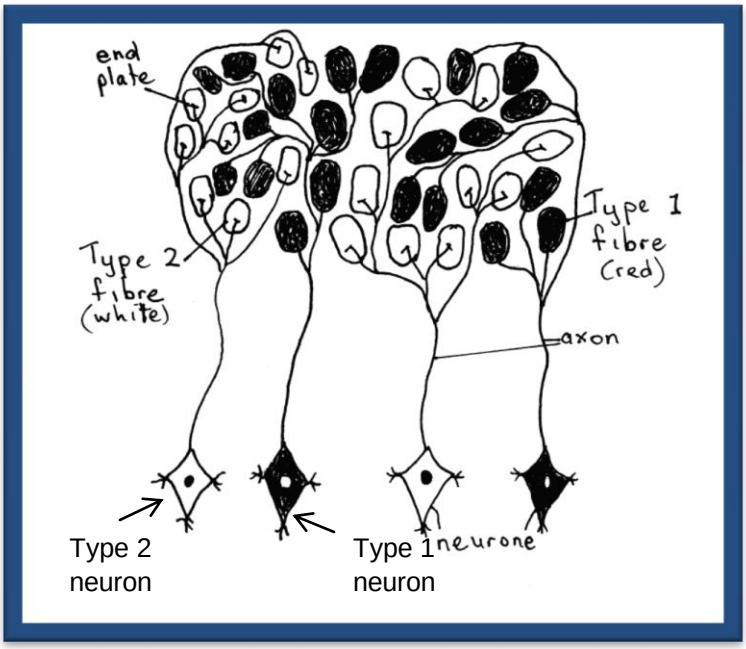
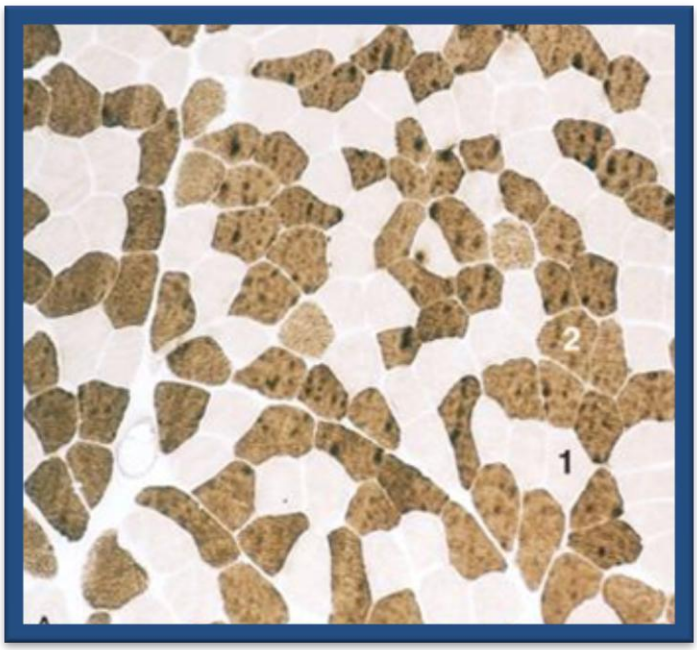
Myopathies

Myo = Muscle

Pathy = Disease





A single "type I" or "type II" neuron will innervate multiple muscle fibers and these fibers are usually randomly scattered in a *"check board pattern"* within a circumscribed area within the larger muscle.

