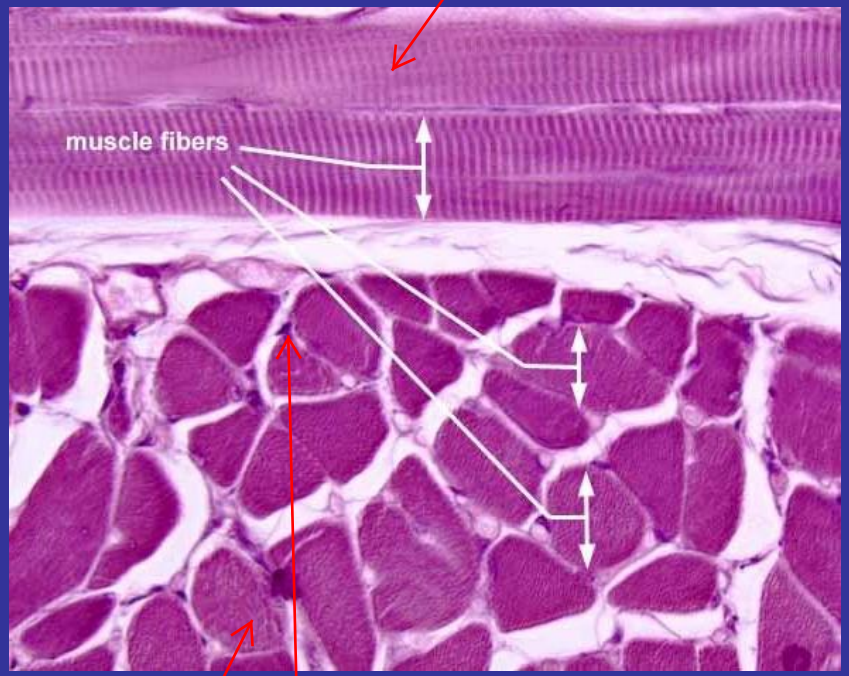


Figure 1: Muscle belly split into various component parts (from Essentials of Strength Training & Conditioning, National Strength & Conditioning Association)

fascicle of individual myocytes

longitudinal view



anatomyforme.blogspot.com

cross section view

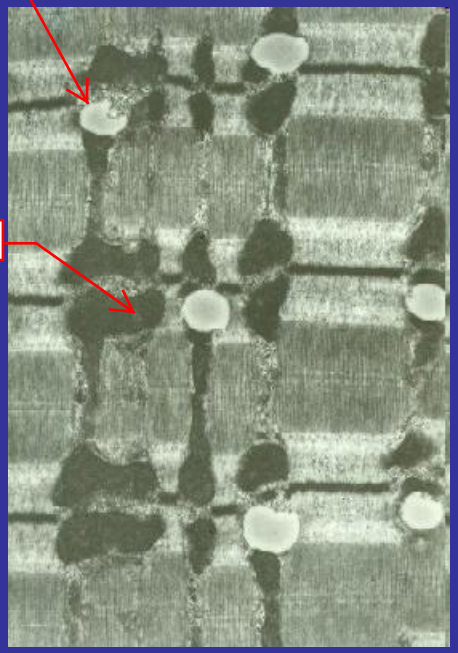
Nucleus. Should be peripheral like this in normal muscle. Myocytes should all be about the same size.

Type 1 and Type 2 fibers

(ultrastructure)

lipid droplets

mitochodria



Type 1

Aerobic, oxidative

Abundant, large mitochondria

Numerous lipid droplets

Slow twitch

less mitochodria, and can't see lipid droplets

Type 2

Anaerobic, glycolytic

fast twitch

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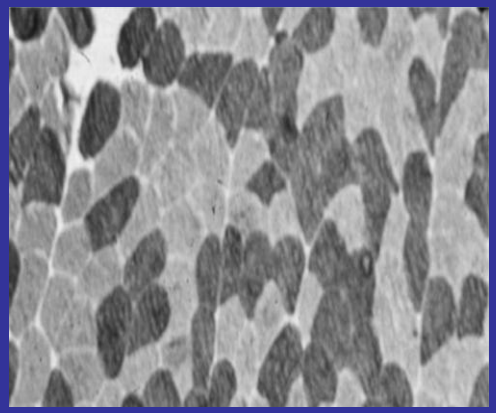
5. **Inflammatory myopathies**
6. **Toxic myopathies**
7. **Diseases of the neuromuscular junction**

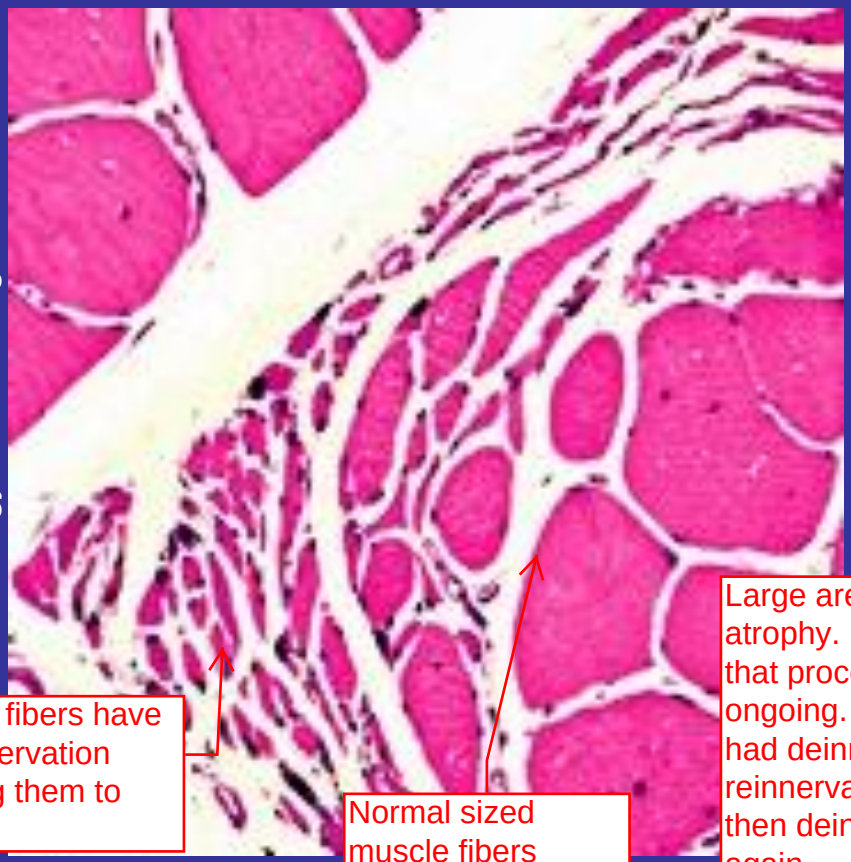
Histopathology of neurogenic atrophy

Normal



ATPase stain: see checkerboard pattern of type 1 and type 2 fibers. Good distribution

Atrophied fibers

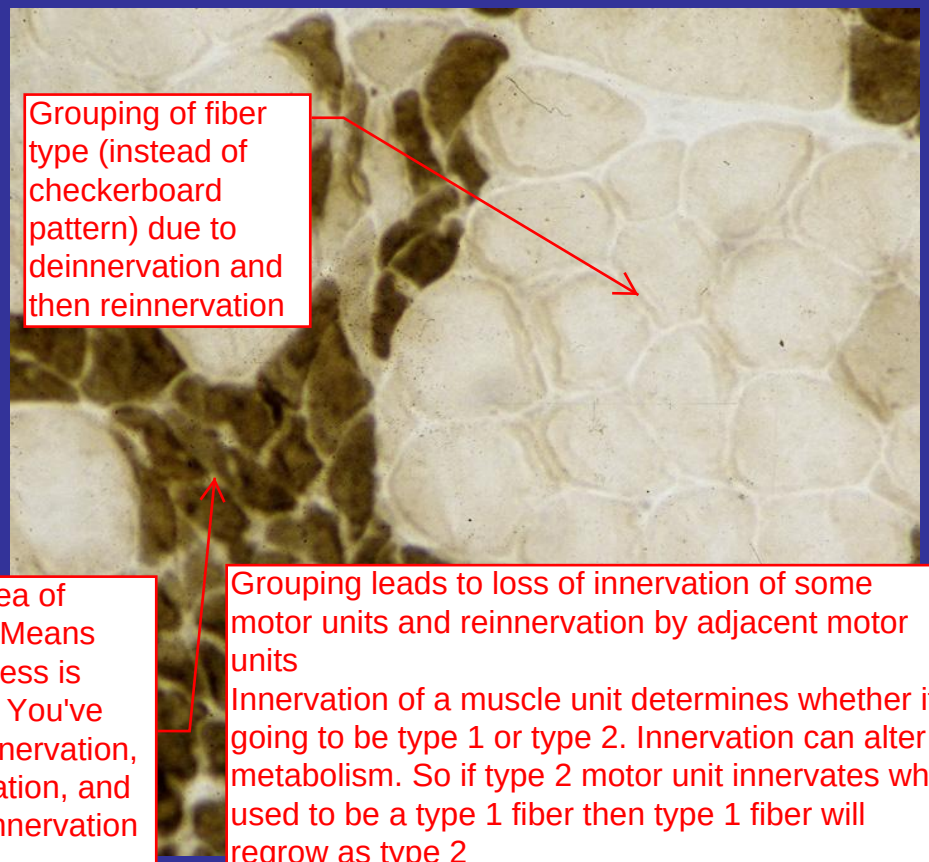


Muscle fibers have lost innervation causing them to shrink

Normal sized muscle fibers

Large area of atrophy. Means that process is ongoing. You've had deinnervation, reinnervation, and then deinnervation again

