Pathology Team

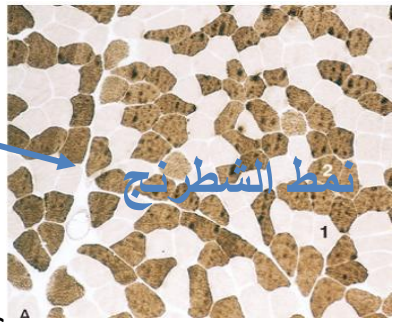
Introduction to myopathies and Muscular dystrophy

المحدد والمكتوب باللون
الاحمر هو ما ركزت عليه
الدكتور

المحدد و المكتوب باللون
الازرق هو ما نراه مهم و
معلومات اضافية مهمة للفهم

Skeletal muscle “Fiber types”

- Depending on the nature of the **nerve fiber** doing the innervation, the associated skeletal muscle develops into one of two major subpopulations
- A single "type I" or "type II" neuron will innervate multiple muscle fibers and these fibers are usually randomly scattered in a **"checkerboard pattern"** within a circumscribed area within the larger muscle.



- The different fibers can be identified using specific staining techniques:

1-type I:

  - "**slow** twitch“
  - more dependent on **fat catabolism** for energy through mitochondrial oxidative phosphorylation
  - **red**, refers to this being the **dark (red)** meat on birds where fiber type grouping in different muscles (e.g., thigh vs. breast meat) is quite pronounced

2-type II:

  - "**fast** twitch“
  - more dependent on **glycogen catabolism** for energy through glycolysis
  - **white.**

Myopathy

- 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

- **Diseases that affect skeletal muscle can involve any portion of the motor unit:**
  - **primary disorders of the motor neuron or axon**
  - **abnormalities of the neuromuscular junction**
  - **a wide variety of disorders primarily affecting the skeletal muscle itself (*myopathies*)**
- skeletal muscle disease can be divided into:
    - Neurogenic **(myofiberatrophy)**
    - Muscular dystrophies **(most common)**
    - Congenital
    - Toxic (inflammatory myopathies undergoes toxic)
    - Infectious
    - Disorders of the neuromuscular junction (e.g. myasthenia gravis)

Remember:

myasthenia gravis

- It is an autoimmune disease in which autoantibodies attach to acetylcholine receptors, blocking their availability to acetylcholine.

- Skeletal muscles including diaphragm weaken gradually.

1-MUSCLE ATROPHY

- 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

Morphology: the study of the form and structure and their specific structural features.

• Causes of muscle atrophy:

- ✓ **Simple disuse** (e.g., prolonged bed rest, immobilization to allow healing of a bone fracture, etc.) can cause profound atrophy.
- ✓ **Exogenous glucocorticoids or endogenous hypercortisolism** (e.g., in Cushing syndrome) are another cause of muscle atrophy, typically involving **proximal muscle groups** more than distal ones.
- ✓ **Disuse- and steroid-induced atrophy** primarily affects the **type II** fibers and causes a random distribution of the atrophic myofibers.
- ✓ **Atrophic myofibers** are also found in myopathies
  - the finding of additional morphologic changes like myofiber degeneration and regeneration or inflammatory infiltrates are features that suggest a myopathic etiology.

Neurogenic Atrophy

- 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.
- However, following re-enervation, adjacent intact neurons send out sprouts**(budding)** to engage the neuromuscular junction of the previously de-enervated fibers→ new connection is established → these fibers assume the type of the innervating neuron → whole groups of fibers can eventually fall under the influence of the same neuron, and become the same fiber type ***(fiber type grouping)*** **(see fig B)**
- In that setting, if the relevant enervating neuron now becomes injured, rather large coalescent**(grow together)** groups of fibers are cut off from the trophic stimulation and wither away ***(grouped atrophy)*** **(see fig C)**, a hallmark of recurrent neurogenic atrophy.- ("Grouping" is specific for neurogenic atrophy)