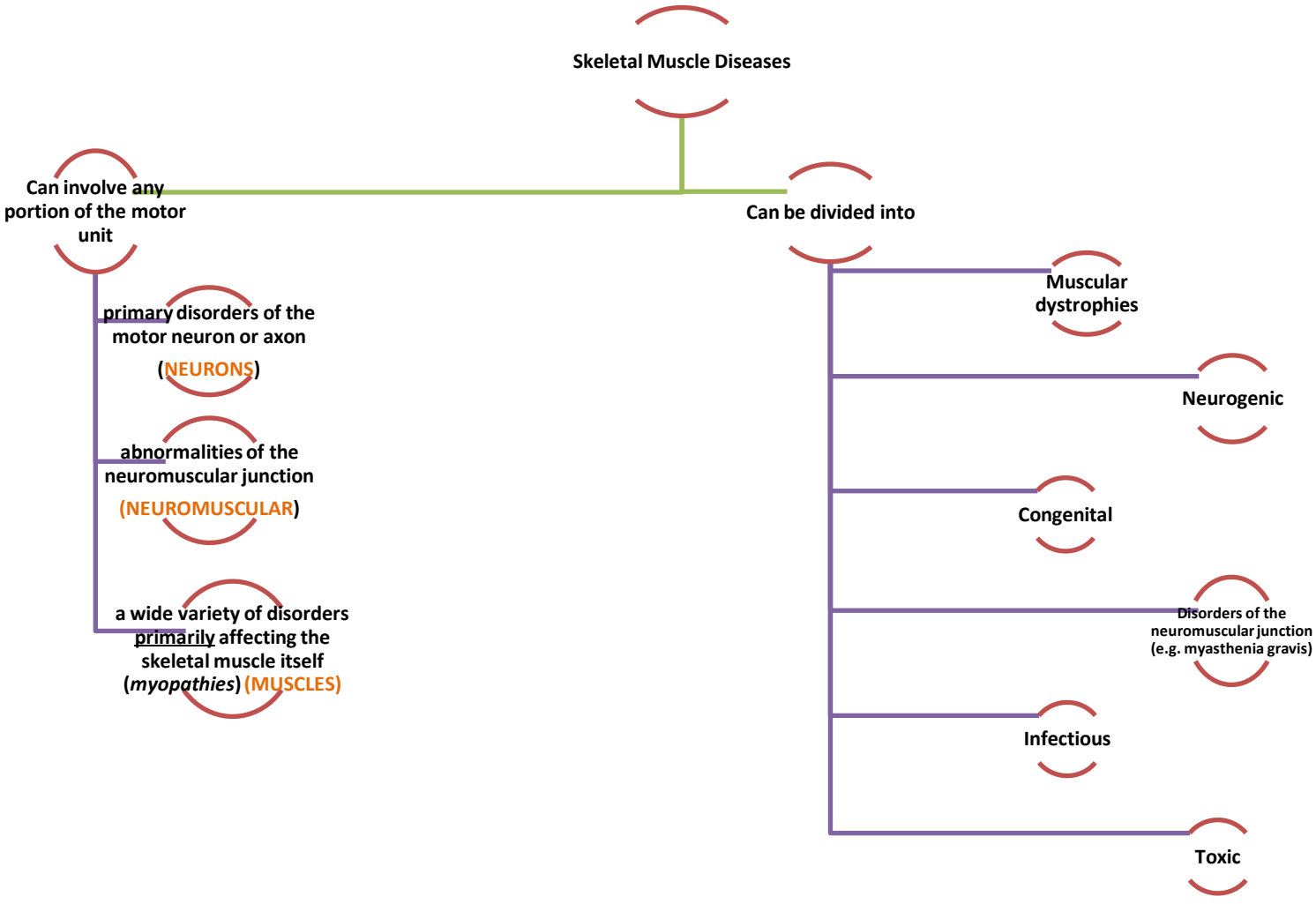
Depending on the nature of the **nerve fiber (axon)** doing the innervation, the associated skeletal muscle develops into one of two major subpopulations (Red and White)

The different fibers can be identified using specific staining techniques into type 1 and type 2 muscle fibers (Red and white muscle fibers respectively)

	Type 1	Type 2
Contraction (Twitch)	Slow	Fast
Color	Red	White
Catabolism depends on	Fat	Glycogen
Oxidative phosphorylation (In Mitochondria)	High	Low
Glycolysis	Low	High
Mitochondria	Abundant	Sparse
Glycogen	Scant	Abundant

- ***Myopathy*** as a term may encompasses a heterogeneous group of disorders, both morphologically and clinically

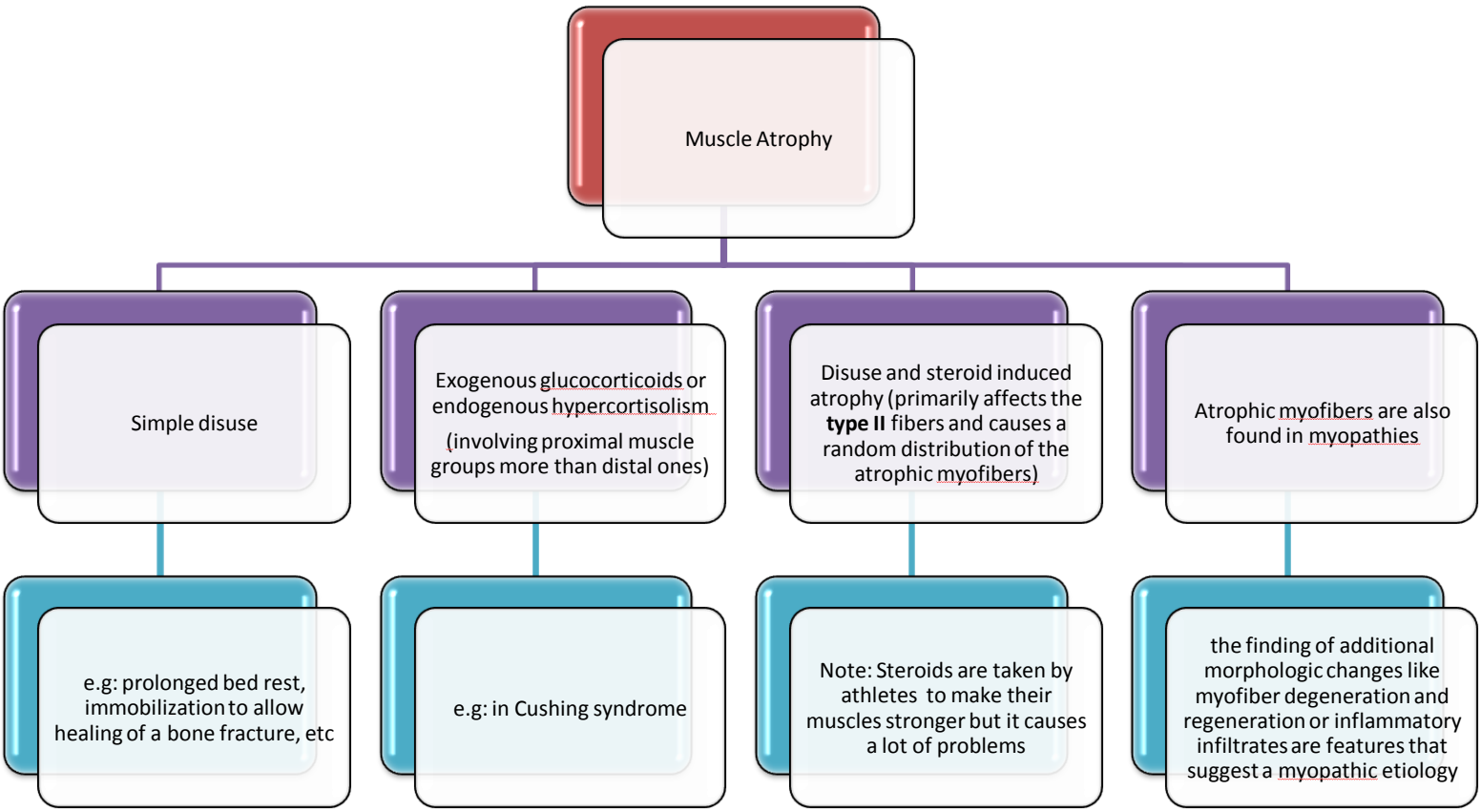
Recognition of these disorders is important for genetic counseling or appropriate treatment of acquired disease