Type grouping & grouped atrophy



Grouping of fiber type (instead of checkerboard pattern) due to deinnervation and then reinnervation

Grouping leads to loss of innervation of some motor units and reinnervation by adjacent motor units

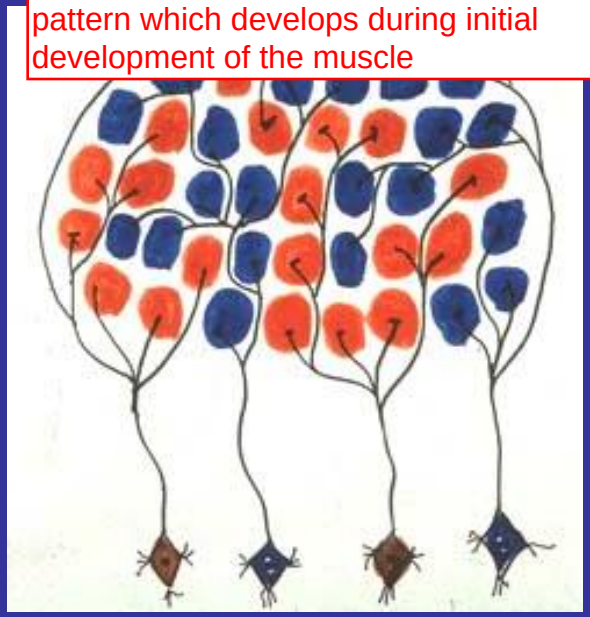
Innervation of a muscle unit determines whether its going to be type 1 or type 2. Innervation can alter metabolism. So if type 2 motor unit innervates what used to be a type 1 fiber then type 1 fiber will regrow as type 2

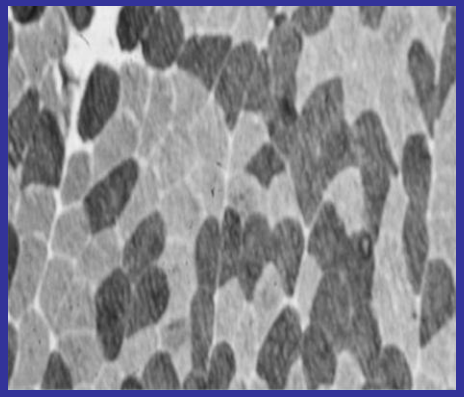
Histology for Pathologists

Courtesy Ed Bosser

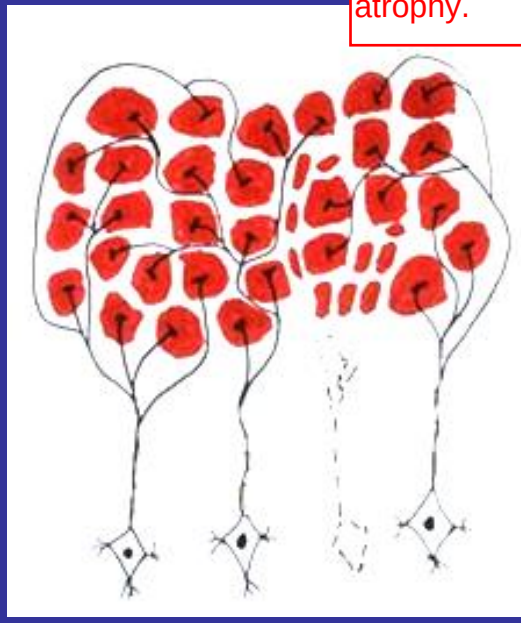
How fiber type grouping occurs in denervating (neurogenic) disorders

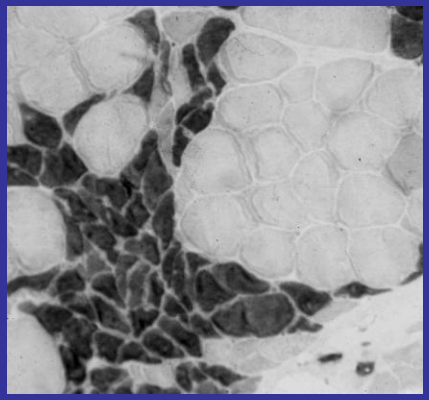
Picture of motor units. Checkerboard pattern which develops during initial development of the muscle





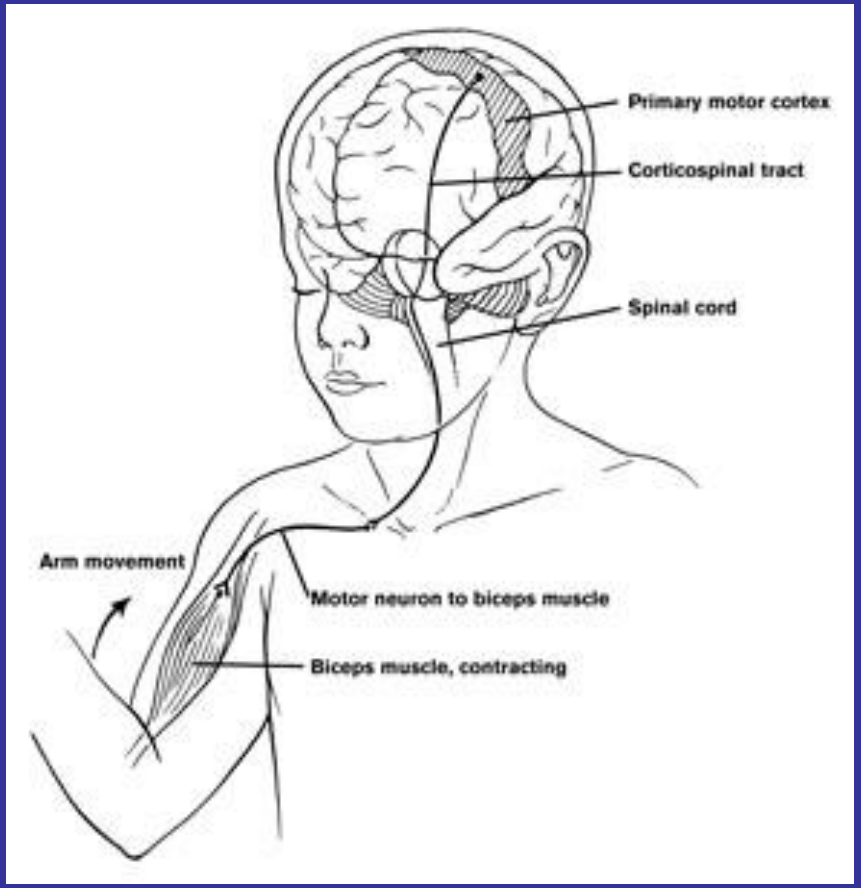
Loss of innervation leads to atrophy. Adjacet reinnervation leads to grouped atrophy.





Read slide.

Causes of neurogenic atrophy



http://brainnmind.com

Peripheral nerve damage

- Diabetes mellitus
- Demyelinating disorders

Motor neuron disorders

- Amyotrophic lateral sclerosis (upper & lower motor neurons)
- Spinal muscular atrophy (lower motor neurons)