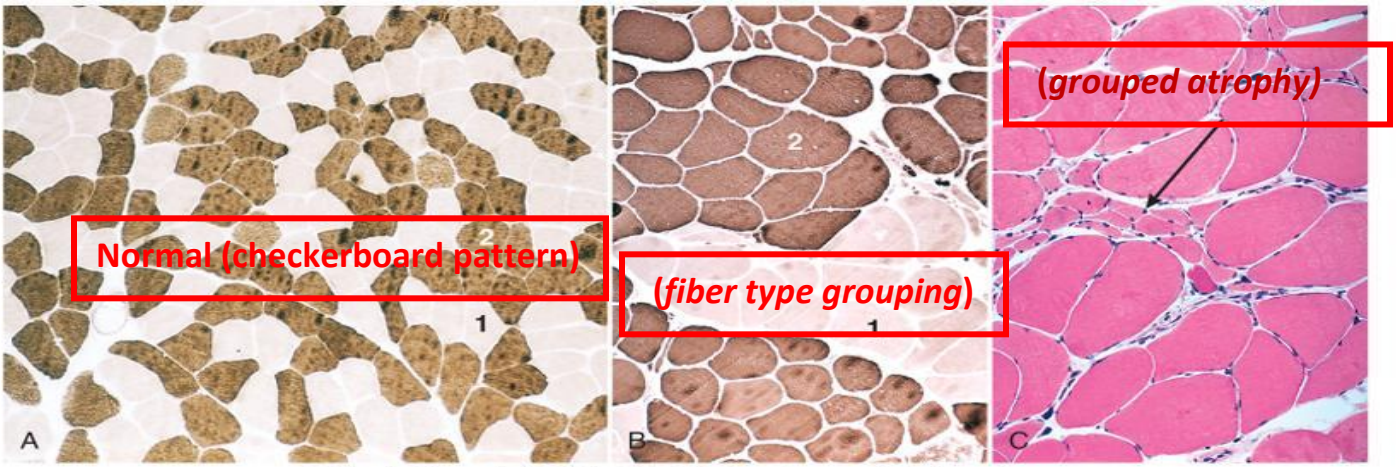


Figure 21-22 **A,** ATPase histochemical staining, at pH 9.4, of normal muscle showing checkerboard distribution of intermingled type 1 (*light*) and type 2 (*dark*) fibers. **B,** in contrast, fibers of either histochemical type are grouped together after reinnervation of muscle. **C,** A cluster of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

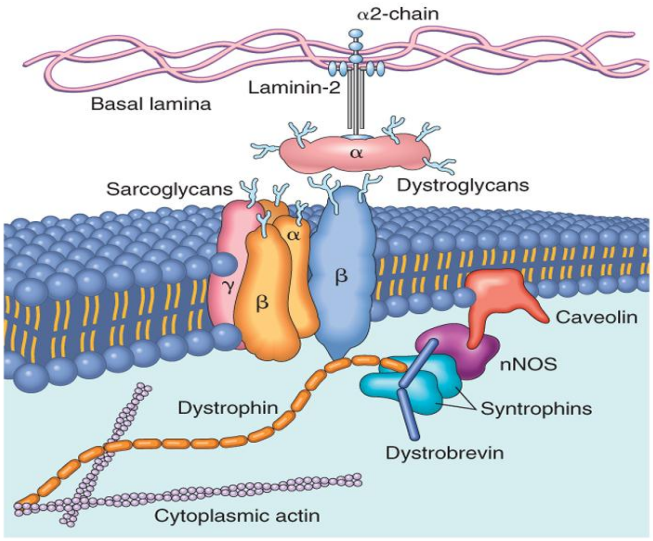
(ATPase is a stain used in pathology.)

2-MUSCULAR DYSTROPHY

(Muscular dystrophies = diseases in proteins in muscle.)

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*



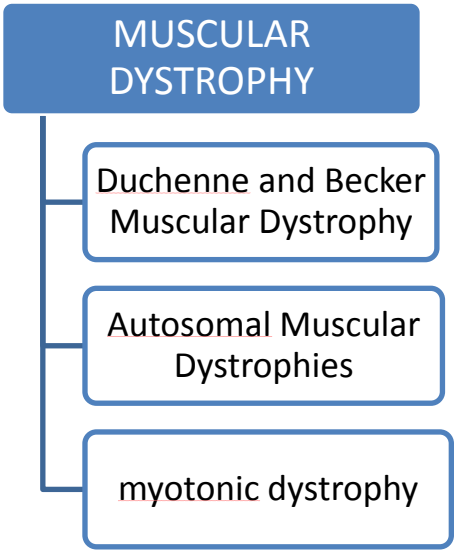
The relationship between the cell membrane (sarcolemma) and the sarcolemmal associated proteins

- **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**

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 **(in short arm of chromosome x)** (Xp21) 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**.(حجمه الضخم هو الذي زاد قابليته ليصبح ذو طفرة جينية)
- **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**.



