

MUSCULOSKELETAL SYSTEM BLOCK

**An introduction to myopathies and
muscular dystrophy**

Pathology

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Objectives:

At the end of this lecture, the students should be able to:

- Understand the structure of the various types of muscle fibers.
- Acquire a basic knowledge of the classification of myopathies and give examples of these disorders.
- Understand the meaning of the term muscular dystrophy and have a basic knowledge of the incidence and clinicopathological manifestations of Duchenne's and Becker's muscular dystrophies.
- Know the pattern of inheritance of myotonic dystrophy and its clinicopathological presentations.

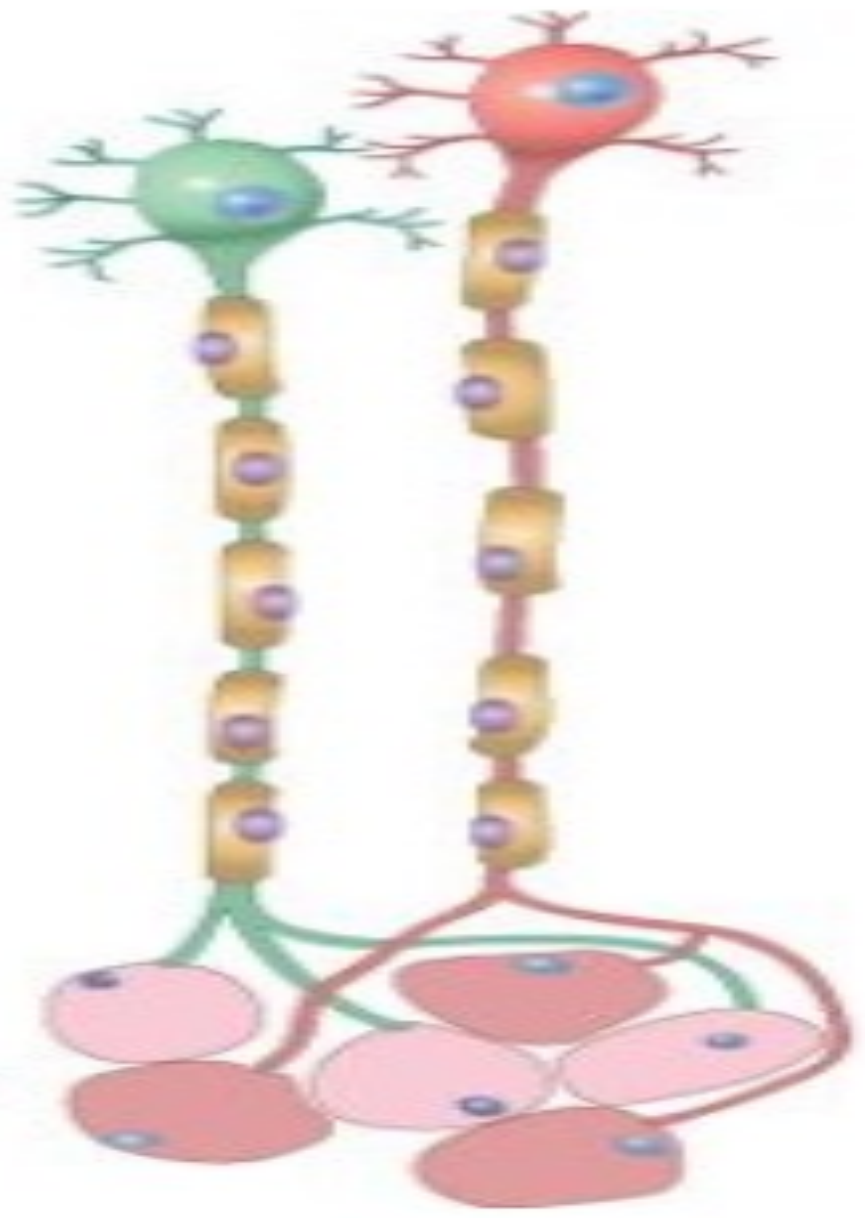
Normal motor units