Spinal Muscular Atrophy

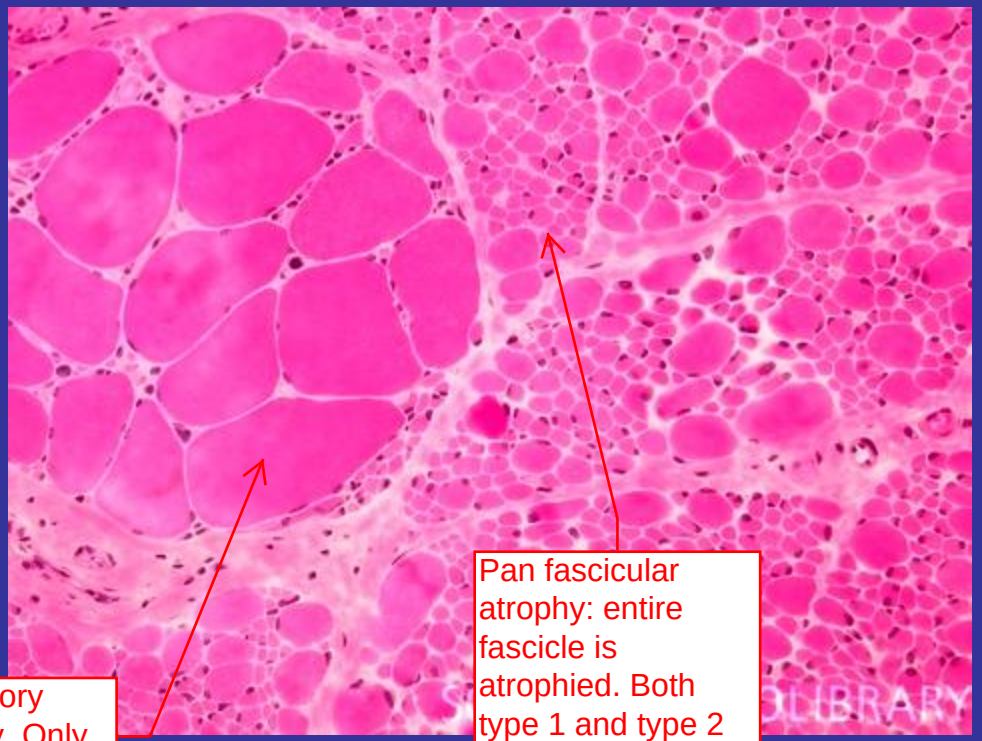
(infantile motor neuron disease: SMN1 mutations)

disease will depend on amount of loss of SMN1 and how much SMN2 is present. SMN2 can compensate for SNM1 loss

the earlier the disease arises, the more severe it is. Children most affected will die of aspiration pneumonia.

Arch Iranian Med (2004) 7: 47

SMA Type 1 (in utero … 3 years)
SMA Type 2 (3 months … 4+ years)
SMA Type 3 (2+ years … adulthood)



Compensatory hypertrophy. Only type 1 fibers.

Pan fascicular atrophy: entire fascicle is atrophied. Both type 1 and type 2 will be atrophied

Chapter 27 R&C

1. Neurogenic atrophy
2. **Muscular dystrophies**
3. “Congenital” myopathies
4. Metabolic myopathies
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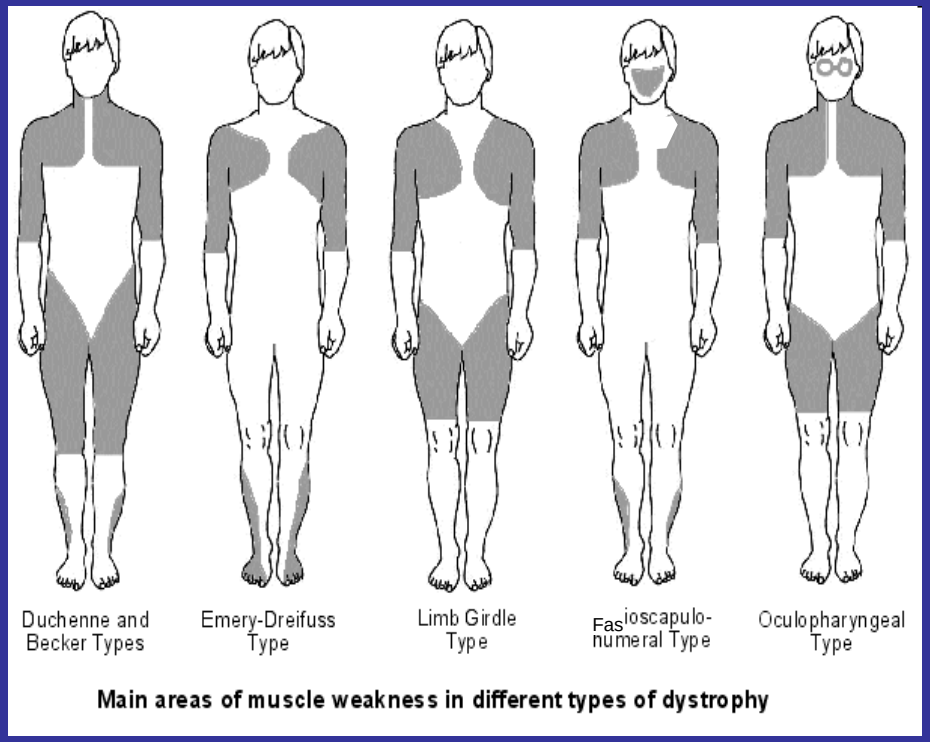
Muscular dystrophies:

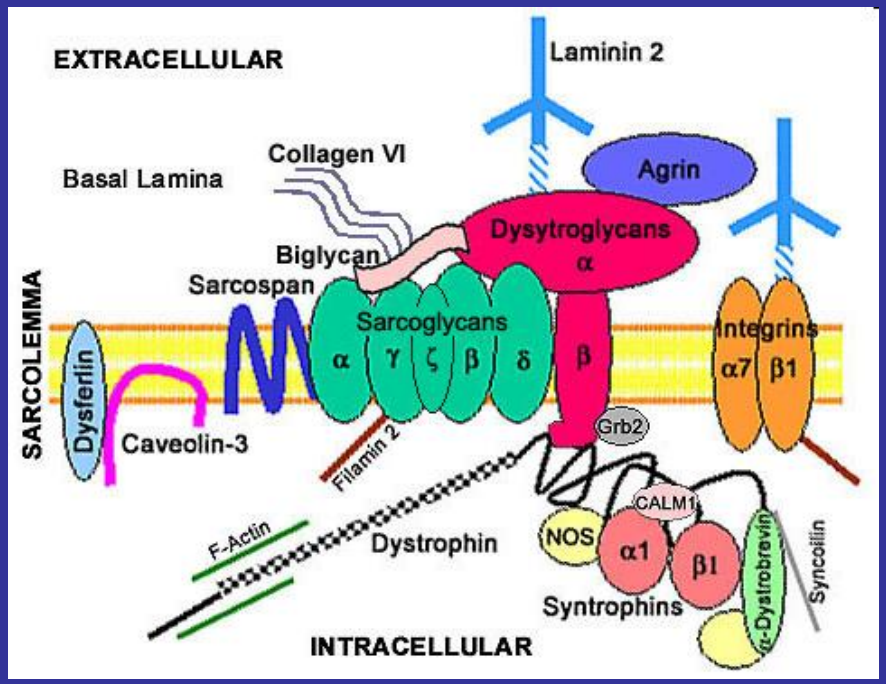
>100 disorders of the sarcolemma

Actually systemic disorders. Cognitive, respiratory, GI, bone, and liver problems. Muscle sypmtoms stick out because having a good grip on cellular stroma is key to muscle function



Main areas of muscle weakness in different types of dystrophy

http://www.indianews365.com

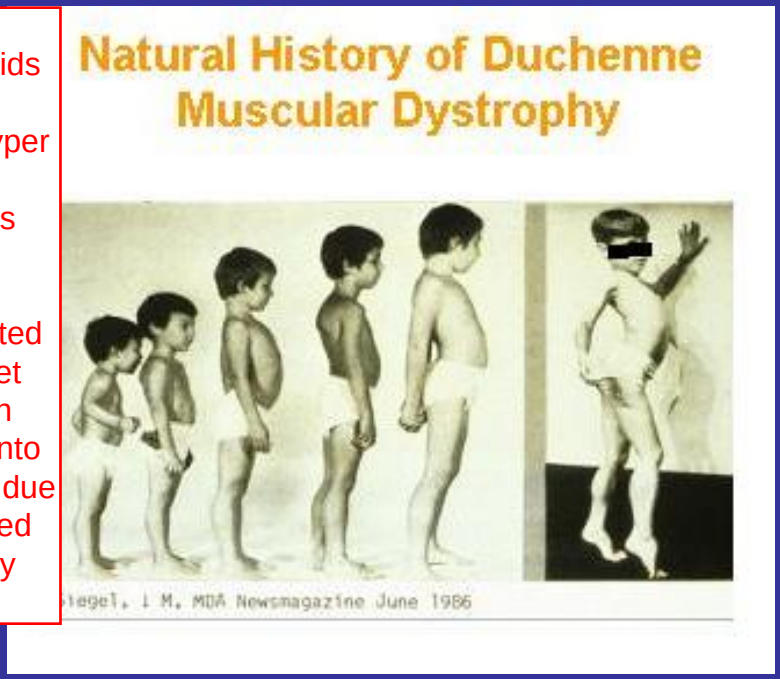


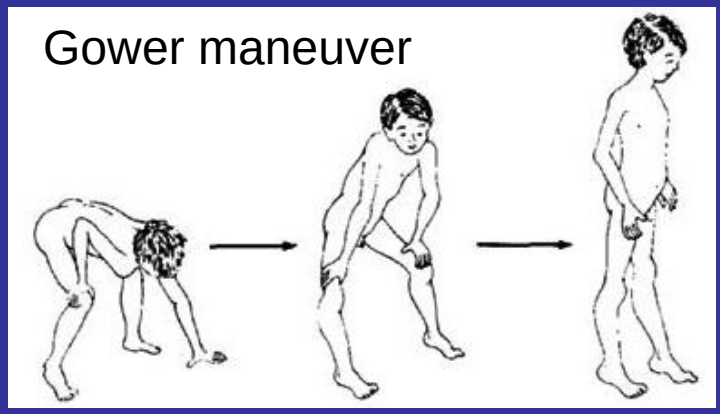
neuromuscular.wustl.edu

A muscular dystrophy: Duchenne

not commom but distinctive.

