PATHOLOGY TEAM
430

DONE BY:

Abdulaziz Al Hakbani
Abdulrahman Alkadheeb
Abdulrahman Khoja

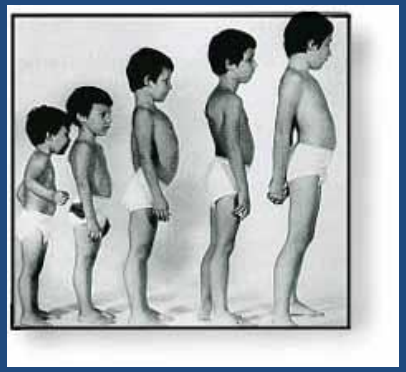
Basil Ahmad Alanazi
Mohammed Bohlega
Mohanned Al Essa

Alanoud AlOmair
Kholoud AlAmari

Jawaher AlFaraydi
Marwah Bafadel

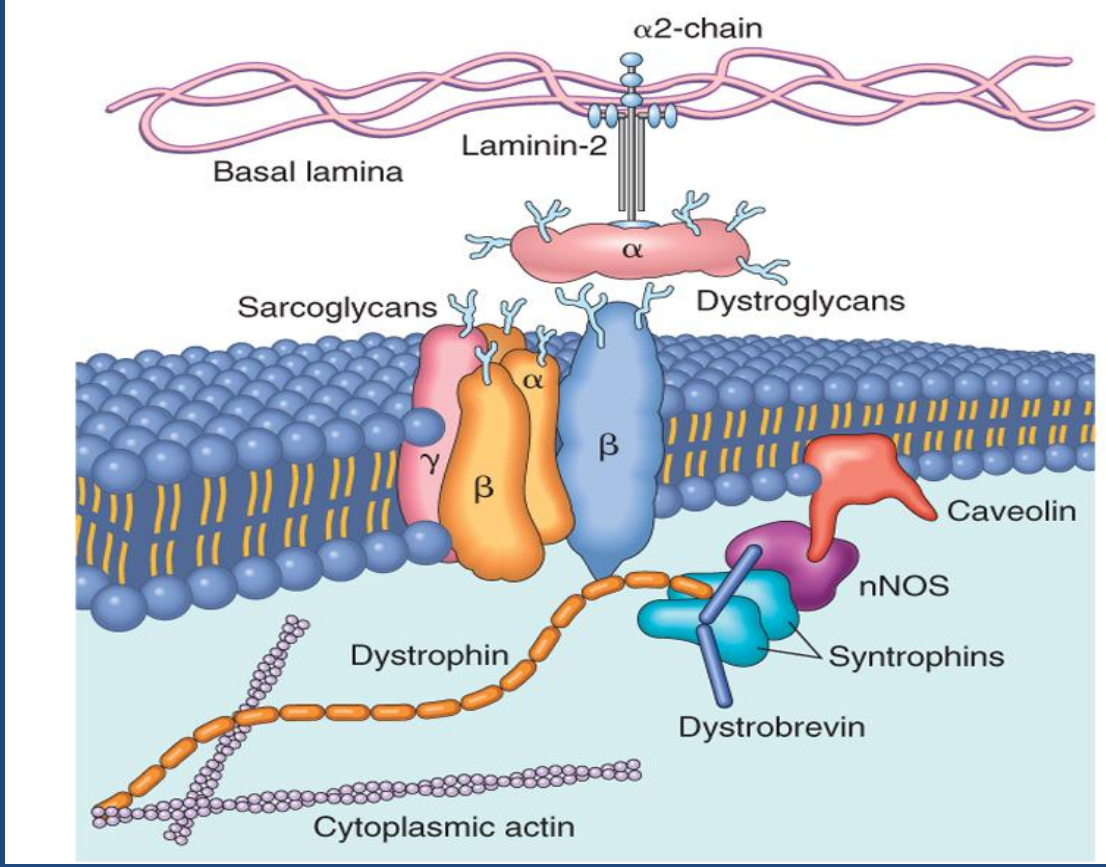
Myopathies
Muscular dystrophy

Pathology



MUSCULAR DYSTROPHY

- A heterogeneous group of inherited disorders
  - Often presenting in childhood
  - Characterized by progressive degeneration of muscle fibers leading to muscle weakness and wasting
  - Histologically, in advanced cases muscle fibers are replaced by fibrofatty tissue
    - *This distinguishes dystrophies from myopathies, which also present with muscle weakness*