Neurons

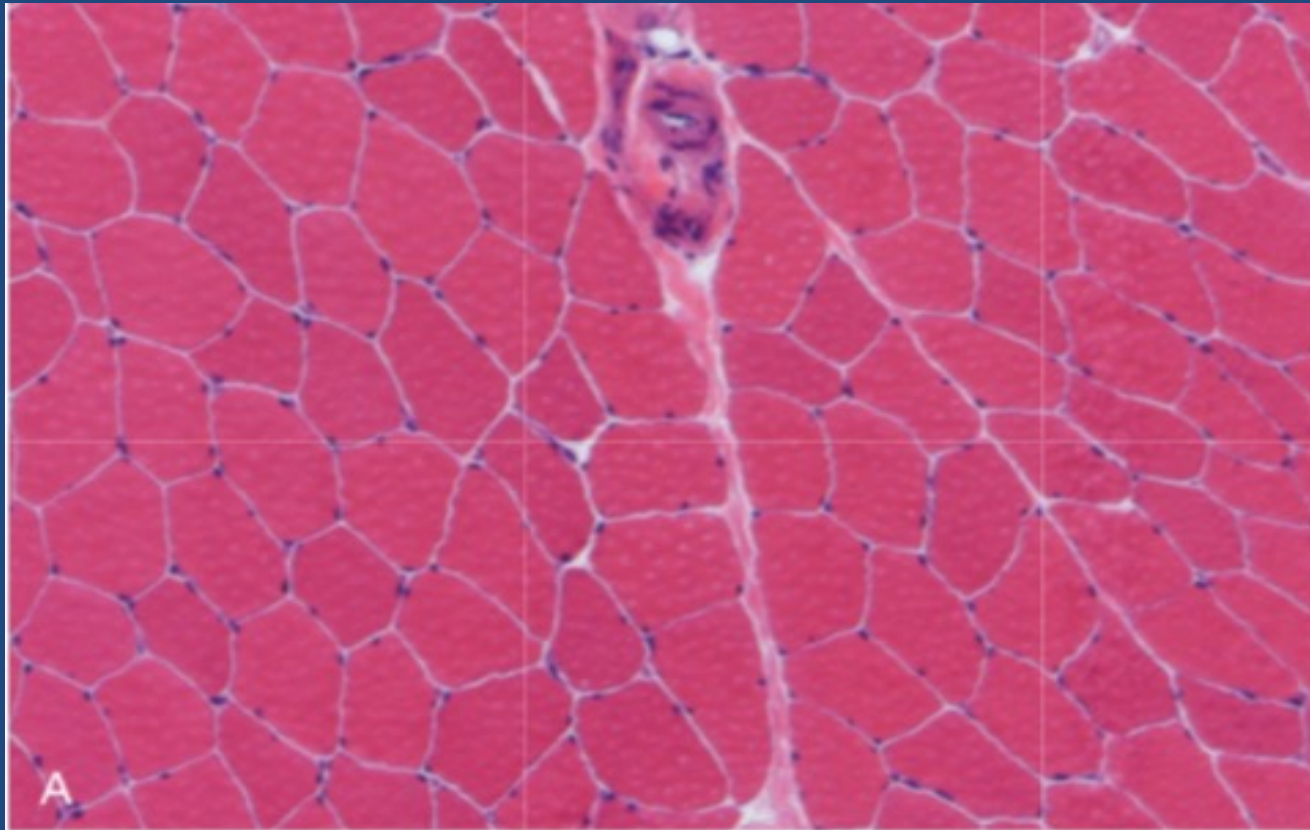
Myelin

Axon

Myocytes



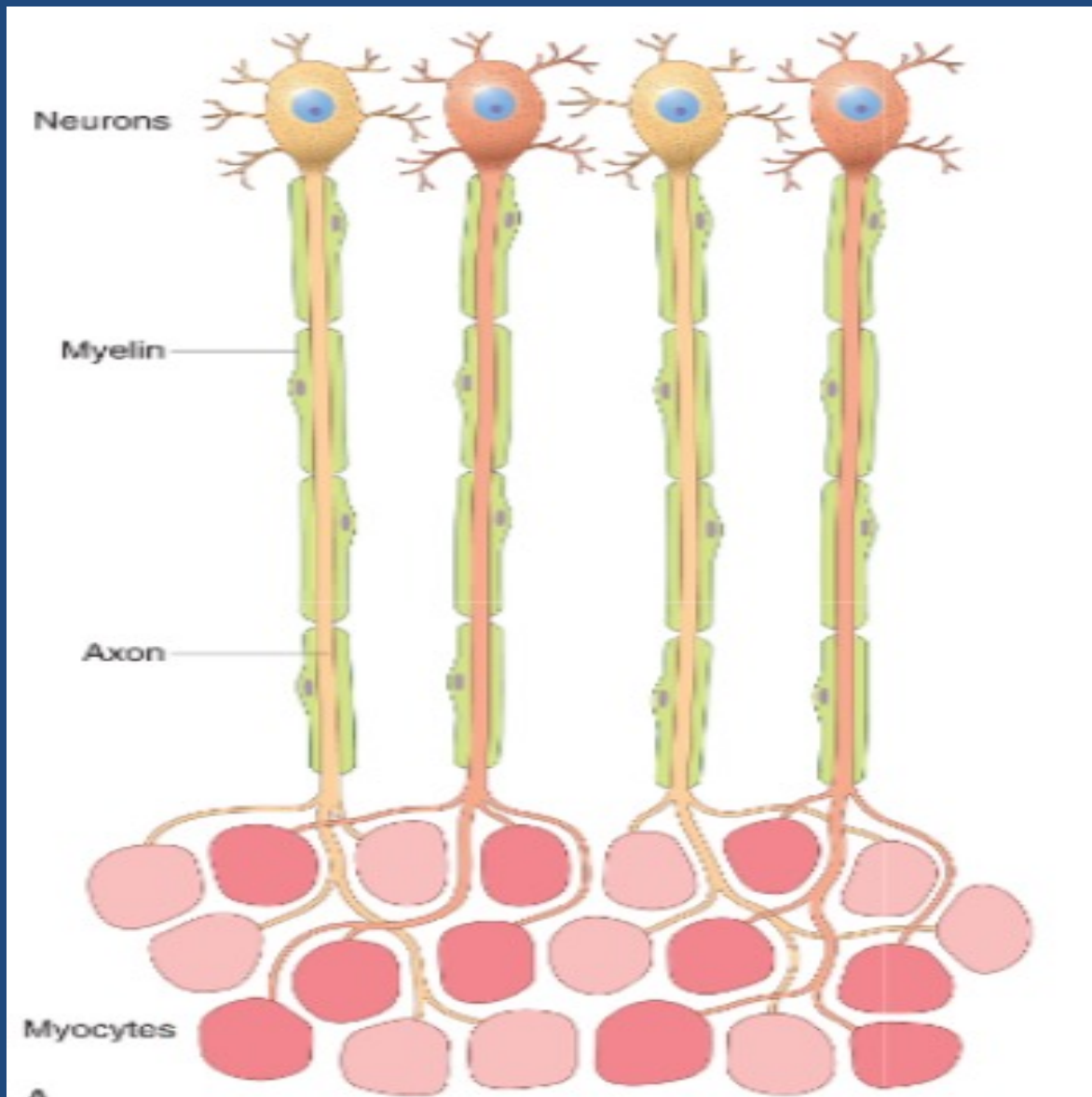
Normal skeletal muscle has relatively uniform polygonal myofibers with peripherally placed nuclei that are tightly packed together into fascicles separated by scant connective tissue. A perimysial interfascicular septum containing a blood vessel is present