loss of muscle. kids get calf pseudohyper trophy. Symptoms become more exaggerated as they get older. Can now live into their 20's due to improved respiratory care

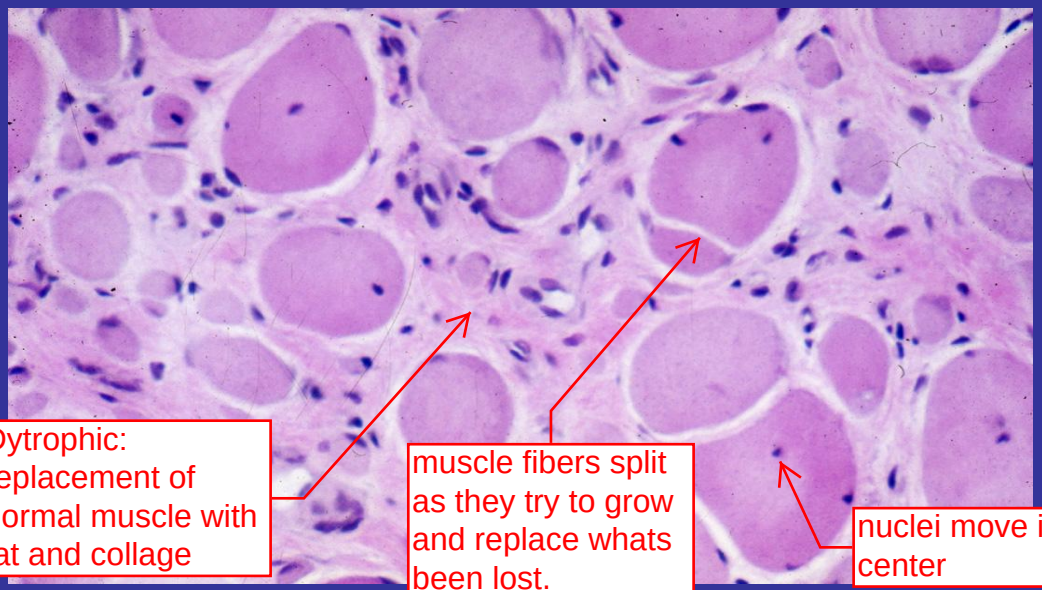




http://picasaweb.google.com

classic symptom

Courtesy Ed Bossen

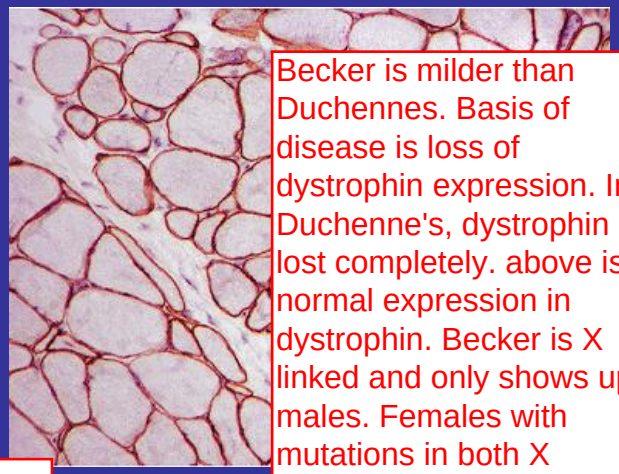


Dytrophic: replacement of normal muscle with fat and collage

muscle fibers split as they try to grow and replace whats been lost.

nuclei move into center

Dystrophin expression



Becker is milder than Duchennes. Basis of disease is loss of dystrophin expression. In Duchenne's, dystrophin is lost completely. above is normal expression in dystrophin. Becker is X linked and only shows up in males. Females with mutations in both X chromosomes will not be born.

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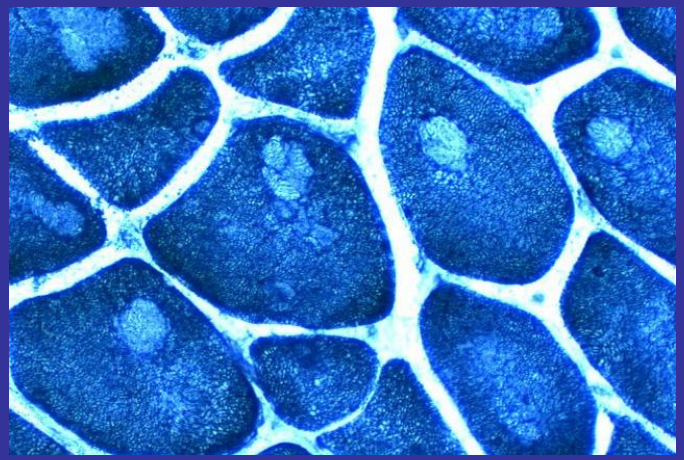
“Congenital” myopathies (floppy babies):

Problem with ryanodine receptor. Clinical symtoms include periodic paralysis.

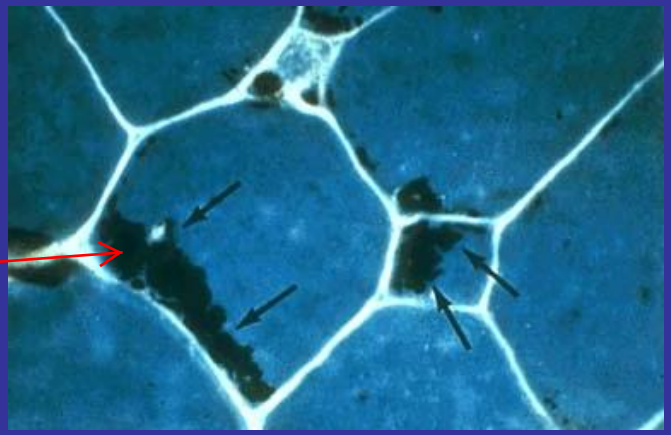
Central core disease (an ion channel myopathy)



http://www.gfmer.ch

Nemaline rod myopathy

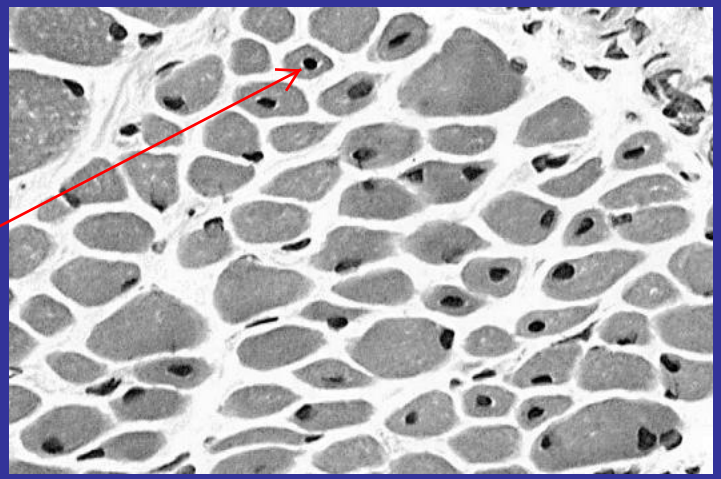
accumulation of proteins



www.pathology.vcu.edu

Centronuclear myopathy

central nucei. generally static disease, but sometimes progressive.



JRare Diseases (2008) 3:26

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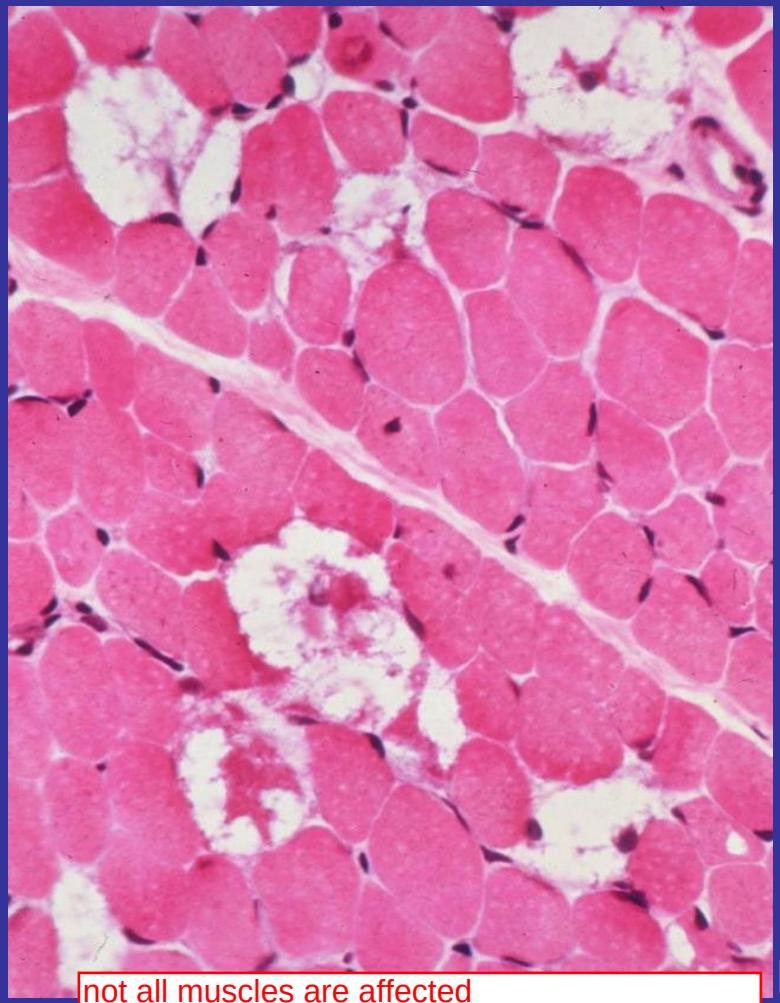
Glycogen storage disease. Most servere form is Pompe's disease which is GSD II