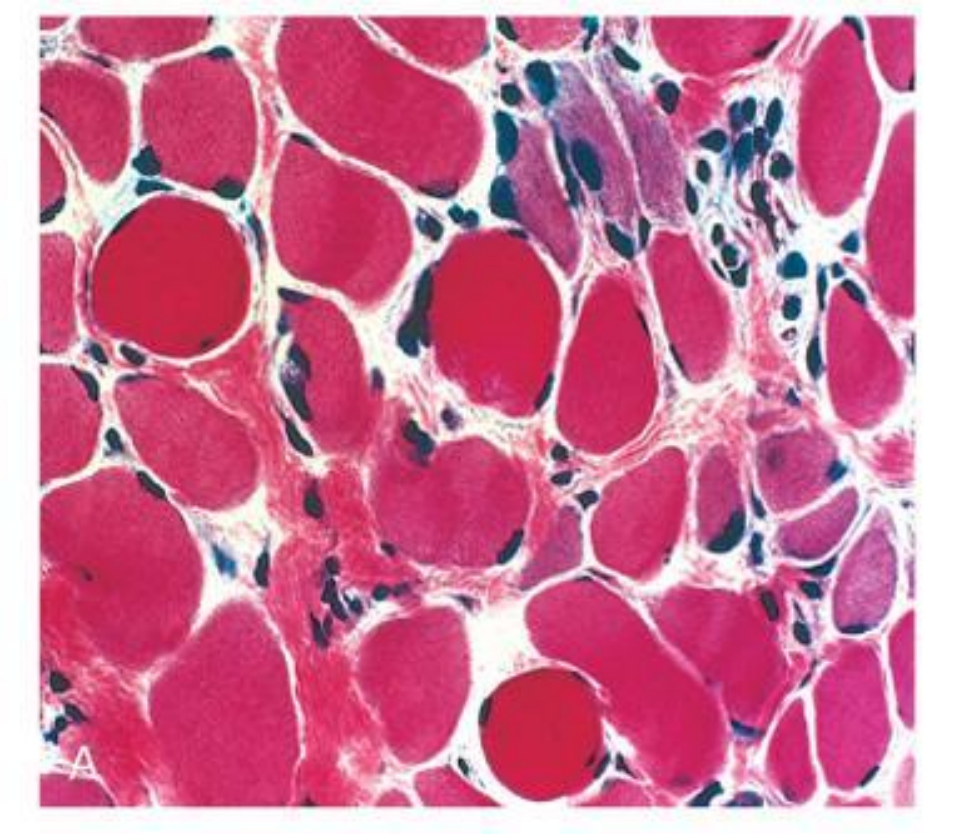


The relationship between the cell membrane (sarcolemma) and the sarcolemmal associated proteins

- Dystrophin forms an interface between the cytoskeletal proteins and a group of transmembrane proteins, the dystroglycans and the sarcoglycans. These transmembrane proteins interact with the extracellualr material, including the laminin proteins.
- mutations in caveolin and the sarcoglycan proteins with the autosomal limb girdle muscular dystrophies

Duchenne and Becker Muscular Dystrophy

- X-Linked Muscular Dystrophy
- The two most common forms of muscular dystrophy
- DMD is the most severe and the most common form of muscular dystrophy, with an incidence of about 1 per 3500 live male births
- DMD becomes clinically evident by age of 5, →progressive weakness leading to wheelchair dependence by age 10 to 12 years →death by the early 20s
- Although the same gene is involved in both BMD and DMD, BMD is less common and much less severe



Note the varied size of muscle fibers and the increased extracellular matrix.

Duchenne and Becker Muscular Dystrophy

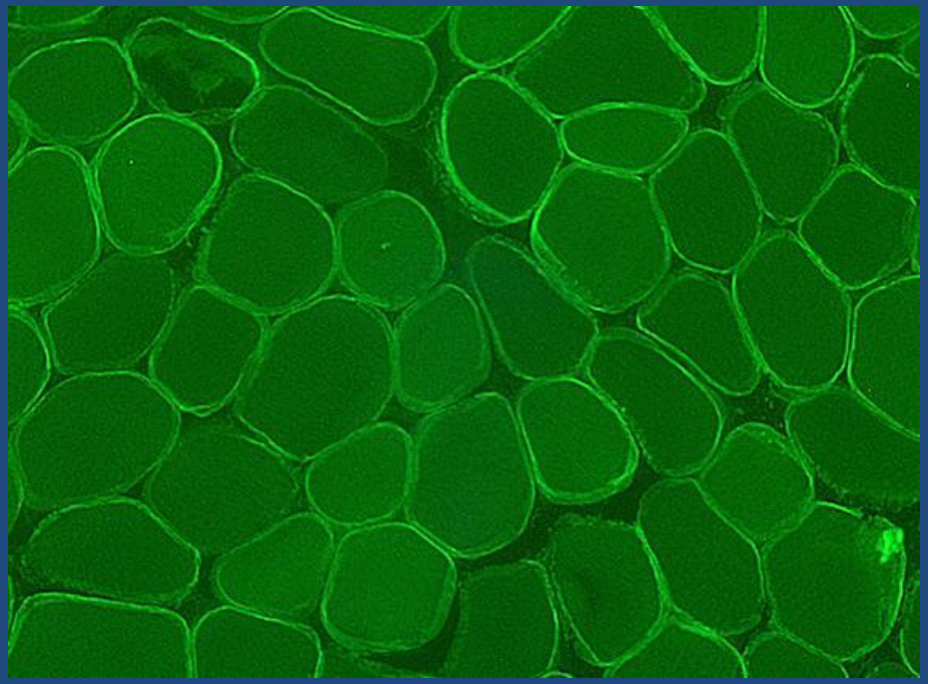
- Morphology:
  - The histologic features of DMD and BMD are similar
  - **Marked variation in muscle fiber size,** caused by concomitant myofiber hypertrophy, which means an increase in cells size without changing their count, and atrophy
  - Many show a range of **degenerative changes,** including fiber splitting and necrosis
  - Other fibers show evidence of **regeneration,** including sarcoplasmic basophilia, nuclear enlargement, and nucleolar prominence (the nucleolus is immediately noticeable)
  - **Connective tissue is increased** throughout the muscle
  - The definitive diagnosis is based on the demonstration of **abnormal staining for dystrophin** in immunohistochemical preparations or by western blot analysis of skeletal muscle
  - In the late stages of the disease, extensive fiber loss and adipose tissue infiltration are present in most muscle groups.