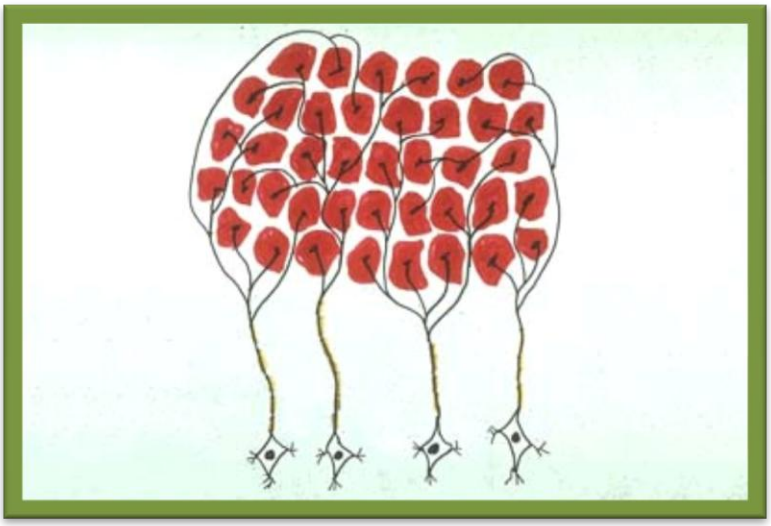
Muscle atrophy: (Happens mostly in type 2)

- A non-specific response
- Characterized by abnormally small myofibers

The type of fibers affected by the atrophy, their distribution in the muscle, and their specific morphology help identify the etiology of the atrophic changes

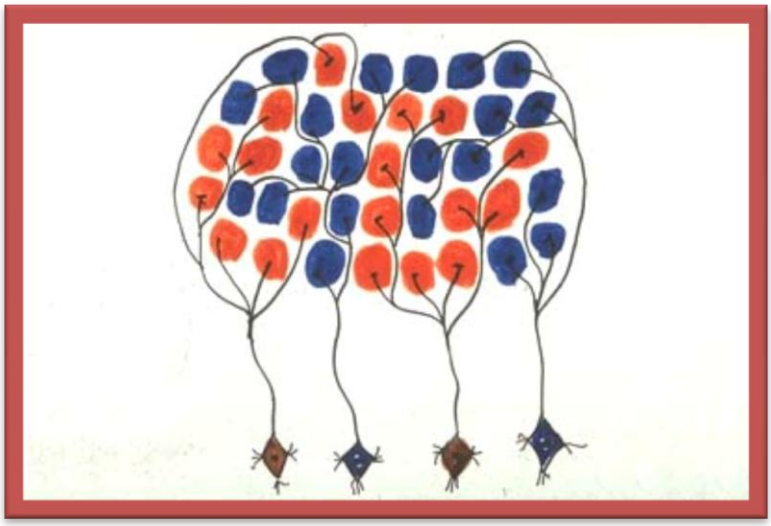


Neurogenic Atrophy (Happens in type 1 and 2)