A metabolic myopathy:

McArdle Disease (GSD IV)

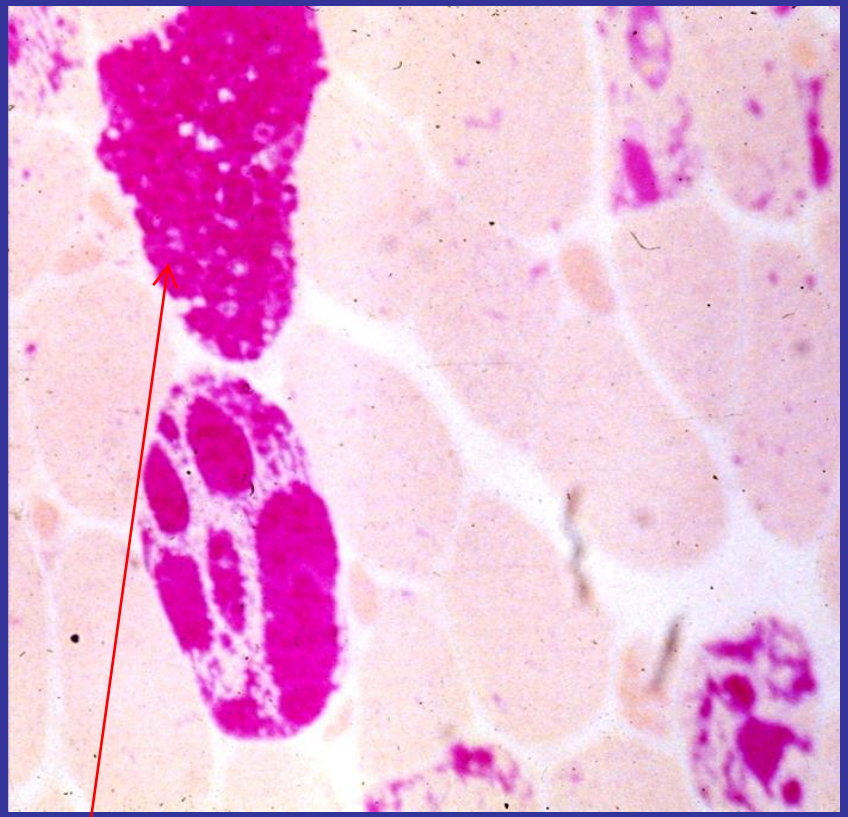
- Myophosphorylase deficiency
- Exertional myalgia, rhabdomyolysis

can cause kidney failure. life threatening



not all muscles are affected

H&E stain



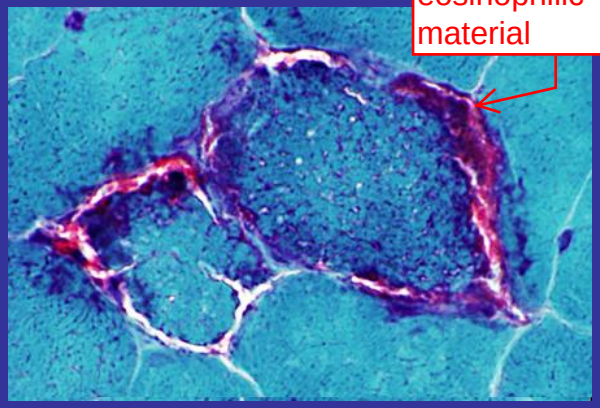
glycogen buildup

PAS stain for glycogen

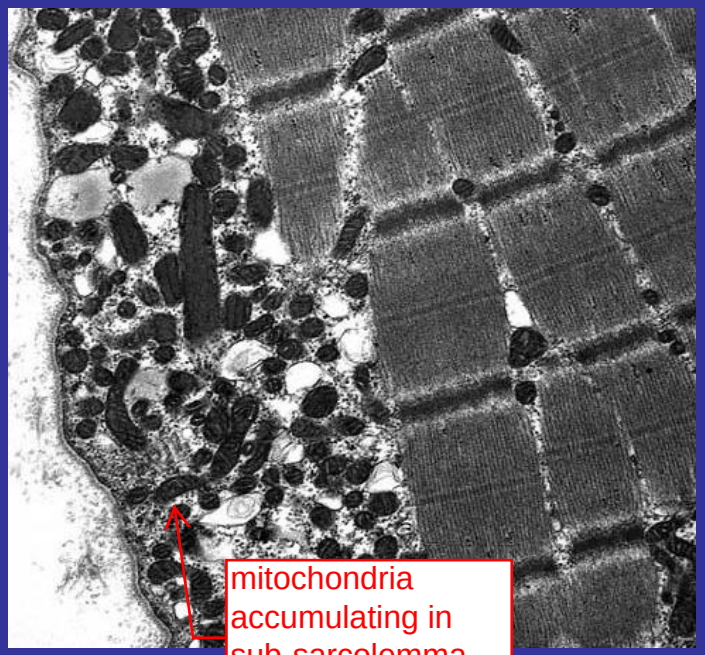
Courtesy Ed Bossen

A metabolic disorder: **Mitochondrial myopathy**

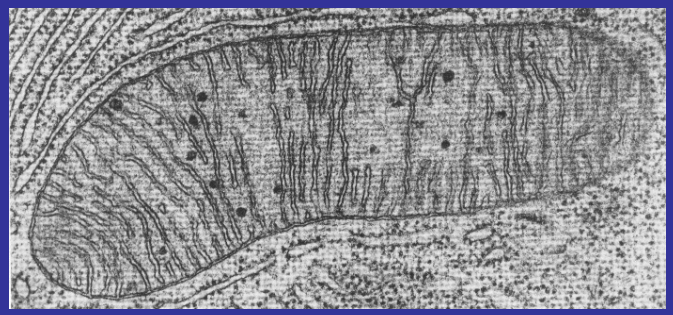
neuromuscular.wustl.edu



“ragged red” fiber

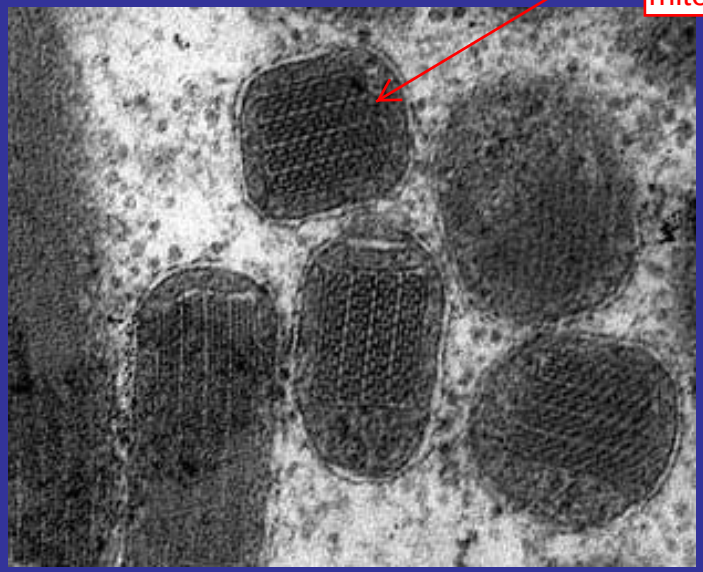


Normal mitochondrian



http://course1.winona.edu

Paracrystalline arrays



sometimes you will have normal looking mitochondria and have disease

www.pathology.vcu.edu

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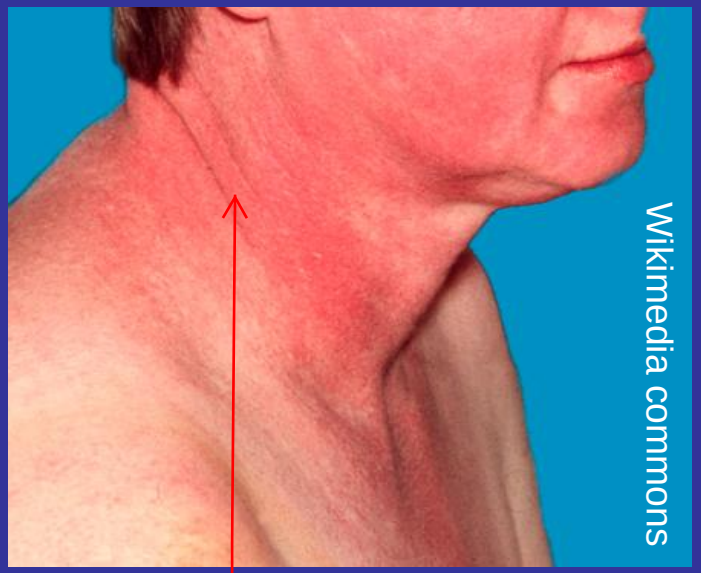
5. **Inflammatory myopathies** more common. often autoimmune
6. Toxic myopathies
7. Diseases of the neuromuscular junction