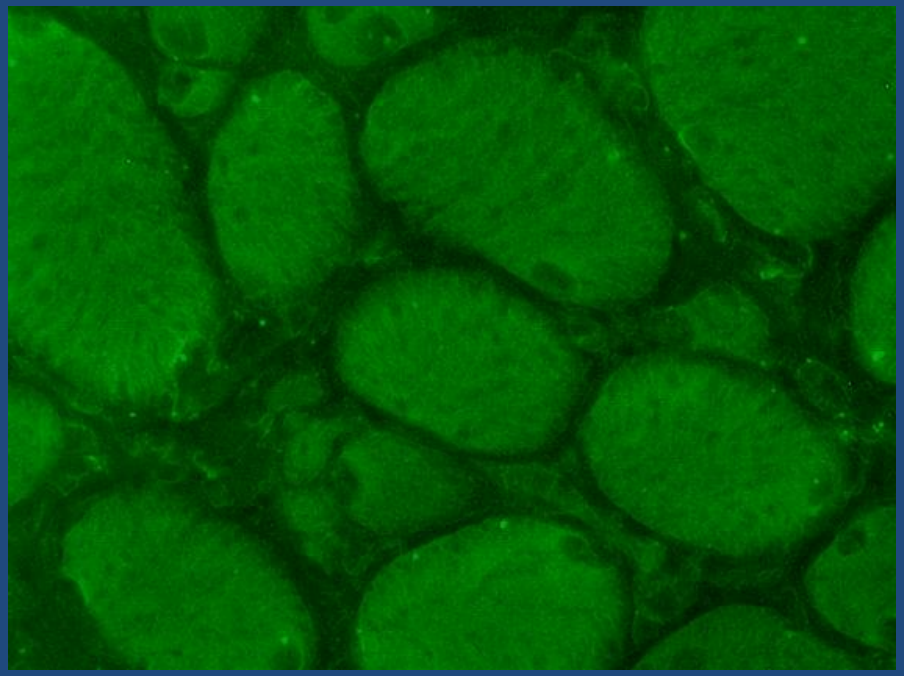
Dystrophin

- Dystrophin is a large protein (427 kD) that is expressed in a wide variety of tissues, including muscles of all types, brain, and peripheral nerves
- Dystrophin attaches portions of the sarcomere to the cell membrane, maintaining the structural and functional integrity of skeletal and cardiac myocytes
- The dystrophin gene (Xp21) spans roughly 2400 kilobases (~1% of the total X chromosome), making it one of the largest in the human genome; its enormous size is a probable explanation for its particular vulnerability to mutation
- Deletions appear to represent a large proportion of the genetic abnormalities, with frameshift and point mutations accounting for the rest
- Approximately two-thirds of the cases are familial, with the remainder representing new mutations
- In affected families, females are carriers; they are clinically asymptomatic but often have elevated serum creatine kinase and can show mild histologic abnormalities on muscle biopsy

Pathogenesis

- DMD and BMD are caused by abnormalities in the dystrophin gene
- The role of dystrophin in transferring the force of contraction to connective tissue has been proposed as the basis for the myocyte degeneration that occurs with dystrophin defects, or with changes in other proteins that interact with dystrophin
- If dystrophin gene got mutated , several abnormal intracellular signaling pathways generate, which leads to necrosis.





Clinical Features

- Boys with DMD:
  - Normal at birth, and early motor milestones are met on time
  - Walking is often delayed
  - Weakness begins in the pelvic girdle muscles and then extends to the shoulder girdle
  - Enlargement of the calf muscles associated with weakness, a phenomenon termed *pseudohypertrophy,* is an important clinical finding
    - The increased muscle bulk is caused initially by an increase in the size of the muscle fibers and then, as the muscle atrophies, by an increase in fat and connective tissue

    That means as the muscle fibers decrease in count and size, the enlargement occurs due to increase in fats not muscle fibers (less muscle fibers, more adipose tissue).
  - Pathologic changes are also found in the heart, and patients may develop heart failure or arrhythmias

Clinical Features

- Cognitive impairment (lack of ability to think, learn and memorize) seems to be a component of the disease and is severe enough in some patients to be considered mental retardation
- Serum creatine kinase is elevated during the first decade of life but returns to normal in the later stages of the disease, as muscle mass decreases
- Death results from respiratory insufficiency, pulmonary infection, and cardiac decompensation (the failure of the heart to provide sufficient circulation to body tissues)

BMD

- Boys with BMD develop symptoms at a later age than those with DMD. The onset occurs in later childhood or in adolescence (the period from puberty to complete maturity), and it is accompanied by a generally slower and more variable rate of progression
- Although cardiac disease is frequently seen in these patients, many have a nearly normal life span