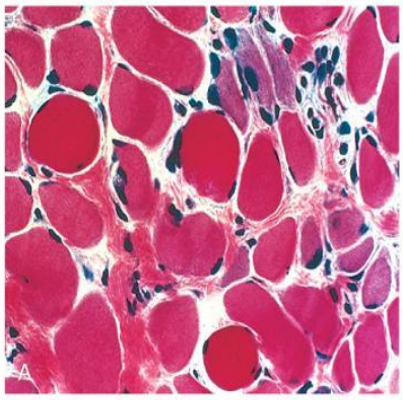
1-Duchenne and Becker Muscular Dystrophy

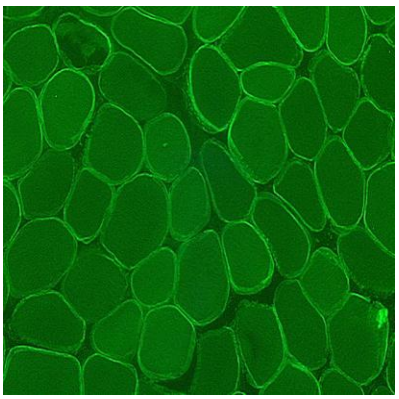
(Duchenne and Becker caused by mutation in dystrophin)

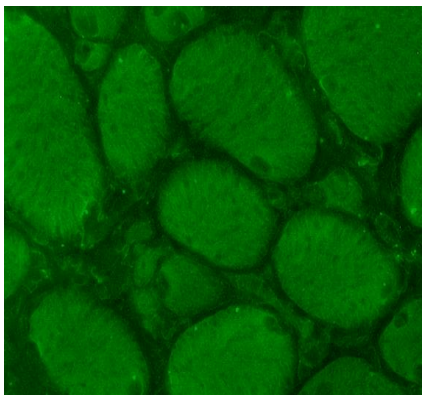
- ✓ **X-Linked** Muscular Dystrophy
- ✓ The two **most common** forms of muscular dystrophy

- ✓ 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	Pathogenesis
○ 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.	○ 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.







Clinical Features	
Boys with DMD	Boys with BMD
• **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** • Pathologic changes are also found **in the heart**, and patients may develop **heart failure or arrhythmias** • 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.**	• 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**

TO ARRANGE YOUR Knowloage:

The difference between DMD & BMD

	DMD Duchenne muscular dystrophy	BMD Becker muscular dystrophy
Severity	the most severe	much less severe
common	the most common	less common than DMD
age	becomes clinically evident by age of 5	develop symptoms at a later age
Life span	Short (death by the early 20s)	nearly normal life span
Gene	abnormalities in the dystrophin gene	abnormalities in the dystrophin gene
Histologic features	DMD and BMD are similar	DMD and BMD are similar

2-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* are a classic example of limb girdle muscular dystrophy.

3- myotonic dystrophy

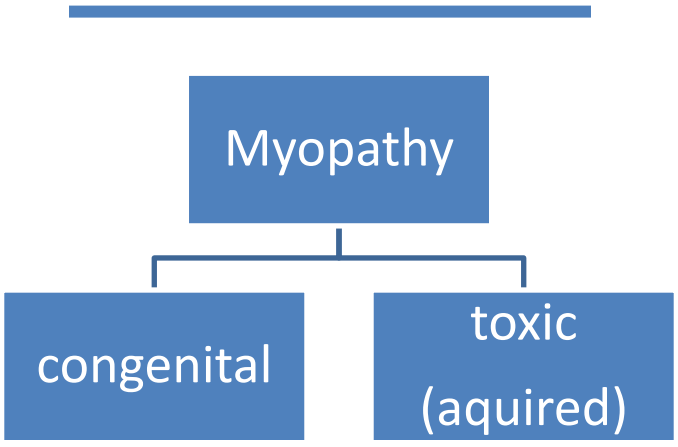
(OUR HOMEWORK -LAST SLIDE-)

- **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.**



(pathy = disease myo =muscle)