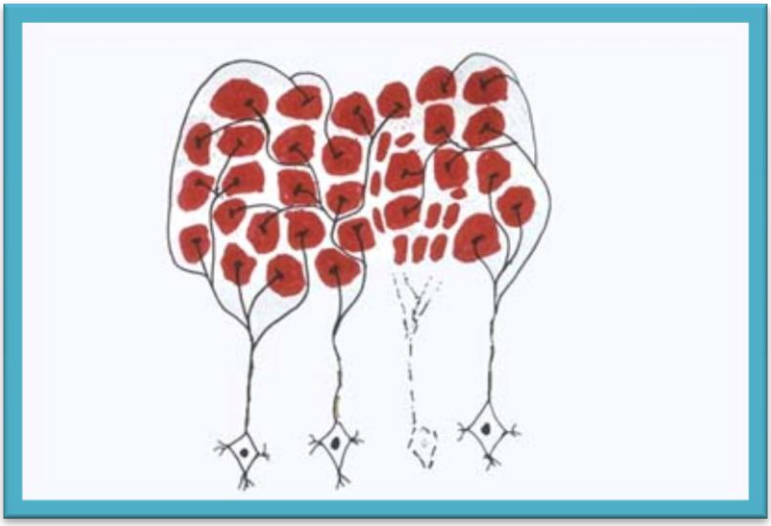
The functional and structural integrity of skeletal muscle depend on its nerve supply. Each motor neuron in the spinal cord or brain stem supplies many muscle fibers, usually several hundreds in large muscles. The motor neuron, its axon and the muscle fibers supplied by it, are known as a motor unit.

This image shows a diagram of four motor units



All of the muscle fibers in a given motor unit are of the same types, either type 1 or type 2, suggesting that the neuron determines the type of muscle fibers. The fibers of adjacent motor units overlap and intermingle resulting in a characteristic mosaic or checkerboard pattern

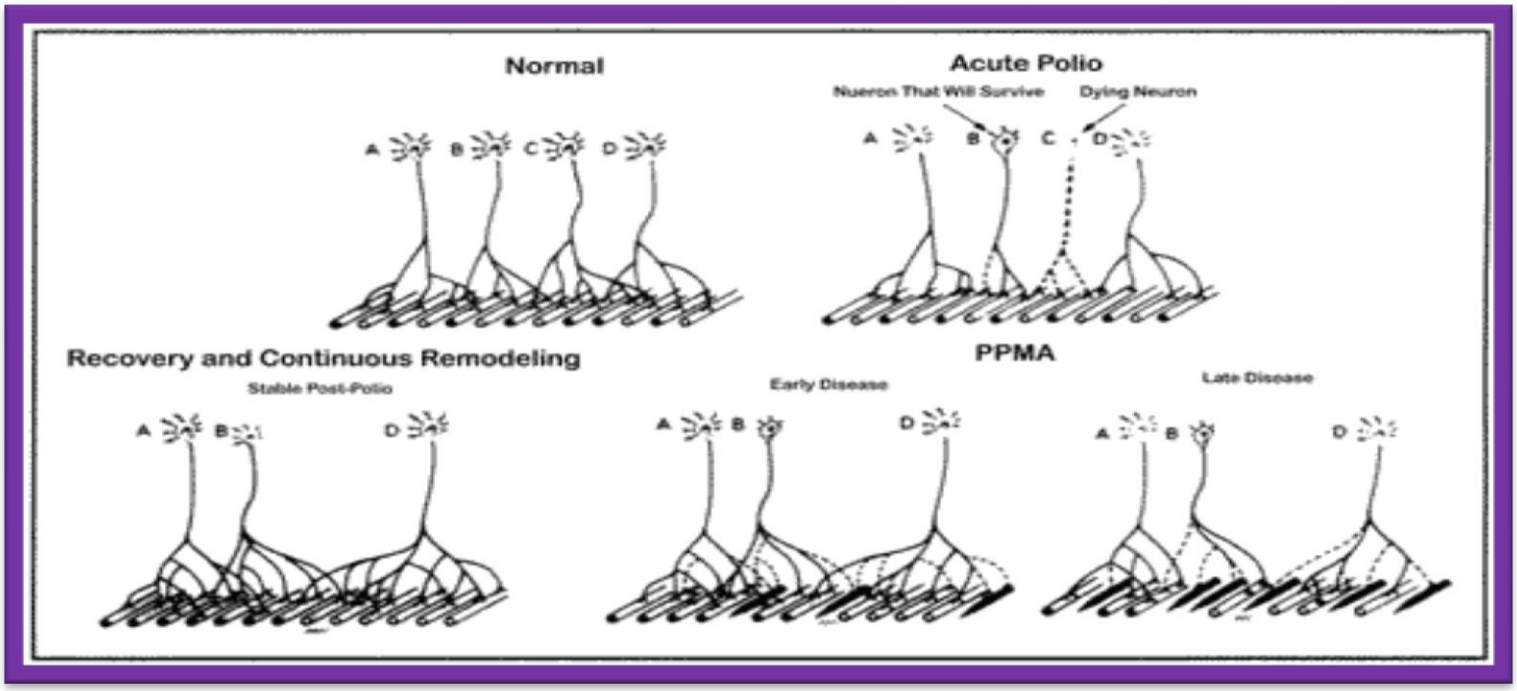
This image diagrammatically illustrates this phenomenon.