Autosomal Muscular Dystrophies

- Other forms of muscular dystrophy share many features of DMD and BMD but have distinct clinical and pathologic characteristics
- Some of these muscular dystrophies affect specific muscle groups, and the formal diagnosis is based largely on the clinical pattern of muscle weakness
- Several autosomal muscular dystrophies affect the proximal musculature of the trunk and limbs (similar to the X-linked muscular dystrophies), and are termed ***limb girdle muscular dystrophies***
- Limb girdle muscular dystrophies can be inherited either as autosomal dominant or autosomal recessive disorders
- Mutations of the ***sarcoglycan*** *complex of proteins* (transmembrane proteins involved in the protein complex responsible for connecting the muscle fibre cytoskeleton to the extracellular matrix**)** cause four of the recessive forms of these dystrophies, with other forms being associated with **other** cytoskeletal proteins (e.g. actin) or **caveolin** (integral membrane proteins).

Myotonic Dystrophy

- *Myotonia:*
  - A sustained involuntary contraction of a group of muscles; it is the cardinal neuromuscular symptom in myotonic dystrophy
- Patients often complain of "stiffness" joints are not moving easily or freely and have difficulty in releasing their grip, for instance, after a handshake
- The disease often presents in late childhood with gait abnormalities attributable to weakness of foot dorsiflexors; it progresses to weakness of the intrinsic muscles of the hands and wrist extensors; atrophy of facial muscles with ptosis ensues **(**an abnormal low-lying upper eyelid margin with the eye**)**

MEDICAL DISEASES OF THE PERIPHERAL NERVOUS SYSTEM

Causes and types of peripheral neuropathy

- **Nutritional and Metabolic Neuropathies**
  - Examples: Diabetes, alcoholism, renal failure
- **Toxic Neuropathies,** caused by drug abuse and chemical exposure
  - Arsenic, vincristine (a type of chemotherapy)
- **Inflammatory Neuropathies**
  - Examples: Guillain-Barré syndrome, chronic inflammatory demyelinating neuropathy, sarcoidosis
- **Hereditary Neuropathies**
  - Example: Hereditary motor and sensory neuropathies (Charcot-Marie-Tooth disease)
- **Miscellaneous** (ischemia and prolonged exposure to cold temperature)
  - Example: Amyloid neuropathy

Patterns of Nerve Injury

- Two main patterns (based on the target of the insult: either the Schwann cell or the axon):
  - Diseases that affect primarily the Schwann cell lead to a loss of myelin, referred to as ***segmental demyelination***
  - primary involvement of the neuron and its axon leads to **axonal degeneration**

Note that atrophy of myofibers within the motor unit (denervation atrophy) occurs only in axonal degeneration, but not in segmental demylination.