3-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**

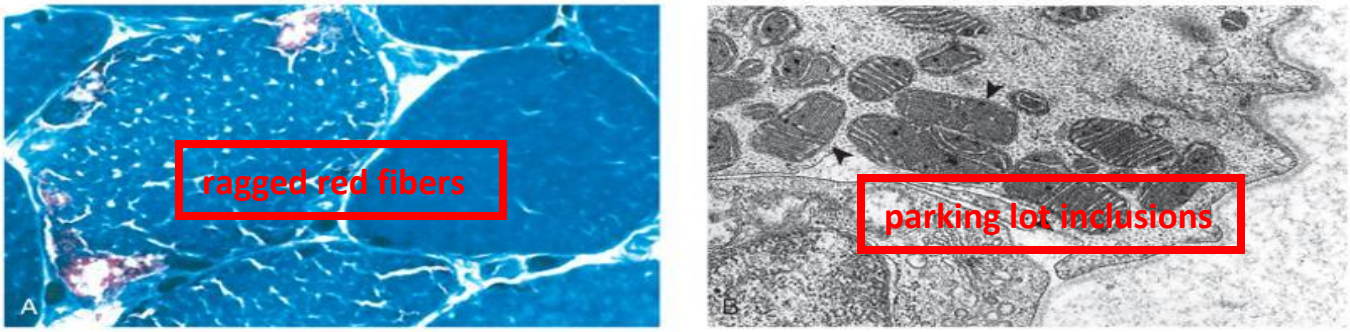


Figure 21-25 **A,** Mitochondrial myopathy showing an irregular fiber with subsarcolemmal collections of mitochondria that stain red with the modified Gomori trichrome stain *(ragged red fiber).* **B,** Electron micrograph of mitochondria from biopsy specimen in **A** showing "parking lot" inclusions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

4-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

EXTRA INFORMATION :
(Rhabdomyolysis is a condition in which damaged skeletal muscle tissue.Breakdown products of damaged muscle cells are released into the bloodstream; some of these, such as the protein myoglobin, are harmful to the kidneys and may lead to kidney failure)

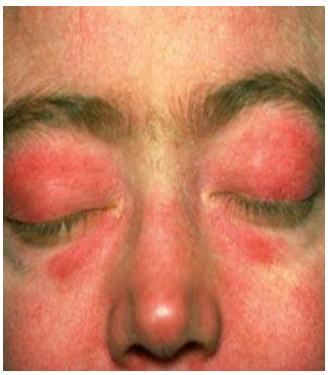
    - On histology, there is myocyte swelling and necrosis, myophagocytosis, and regeneration
  - *Chloroquine* can also produce a proximal myopathy
    - The most prominent finding is myocyte vacuolization, and with progression, myocyte necrosis

5-Inflammatory Myopathies

(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



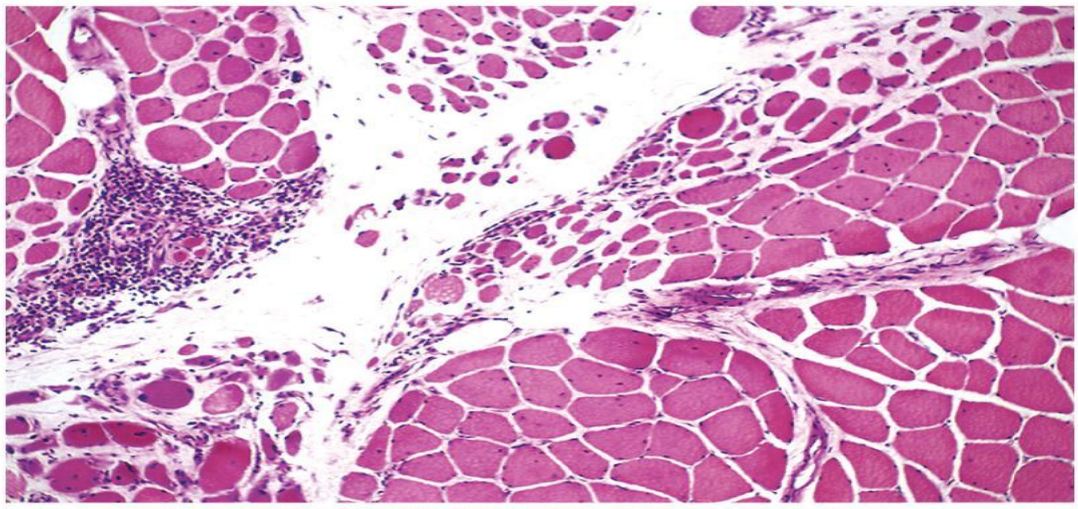


Figure 5-28 Dermatomyositis. Perifascicular inflammation and atrophy in a skeletal muscle. (Courtesy of Dr. Dennis Burns, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

This is a muscle biopsy from a patient which shows the muscle fibers (pink) being attacked by the inflammatory cells (purple).