Chapter 27 R&C

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

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

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
- 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)

Type 1
Aerobic, oxidative
Abundant, large mitochondria
Numerous lipid droplets

Type 2
Anaerobic, glycolytic
Fast twitch

Less mitochondria, and can't see lipid droplets
Chapter 27 R&C

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

Atrophied fibers

Type grouping & grouped atrophy

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

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 it's 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

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
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. Adjacent reinnervation leads to grouped atrophy.
Causes of neurogenic atrophy

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)

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

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

Compensatory hypertrophy. Only type 1 fibers.

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

disease will depend on amount of loss of SMN1 and how much SMN2 is present. SMN2 can compensate for SMN1 loss.
Chapter 27 R&C

1. Neurogenic atrophy
2. Muscular dystrophies
3. “Congenital” myopathies
4. Metabolic myopathies
5. Inflammatory myopathies
6. Toxic myopathies
7. Diseases of the neuromuscular junction
Muscular dystrophies: >100 disorders of the sarcolemma

Main areas of muscle weakness in different types of dystrophy

http://www.indianews365.com

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

http://www.neuromuscular.wustl.edu
A muscular dystrophy: Duchenne

Loss of muscle. Kids get calf pseudohypertrophy. Symptoms become more exaggerated as they get older. Can now live into their 20's due to improved respiratory care.

Natural History of Duchenne Muscular Dystrophy

Gower maneuver

Dystrophin expression

Becker is milder than Duchenne's. 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.
Chapter 27 R&C

1. Neurogenic atrophy
2. Muscular dystrophies
3. “Congenital” myopathies
4. Metabolic myopathies
5. Inflammatory myopathies
6. Toxic myopathies
7. Diseases of the neuromuscular junction
“Congenital” myopathies (floppy babies):

Central core disease (an ion channel myopathy)

Problem with ryanodine receptor. Clinical symptoms include periodic paralysis.

Nemaline rod myopathy

accumulation of proteins

Centronuclear myopathy

central nuclei. Generally static disease, but sometimes progressive.

Sources:
http://www.gfmer.ch
www.pathology.vcu.edu
J Rare Diseases (2008) 3:26
Chapter 27 R&C

1. Neurogenic atrophy
2. Muscular dystrophies
3. “Congenital” myopathies
4. Metabolic myopathies
5. Inflammatory myopathies
6. Toxic myopathies
7. Diseases of the neuromuscular junction
A metabolic myopathy:
**McArdle Disease (GSD IV)**

- Myophosphorylase deficiency
- **Exertional myalgia,** rhabdomyolysis

Glycogen storage disease. Most severe form is Pompe’s disease which is GSD II

Can cause kidney failure. Life threatening

PAS stain for glycogen

Not all muscles are affected

H&E stain

Glycogen buildup
A metabolic disorder: **Mitochondrial myopathy**

- **Normal mitochondrion**
- **“ragged red” fiber**
- **Paracrystalline arrays**
- **Mitochondria accumulating in sub-sarcolemma space**
- **Accumulation of eosinophilic material**

Called "parking lot mitochondria".

Sometimes you will have normal looking mitochondria and have disease.
Chapter 27 R&C

1. Neurogenic atrophy
2. Muscular dystrophies
3. “Congenital” myopathies
4. Metabolic myopathies
5. Inflammatory myopathies
6. Toxic myopathies
7. Diseases of the neuromuscular junction
An inflammatory myopathy:

**Dermatomyositis**

*Strongly associated with cancer*

Due to antibody mediated attack on blood vessels/capillaries

Sun exposed skin more likely to have rash

Malar rash

*Strongly associated with cancer*
Perivascular inflammation

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

Dermatomyositis

Perifascicular atrophy

fibers in the middle stay the same size
fibers on edges shrink
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.

**finger flexor weakness and intrinsic muscle weakness**

**quadriiceps atrophy and weakness**
Inclusion body myositis

progressive disease. no cure. doesn't respond to steroids.

Rimmed vacuoles

Ultrastructure: filaments in vacuoles

inclusion body filaments are diagnostic feature
Chapter 27 R&C

1. Neurogenic atrophy
2. Muscular dystrophies
3. “Congenital” myopathies
4. Metabolic myopathies
5. Inflammatory myopathies
6. Toxic myopathies
7. Diseases of the neuromuscular junction
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 rhabdomyolysis. Can be life threatening.

Colchicine-induced vacuolar myopathy

Colchicine is used to treat gout. Affects assembly of myofibrils.

Steroid myopathy

corticosteroids. Type 2 fibers are dark. Selective atrophy of type 2 fibers.
Chapter 27 R&C

1. Neurogenic atrophy

2. Muscular dystrophies

3. “Congenital” myopathies

4. Metabolic myopathies

5. Inflammatory myopathies

6. Toxic myopathies

7. Diseases of the neuromuscular junction
A neuromuscular junction disorder:

Myasthenia gravis

Myasthenia gravis is caused by a problem at the junction between the nerve endings and the muscle fibres. Acetylcholine is released from the nerve ending and binds to the receptors on the muscle fibre surface.

During normal muscle contraction, acetylcholine is released from the nerve ending, binds to the receptors on the muscle fibre surface, and causes muscle contraction. However, in myasthenia gravis, antibodies are produced which block or damage the receptors on the muscle fibre surface, preventing muscle contraction.

Initially, patients may experience ptosis (drooping of the eyelids) and diplopia (double vision). These symptoms can be reversed by AchE inhibitors, which increase the availability of acetylcholine at the neuromuscular junction.

Adams and Victor’s Neurology

www.pathology.vcu.edu

adkpathcourse.blogspot.com

healthmad.com
Chapter 27 R&C

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