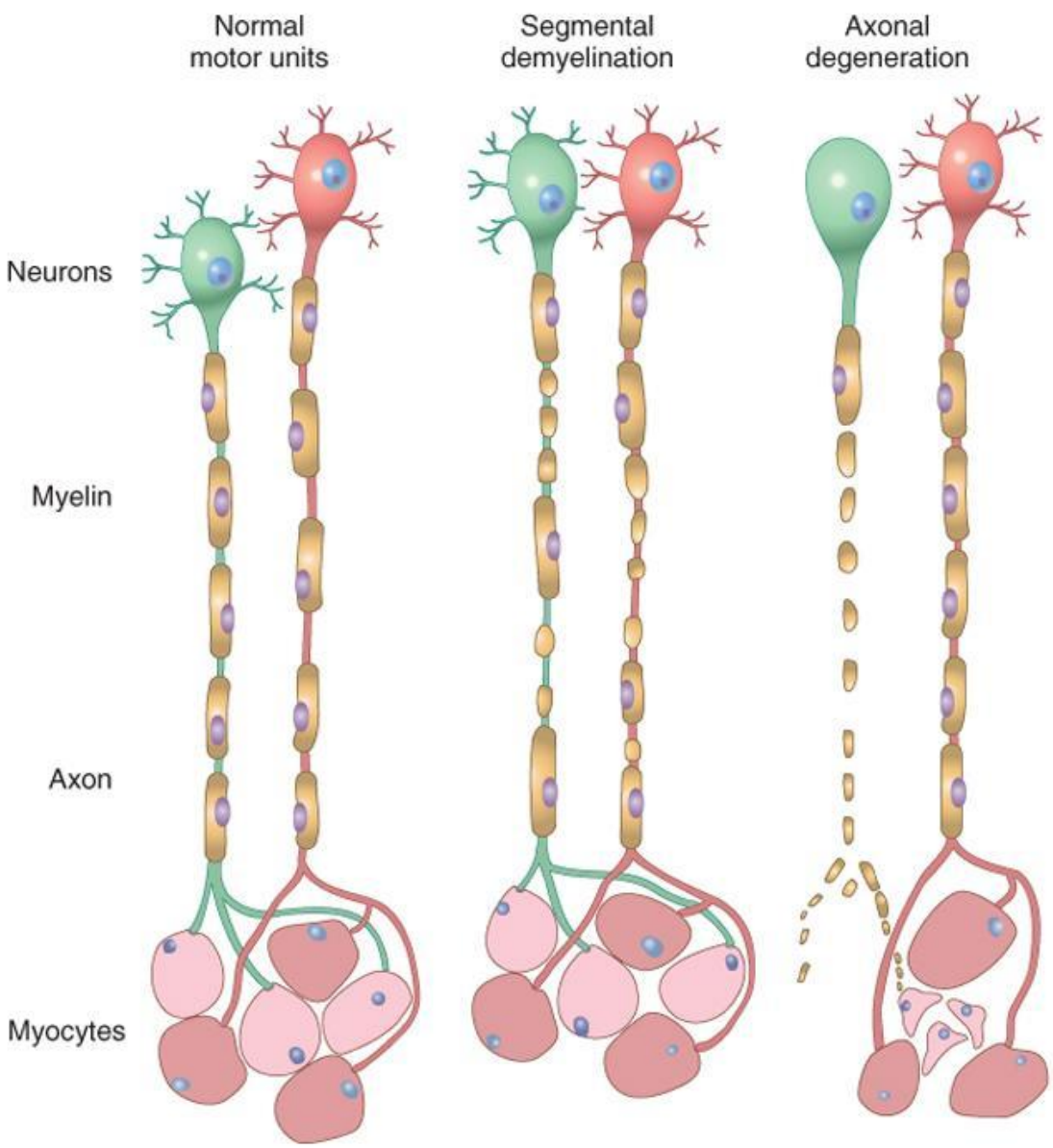
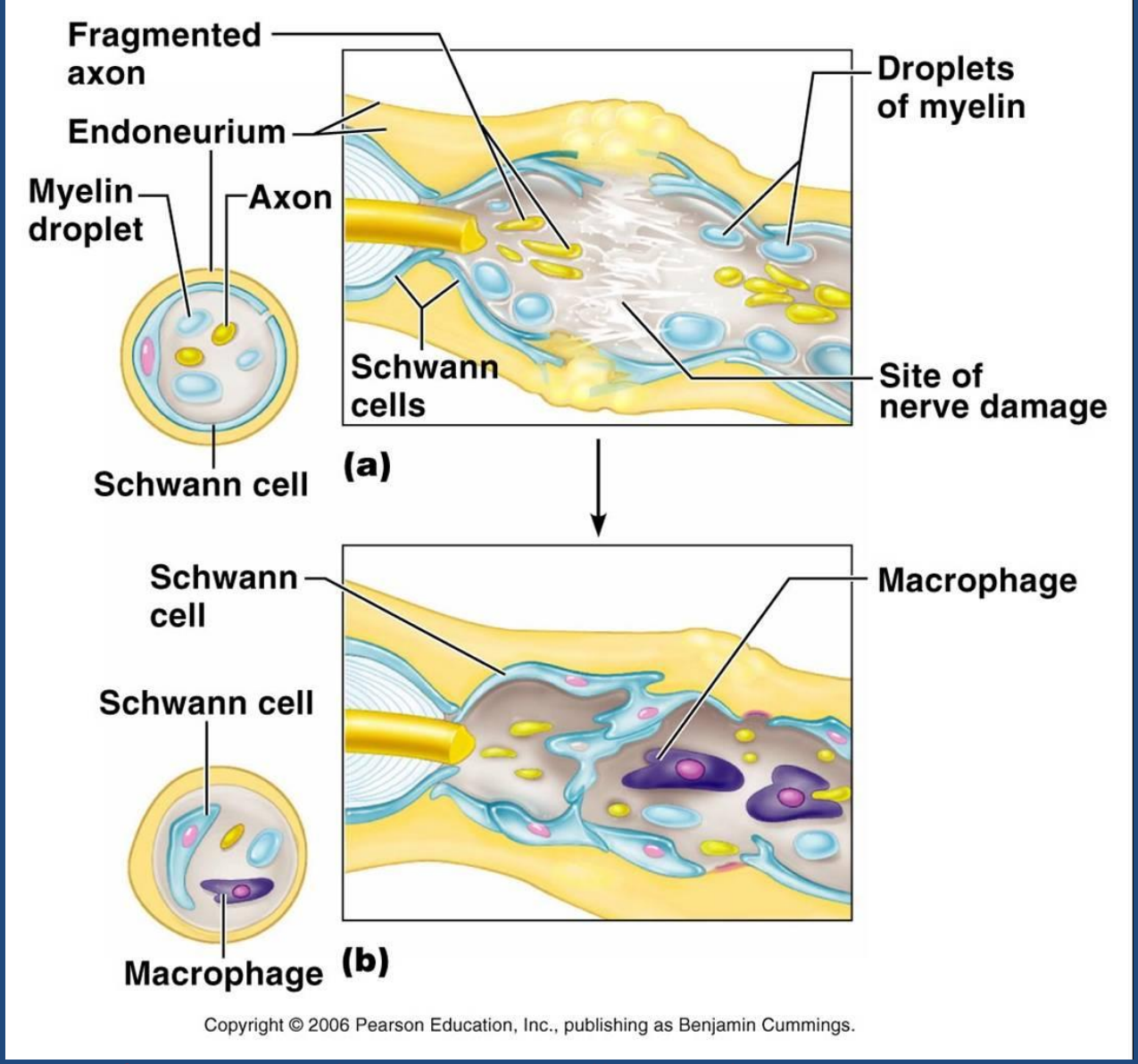
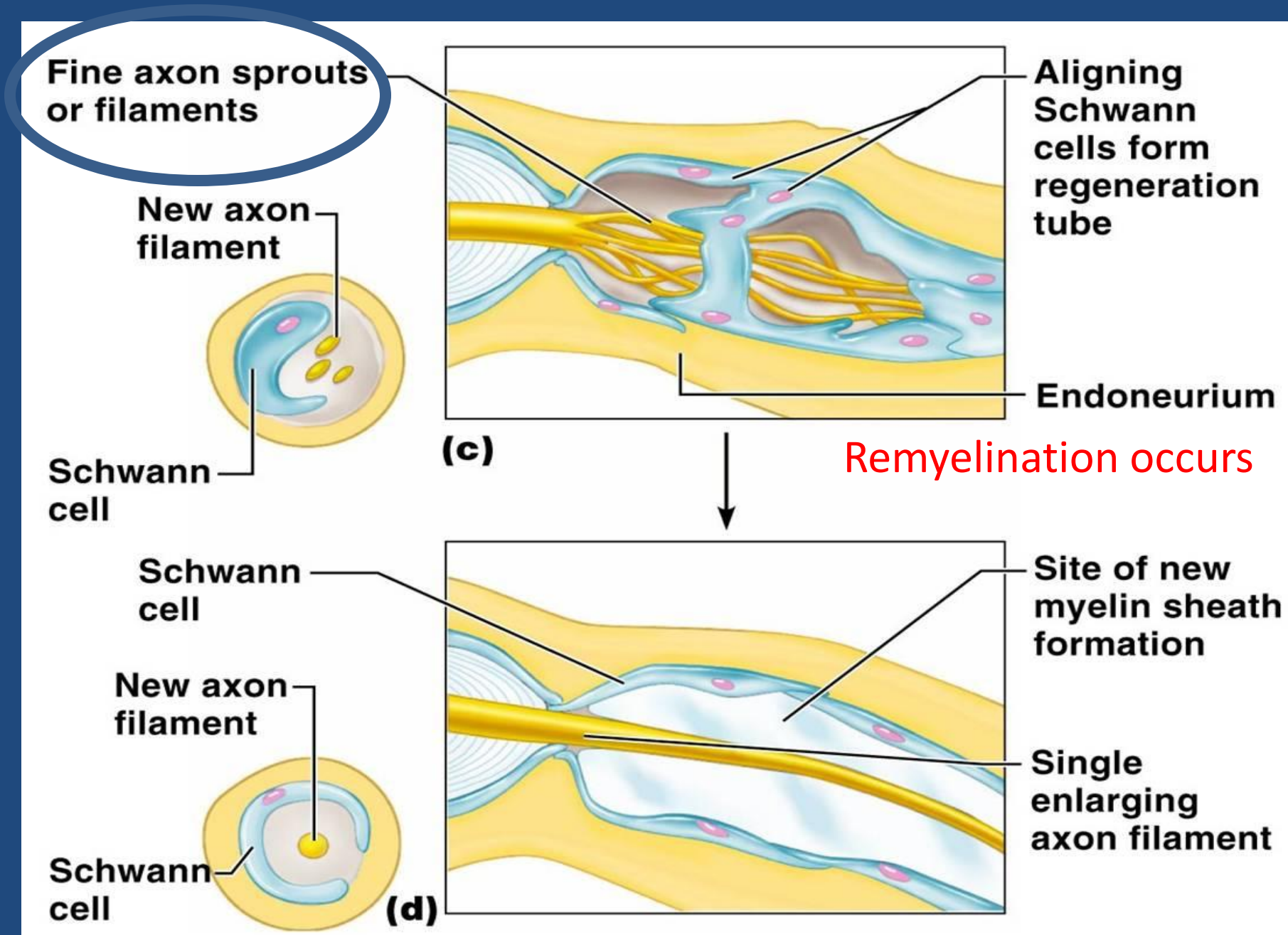