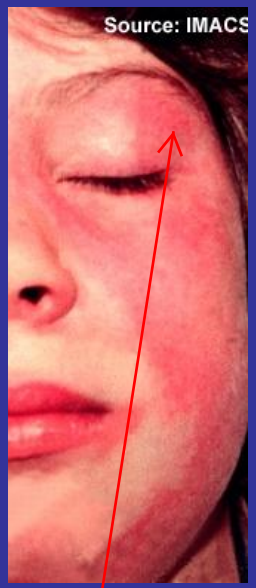
An inflammatory myopathy:

Dermatomyositis

due to antibody mediated attack on blood vessels/capillaries



sun exposed skin more likely to have rash

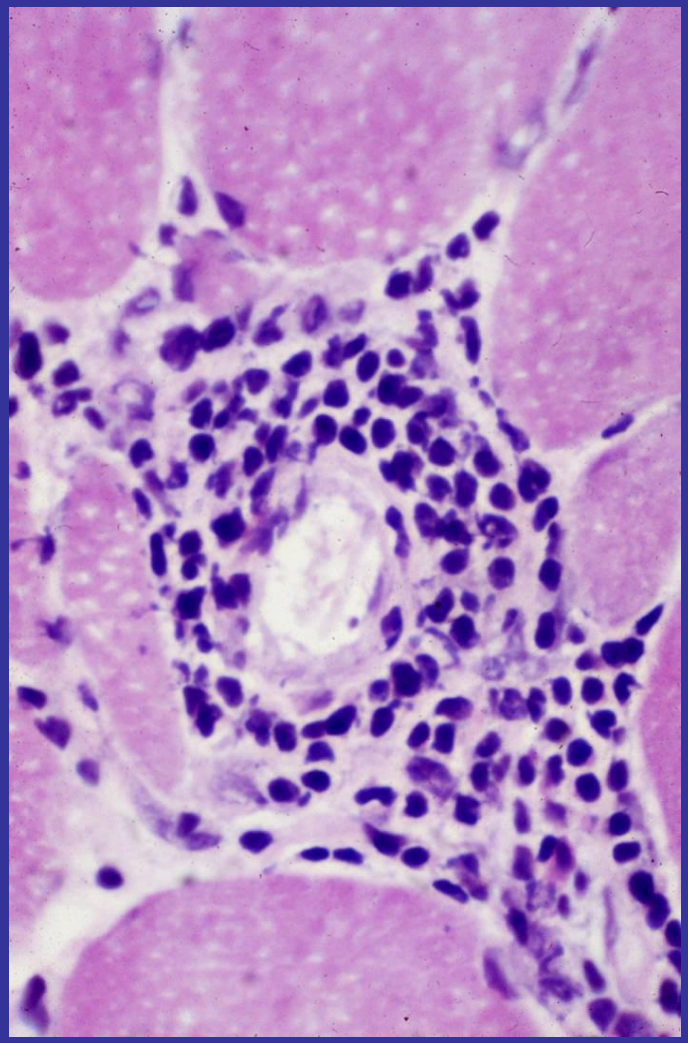


Malar rash

Strongly associated with cancer

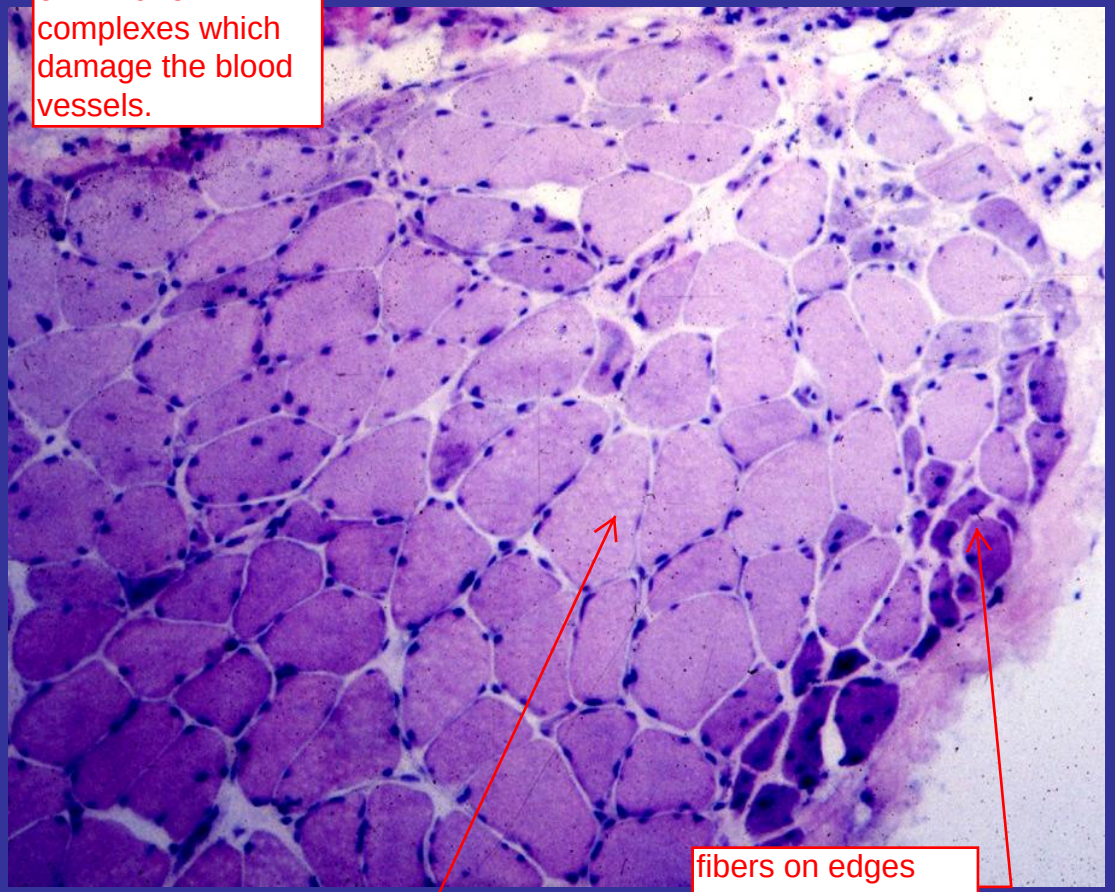
Dermatomyositis

Perivascular inflammation



due to loss of capillaries because of autoantibodies. leads to formation of immune complexes which damage the blood vessels.

Perifascicular atrophy



fibers in the middle stay the same size

fibers on edges shrink

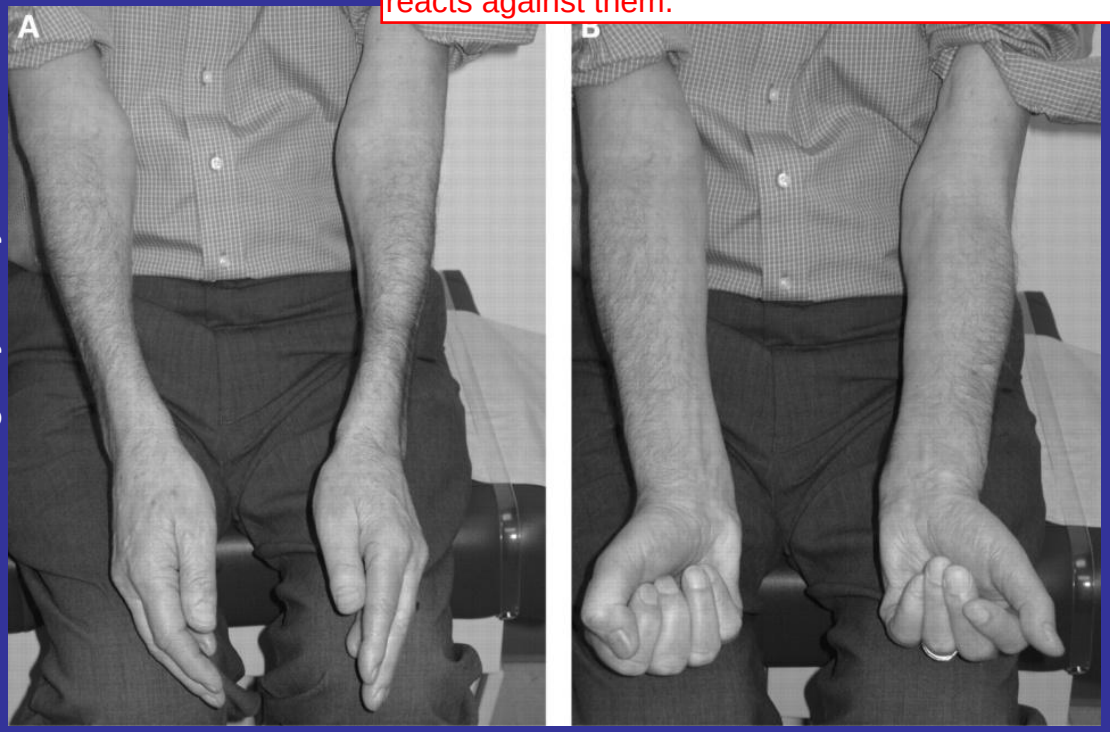
Courtesy Ed Bossen

An inflammatory myopathy:

Inclusion Body Myositis

shows up in patients over 50. Degenerative disease in which there is an accumulation of proteins in muscle over time. Body eventually reacts against them.

J Neurol Neurosurg Psychiatry 2009;80:1186



finger flexor weakness and intrinsic muscle weakness

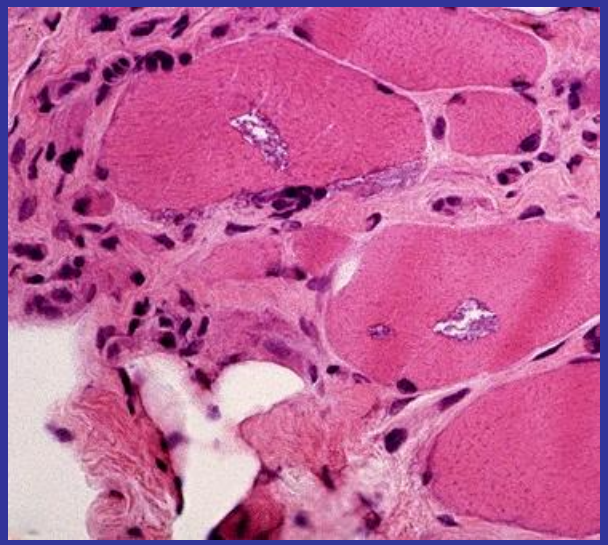
quadricep atrophy and weakness

www.neuropathologyweb.org

Inclusion body myositis

progressive disease. no cure. doesnt respond to steroids.

Rimmed vacuoles



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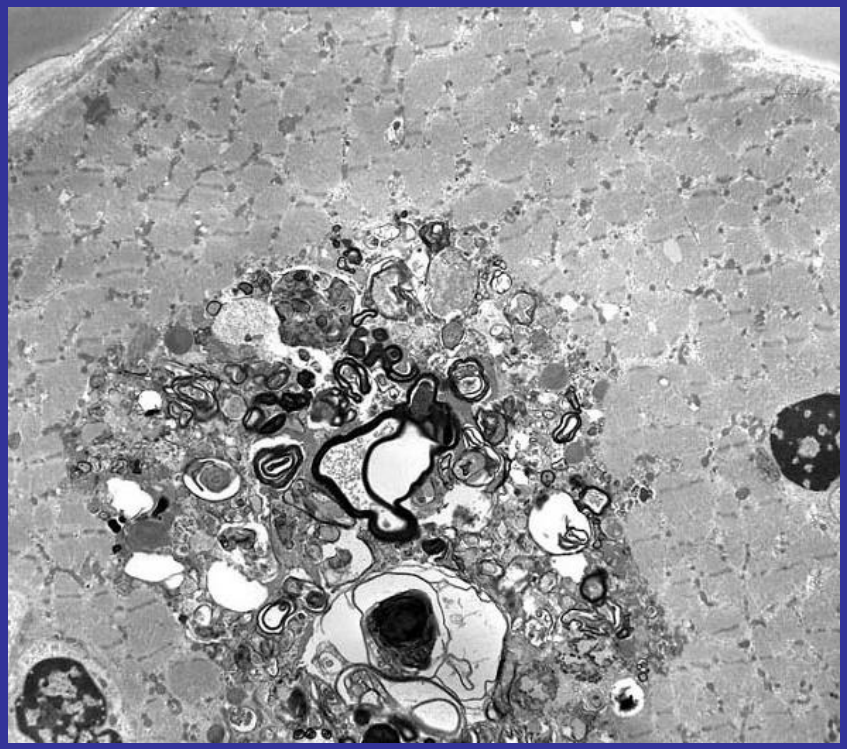
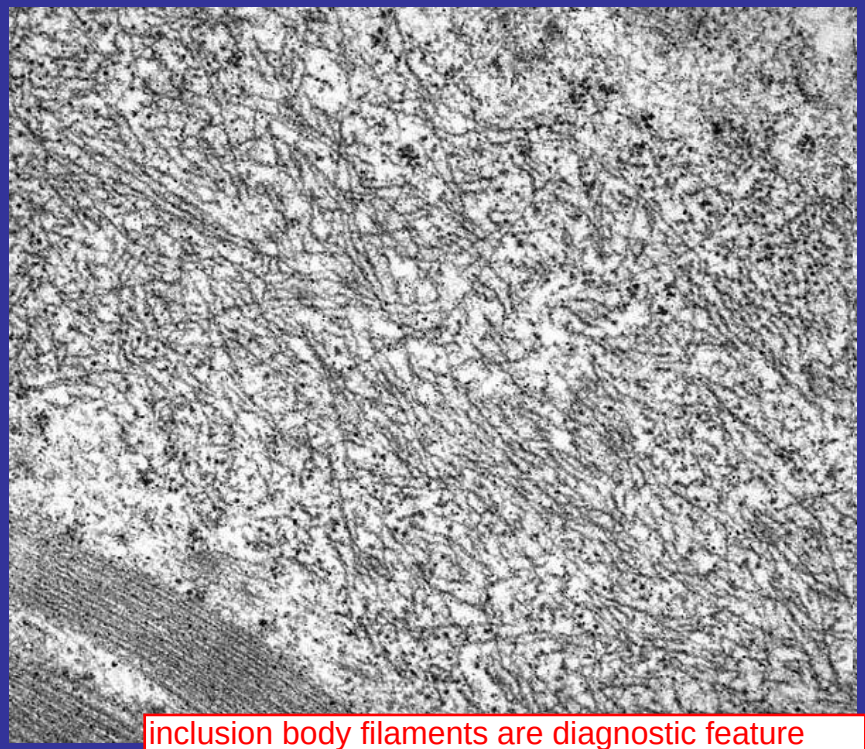
Ultrastructure: filaments in vacuoles





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inclusion body filaments are diagnostic feature

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Toxic myopathies:

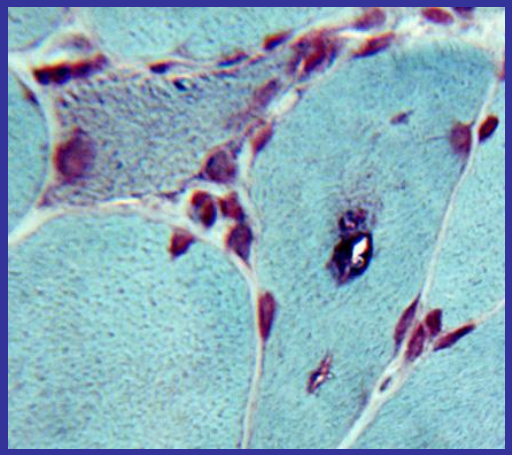
Statin-induced necrotizing myopathy

1-1.5% of people on statins will develop myopathy. statins have deleterious effect on mitochondria. leads to muscle weakness. Can cause rhamdomyolysis. Can be life threatening.