Characterized by involvement of both fiber types and by clustering of myofibers into small **groups**

- Deprived of their normal enervation, skeletal fibers undergo progressive atrophy

- Loss of a single neuron will affect all muscle fibers in a motor unit, so that the atrophy tends to be scattered over the field



- send out sprouts (expantion)

→ whole groups of fibers can eventually fall under the influence of the same neuron, and become the same fiber type **(*fiber type grouping*)**

(*grouped atrophy)*,

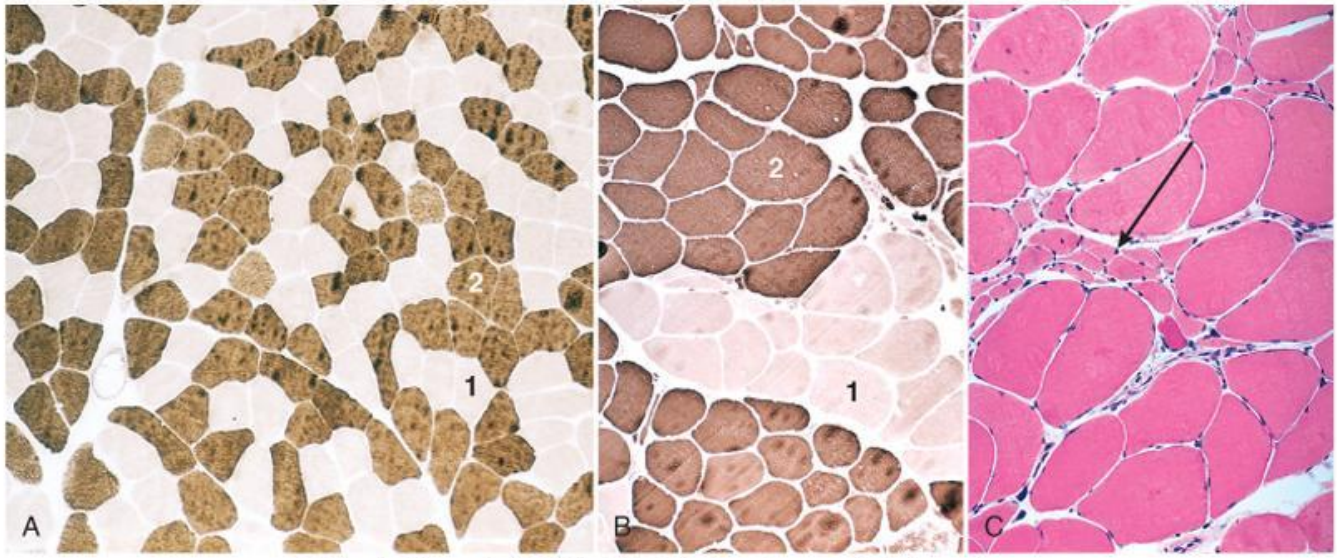
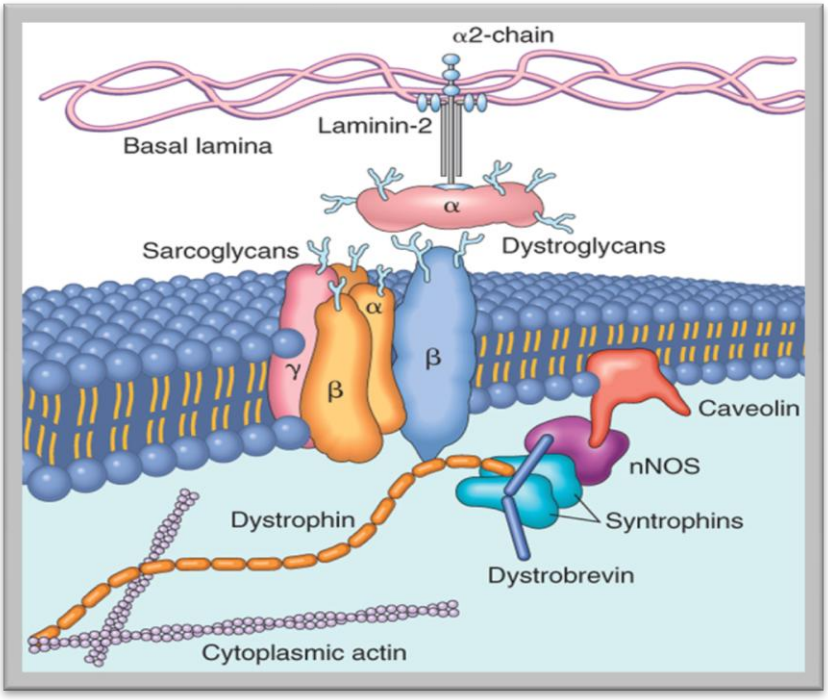


Figure 21-22 **A,** ATPase histochemical staining, at pH 9.4, of normal muscle showing checkerboard distribution of intermingled type 1 (*light*) and type 2 (*dark*) fibers. **B,** in contrast, fibers of either histochemical type are grouped together after reinnervation of muscle. **C,** A cluster of atrophic fibers (group atrophy) in the center (*arrow*).