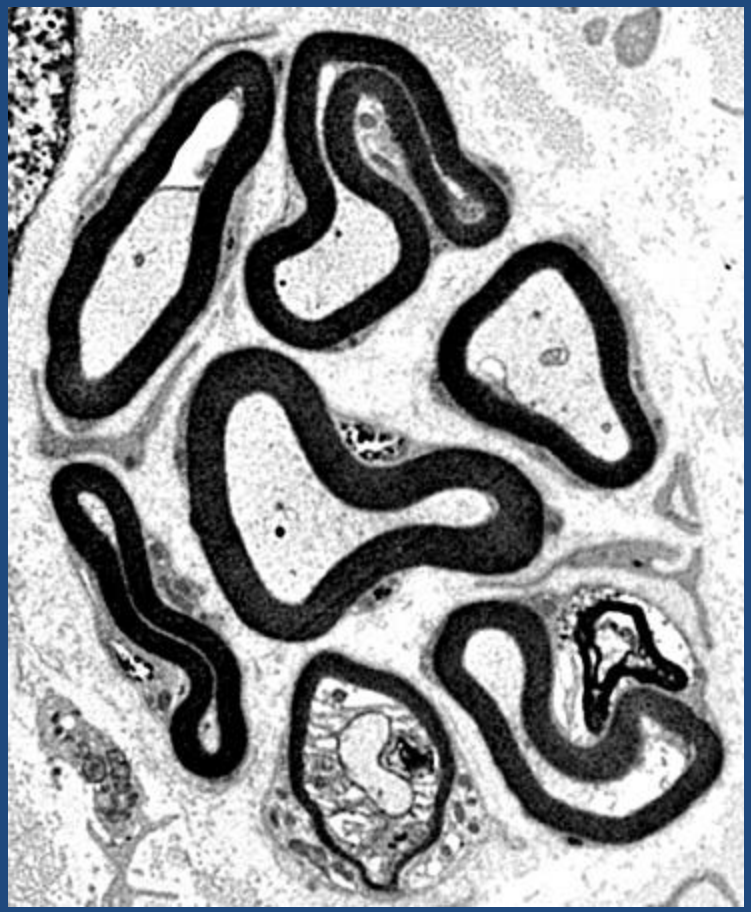
Figure 23-32 Normal and abnormal motor units. *Normal motor units:* Two adjacent motor units are shown. *Segmental demyelination:* Random internodes of myelin are injured and are remyelinated by multiple Schwann cells, while the axon and myocytes remain intact. *Axonal degeneration:* The axon and its myelin sheath undergo anterograde degeneration (shown for the *green* neuron), with resulting denervation atrophy of the myocytes within its motor unit.