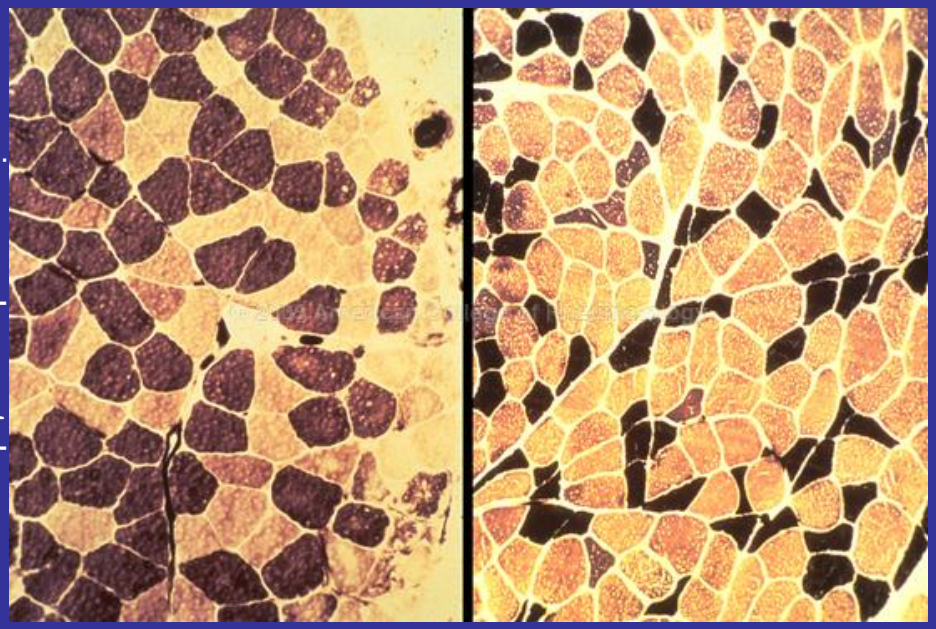
Pract Neurol (2006)6:4

Colchicine-induced vacuolar myopathy

Colchicine is used to treat gout. affects assembly of myofibrils



neuromuscular.wustl.edu



images.rheumatology.org

Steroid myopathy

corticosteroids. type 2 fibers are dark. selective atrophy of type 2 fibers

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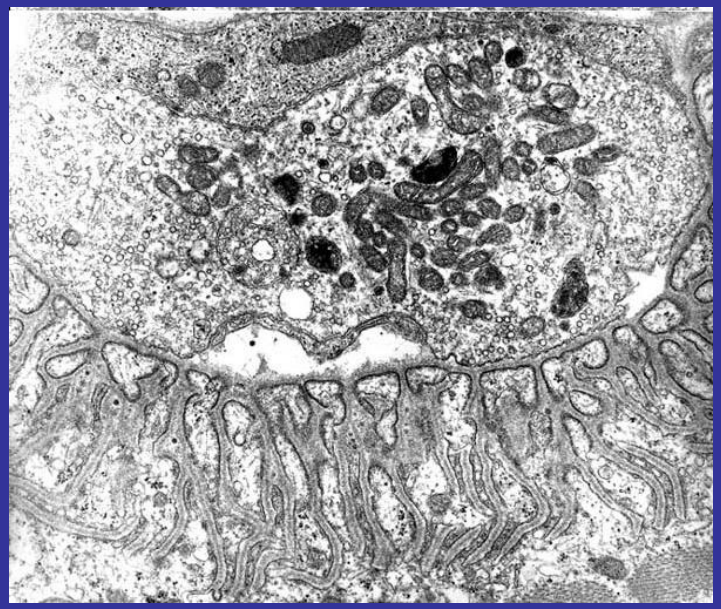
A neuromuscular junction disorder:

Myasthenia gravis



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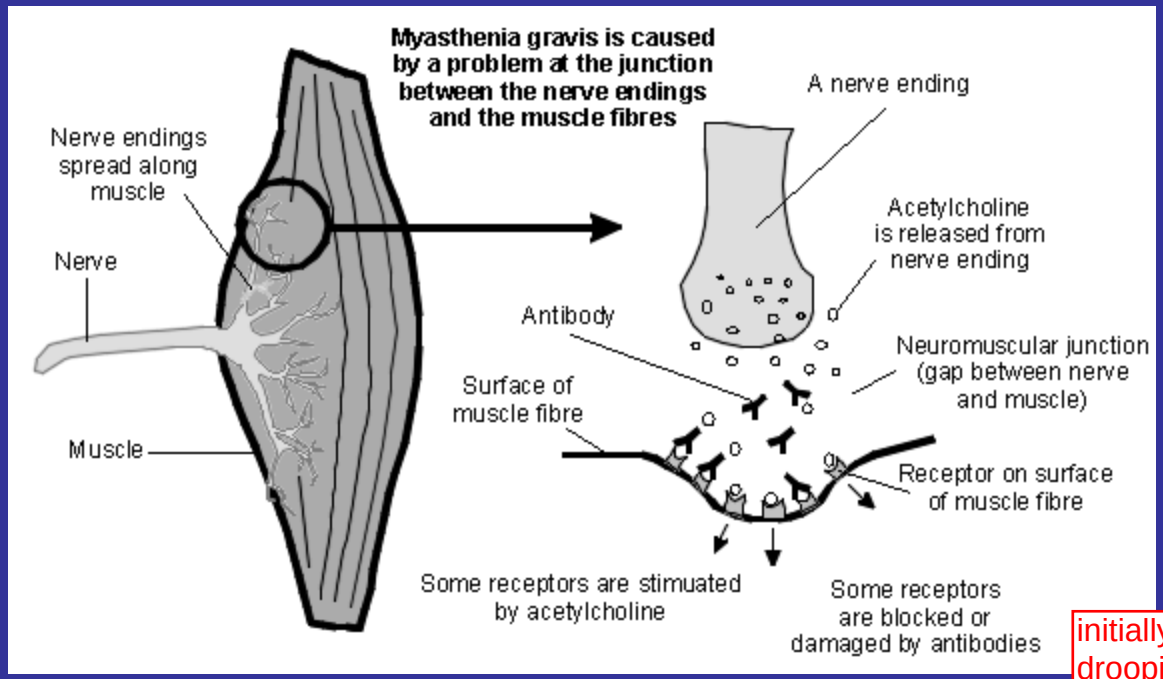
Norma
motor
endpla

autoimmune event which generate antibodies to receptors on postsynaptic membrane. prevents Ach mediated muscle transport. Lambert Eaton Syndrome doesnt respond to AchE inhibitors because it affects presynaptic agents

abnormal motor endplate

Adams and Victor's Neurology



adkpathcourse.blogspot.com

healthmad.com

initially see ptosis, eyelid drooping. effects reversed by AchE inhibitors

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patients with myopathic diseases may be prone to malignant hyperthermia. can be deadly

Malignant Hyperthermia

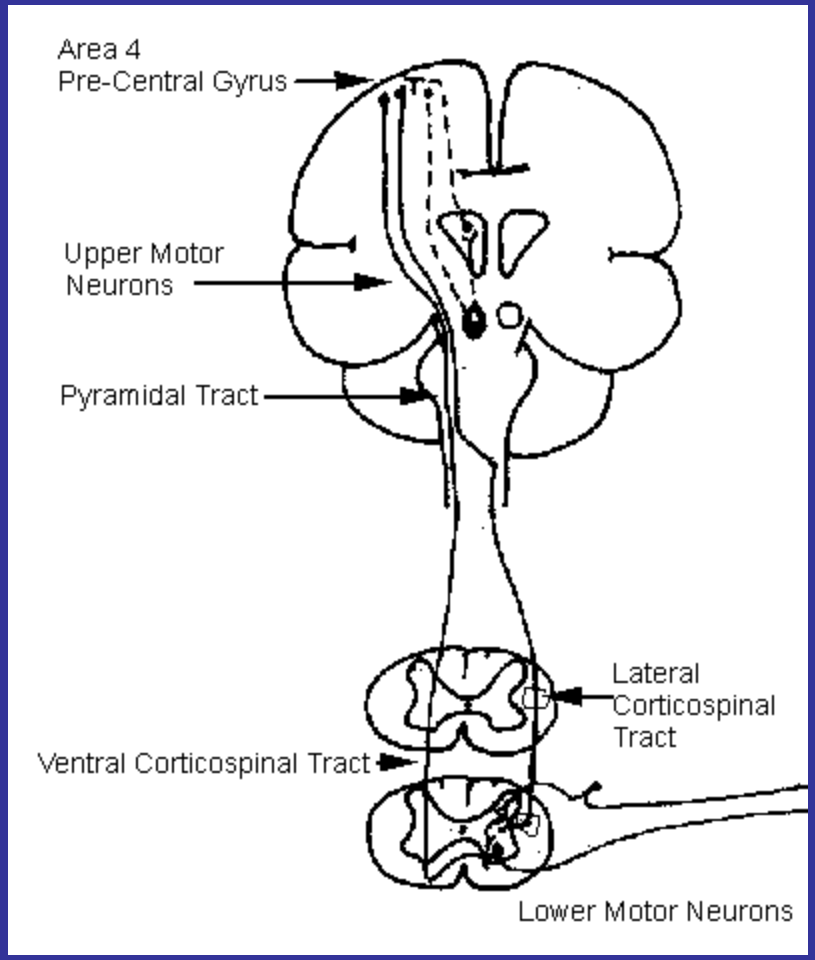
- A hypermetabolic state induced by some general anesthetics

  (tachycardia, tachypnea, muscle spasms, hyperpyrexia)

- Patients with inherited muscle disease are predisposed

  (dystrophinopathies, metabolic, other congenital myopathies)

anne.buckley@duke.edu


Area 4
Pre-Central Gyrus
Upper Motor
Neurons
Pyramidal Tract
Lateral
Corticospinal
Tract
Ventral Corticospinal Tract
Lower Motor Neurons