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)*
- *People with muscular dystrophy die mostly from infection (Their diaphragm which is made of muscles doesn't move therefore they cannot breathe which leads to death due to pneumonia)*

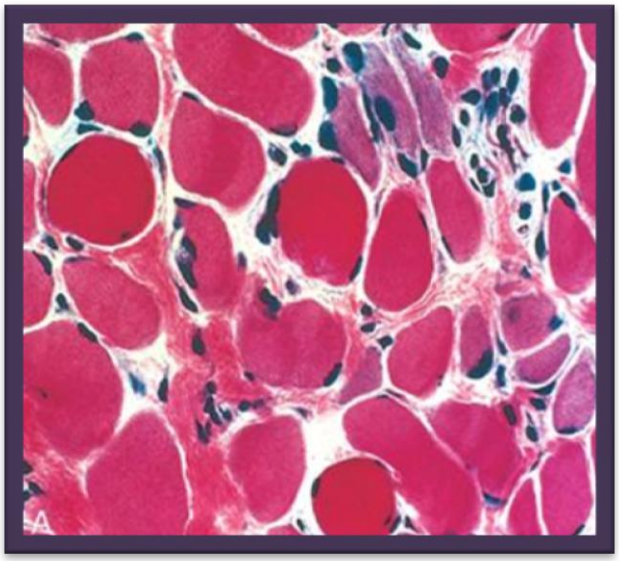


The relationship between the cell membrane (sarcolemma) and the sarcolemmal associated proteins

- 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*



Morphology of Duchenne and Becker Muscular Dystrophy:

- *The histologic features of DMD and BMD are similar*
- *Marked variation in muscle fiber size, caused by concomitant myofiber hypertrophy and atrophy*
- *Many show a range of degenerative changes, including fiber necrosis*
- *Other fibers show evidence of regeneration, including sarcoplasmic basophilia, nuclear enlargement, and nucleolar prominence*
- *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 heart will be effected"

• The dystrophin gene (Xp21) "in the short arm" spans (~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**.

"لان الجين حجمه كبير فزادت قابليته ليصبح فيه طفره"

• **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**. *(When a biopsy is taken, some tissues are put in formalin while others are frozen in(-80) degrees Celsius)*

(Acquired diseases always have better prognosis than congenital)

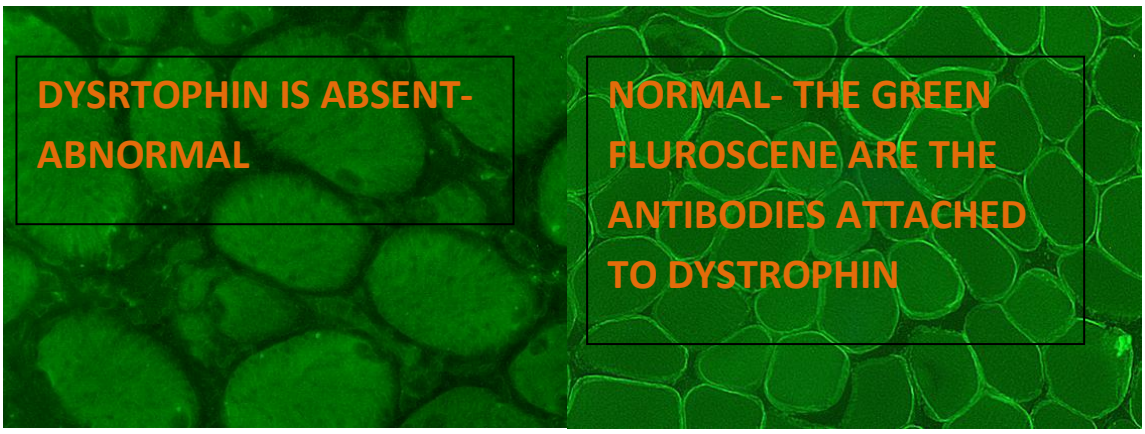
"mothers carry the gene and transmit it to their sons"

Pathogenesis Of DMD &BMD

−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 :

1-dystrophin defects

2-with changes in other proteins that interact with dystrophin.