- At site of damage, the nerve swallows, the axon and schwan cells are ruptured. Results in accumulation of droplets of myelin sheath which needs macrophages to clean the area. The disintegrating myelin is engulfed initially by schwan cells and later by macrophages. Then the myelin sheath disappears at this site.



Regenerating axon cross section



Segmental Demyelination

- Occurs with:
  - dysfunction or death of the Schwann cell
  - damage to the myelin sheath
- No primary abnormality of the axon
- The process affects some Schwann cells, and their corresponding internodes, while sparing others
- Not all schwan cells are affected, some could avoid destroying.
- Classical example: chronic inflammatory demyelinating neuropathy

Segmental Demyelination

- Onion bulbs:
  - The denuded axon (uncovered by myelin sheath) → a stimulus for remyelination, with a population of cells within the endoneurium differentiating to replace injured Schwann cells →These cells proliferate and encircle the axon →remyelinate the denuded portion
  - In addition to being shortened, remyelinated internodes have thinner myelin in proportion to the diameter of the axon than normal internodes
  - With repetitive cycles of demyelination and remyelination, there is an accumulation of tiers of Schwann cell processes that, on transverse section, appear as concentric layers of Schwann cell cytoplasm and redundant basement membrane that surround a thinly myelinated axon (*onion bulbs*)
  - In time, many chronic demyelinating neuropathies give way to axonal injury