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" weakness begin in the pelvic muscle that's why patients with this disease suffer of pain when they go upstairs"
• Enlargement of the **calf muscles(عضله خلف الساق) 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**
• Pathologic changes are also found **in the heart**, and patients may develop **heart failure or arrhythmias** "dystrophin is found in heart and brain also"

• Cognitive impairment 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.** "pulmonary infection is the major cause"

Boys with BMD

• Boys with BMD develop symptoms at **a later age than those with DMD.** The onset occurs in later childhood or in adolescence, 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**

Summary:

Clinical features	DMD	BMD
Severity	Most severe	Less"lighter disease of DMD"
Common	Most common	less
age	Symptoms begin at age 5	Symptoms begin at later age
Life span	Short, death by 20s	Normal life span
gene	Abnormalities in dystrophin	Abnormalities in dystrophin

Autosomal Muscular Dystrophies "effect both male&female"

• 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* are a classic example of limb girdle muscular dystrophy.

Congenital Myopathies

• Important subcategories:
– ***inherited mutations of ion channels*** *(channelopathies), e.g.* H*yperkalemic periodic paralysis*
– ***inborn errors of metabolism*** (exemplified by glycogen and lipid storage diseases)
– ***mitochondrial abnormalities***

Mitochondrial myopathies

• Can involve mutations in either **mitochondrial or nuclear DNA** that encodes mitochondrial constituents

• Mitochondrial myopathies typically present:

– in young adulthood, with proximal muscle weakness, sometimes with severe involvement of the ocular musculature (external ophthalmoplegia)

• There can be neurologic symptoms, lactic acidosis, and cardiomyopathy

• The most consistent pathologic findings in skeletal muscle are irregular muscle fibers and aggregates of abnormal mitochondria; the latter impart a blotchy red appearance to the muscle fiber on the modified Gomori trichrome stain, hence the term **ragged red fibers.(Fig A)**

• The **electron microscopic** appearance is also often distinctive: there are increased numbers of, and abnormalities in, the shape and size of mitochondria, some of which contain **paracrystalline parking lot**

"abnormalities in size and shape of mitochondria can only Recognized by EM"

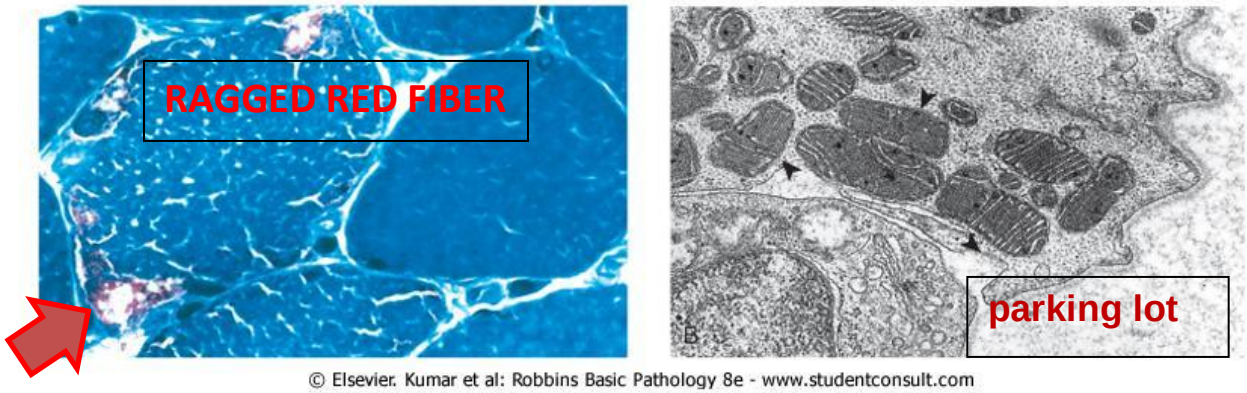
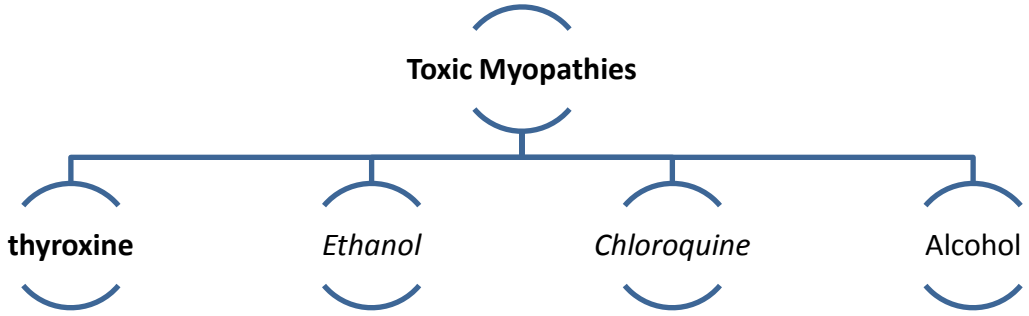


Figure 21-25 **A,** Mitochondrial myopathy showing an irregular fiber with subsarcolemmal collections of mitochondria that stain red with the modified Gomori trichrome stain *(ragged red fiber)*. **B,** Electron micrograph of mitochondria from biopsy specimen in **A** showing "parking lot" inclusions (*arrowheads*).

Toxic Myopathies



• Important subcategories include disorders caused by ***intrinsic*** **exposures (e.g. thyroxine)** versus *extrinsic* exposures (e.g., alcohol, therapeutic drugs)
– ***Thyrotoxic myopathy*** **can present as either acute or chronic proximal muscle weakness, and can precede the onset of other signs of thyroid dysfunction**
• Findings include myofiber necrosis, regeneration, and interstitial lymphocytes
– *Ethanol myopathy* can occur with binge drinking
• Acute toxic rhabdomyolysis with accompanying myoglobinuria that can cause renal failure
Rhabdomyolysis: damaged skeletal muscle tissue -> break down product of damaged muscle cells and realeased into blood stream (myoglobin).
Note:myoglobin is harmful to the kidney leads to kidney failure.
• On histology, there is myocyte swelling and necrosis, myophagocytosis, and regeneration
– *Chloroquine* can also produce a proximal myopathy
• The most prominent finding is myocyte vacuolization, and with progression, myocyte necrosis

Note: if the patient is angry, look for T3T4TSH. It is a hormone secreted by thyroid.
Normally: T3T4 Is high, TSH is low.

Inflammatory Myopathies"related to autoimmune diseases, not infections."

(Inflammatory myopathies undergo the toxic type)

• Inflammatory myopathies make up a heterogeneous group of rare disorders characterized by immune-mediated muscle injury and inflammation

• Based on the clinical, morphologic, and immunologic features, three disorders:

– *Polymyositis*

– *Dermatomyositis*

– *Inclusion body myositis*

• **Occur alone or in conjunction with other autoimmune diseases, such as systemic sclerosis**

• Women with dermatomyositis have a slightly increased risk of developing visceral cancers (of the lung, ovary, stomach)

• Clinically:

– usually symmetric muscle weakness

– initially affecting **large muscles** of the trunk, neck and limbs

• Thus, tasks such as getting up from a chair or climbing steps become increasingly difficult

– In dermatomyositis: an associated rash (classically described as a *lilac* or *heliotrope* discoloration) affects the upper eyelids and causes periorbital edema

• Histologically:

– infiltration by lymphocytes

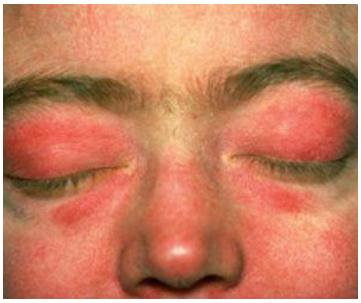
– degenerating and regenerating muscle fibers

• The pattern of muscle injury and the location of the inflammatory infiltrates are fairly distinctive for each subtype

• The immunologic evidence supports **antibody-mediated** tissue injury in dermatomyositis

• **Polymyositis and inclusion body myositis seem to be mediated by CTLs (cytotoxic T cells)**

• The diagnosis of these myopathies is based on clinical features, laboratory evidence of muscle injury (e.g., increased blood levels of creatine kinase), electromyography, and biopsy



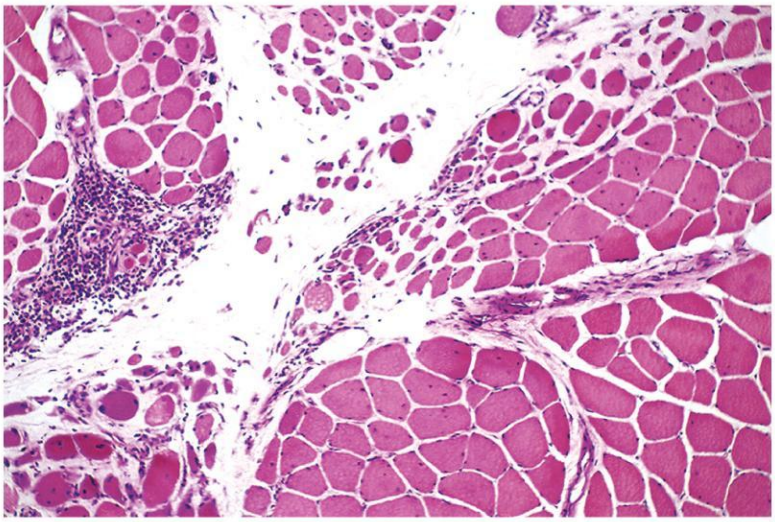


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Figure 5-28 Dermatomyositis. Perifascicular inflammation and atrophy in a skeletal muscle. (Courtesy of Dr. Dennis Burns, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Muscle fibers(pink) attacked by inflammatory cells (purple)

Homework:

• **Define Myotonia?**

✓ Myotonia is **sustained involuntary contraction** of group of muscle.

✓ The most common form is a trinucleotide repeat disorder affecting the synthesis of an intracellular protein kinase.

• **What is the clinical presentation of myotonic dystrophy?**

The disease is often presents **in late childhood** with gait abnormalities attributable **to weakness of foot dorsiflexors** ; it progresses to weakness of intrinsic muscles of **the hands and wrist extensore**; atrophy of **facial muscles with ptosis.**

From 431 work