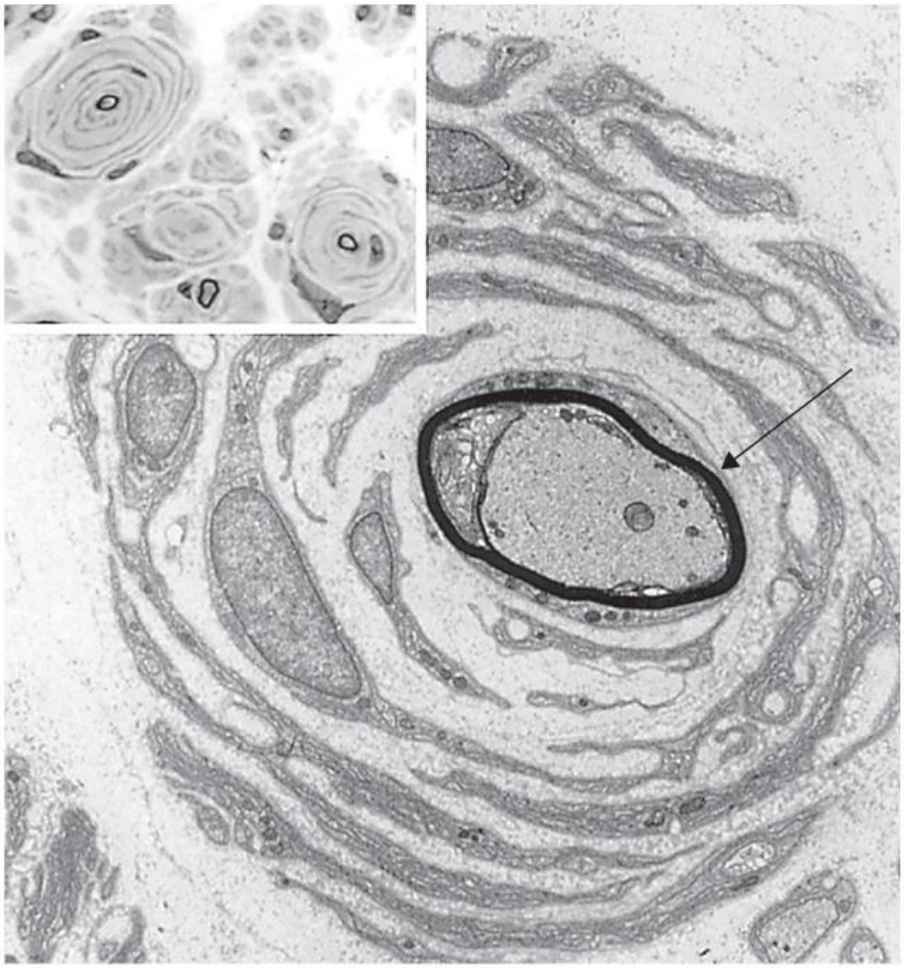


Figure 23-33 Electron micrograph of a single, thinly myelinated axon (*arrow*) surrounded by concentrically arranged Schwann cells, forming an onion bulb. *Inset,* Light microscopic appearance of an onion bulb neuropathy, characterized by "onion bulbs" surrounding axons. (From Dickersin DR: Diagnostic Electron Microscopy: A Text-Atlas. New York, Igaku-Shoin Medical Publishers, 2000, p. 984.)

This collection of overlapping schwan cells encircling the axon called onion bulb, seen when an axon has repeatedly become demyelinated and remyelinated.

Axonal Degeneration

- The result of primary destruction of the axon, with secondary disintegration of its myelin sheath
- Damage to the axon may be due either to a focal event occurring at some point along the length of the nerve (such as trauma or ischemia) or to a more generalized abnormality affecting the neuron cell body (*neuronopathy*) or its axon (*axonopathy*)

- When axonal injury occurs as the result of a **focal lesion**, the distal portion of the fiber undergoes *Wallerian degeneration* (the nerve fiber is cut or crushed, and the distal part separated from its nutritive center (cell body), resulting in atrophy and destruction)
  - Within a day, the axon breaks down, and Schwann cells begin to degrade the myelin and then engulf axon fragments, forming small oval compartments (*myelin ovoids*)
  - Example: traumatic transaction of a nerve

Axonal Degeneration

- In the **slowly** evolving neuronopathies or axonopathies, evidence of myelin breakdown is scant (insufficient) because only a few fibers are degenerating at any given time
  - The stump of the proximal portion of the severed nerve shows degenerative changes involving only the most distal two or three internodes and then undergoes regenerative activity
  - The proximal stumps of degenerated axons can develop new growth cones as the axon regrows
  - These growth cones will use the Schwann cells vacated by the degenerated axons to guide them, if properly aligned with the distal nerve segment.
  - The presence of multiple closely aggregated thinly myelinated small-caliber axons is evidence of regeneration (***regenerating cluster***)
  - Example: adult onset diabetes mellitus
- Regrowth of axons is a slow process, on the order of 1 to 2 mm per day, apparently limited by the rate of the slow component of axonal transport
- Despite its slow pace, axonal regeneration accounts for some of the potential for functional recovery following peripheral axonal injury

- When the axon is cut, it divides into two parts (proximal stump and distal stump) according to the cell body. Because there is no longer a connection between the distal stump and neuronal cell bodies, it is assumed that no neurites (axon) should exist in the distal stump. Thus, it undergoes Wallerian degeneration. Whereas in the proximal stump only the last two or three internodes degenerate, then regeneration occurs.
- Growth cones: actin-supported extension of a developing axon.
- These growth cones use the fragments of the degenerative schwan cells of the distal stump in regeneration.

Guillain-Barré Syndrome

- This is one of the most common life-threatening diseases of the peripheral nervous system
- It may develop spontaneously or after a systemic infection (usually viral) or other stress
- present with rapidly progressive, ascending motor weakness that may lead to death from failure of respiratory muscles
- Sensory involvement is usually much less striking than is motor dysfunction
- The dominant histopathologic findings are **segmental demyelination** along with scant infiltration of peripheral nerves by macrophages and reactive lymphocytes
- The CSF (Cerebrospinal fluid) usually contains increased levels of protein but only a minimal cellular reaction
- Because of those cases with infectious antecedents, an immunologic basis is considered most likely
- Treatments include plasmapheresis (the removal, treatment, and return of (components of) blood plasma from blood circulation) or intravenous immunoglobulin, which can shorten the course of the disease
- With supportive care, most affected individuals recover over time

Homework

- What is the inheritance pattern of myotonic dystrophy?
- Autosomal dominant pattern.
- What is **trinucleotide repeat**? And how does it contribute to the pathogensis of myotonic dystrophy?
- Trinucleotide repeat: an inherited gene undergoes insertion of a triplet of nucleotide that is repeated along the gene.
- Myotonic dystrophy caused by the repetition of CTG and CCTG nucloetides.
- Myotonic dystrophy (as any trinucleotide repeat syndromes) tends to exhibit anticipation. Define “anticipation”.
- is a phenomenon whereby the symptoms of a genetic disorder become apparent at an earlier age as it is passed on to the next generation. In most cases, an increase of severity of symptoms is also noted.

- Check this link:
- http://www.youtube.com/watch?v=6wLnR7GJakY

Source: Robbins basic pathology, 8th edition

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