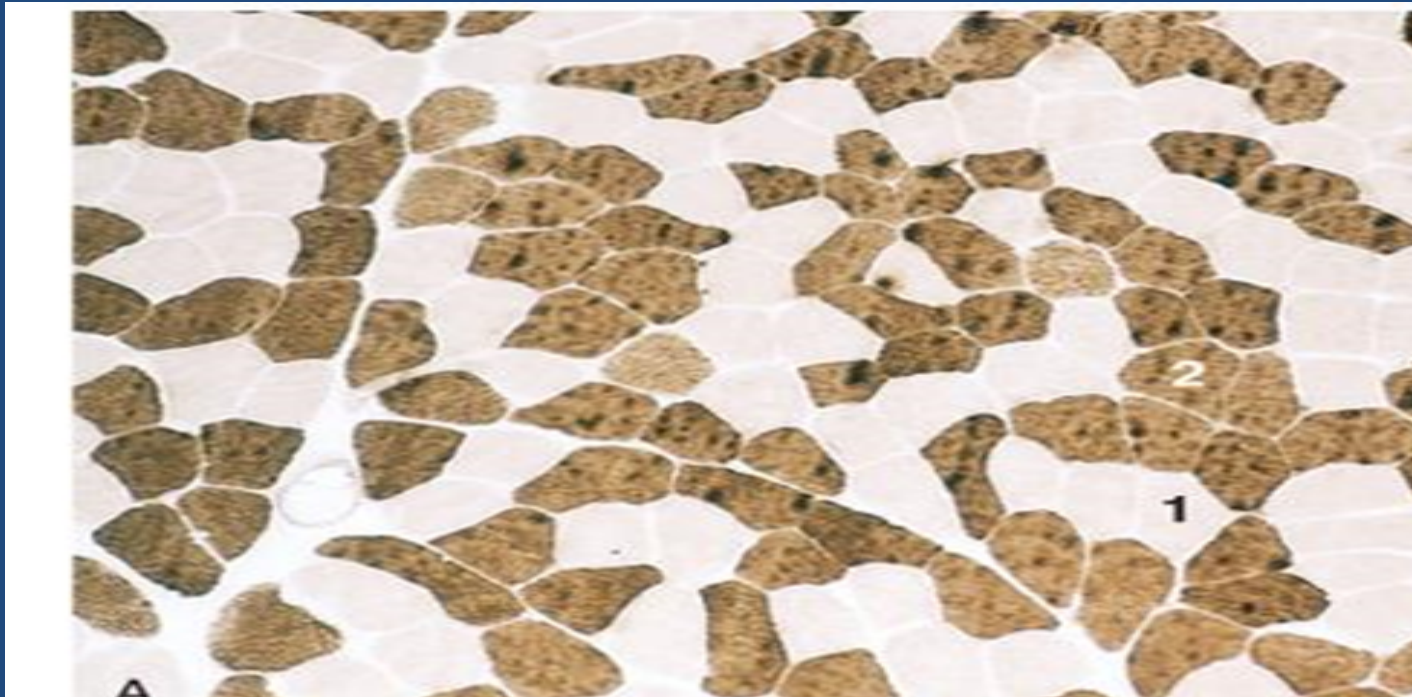


- The two principal pathologic processes seen in skeletal muscle are *denervation atrophy*, which follows loss of axons
- and those due to a primary abnormality of the muscle fiber itself, referred to as *myopathy*

Muscle fiber types

- The fiber types, are determined by the neuron of the motor unit:
- **Type 1 fibers:** slow twitch “aerobic” type I are high in myoglobin and oxidative enzymes and have many mitochondria, in keeping with their ability to perform tonic contraction
- **Type 2 fibers :** fast twitch are rich in glycolytic enzymes and are involved in rapid phasic contractions
- *Since the motor neuron determines fiber type, all muscle fibers of a single unit are of the same type.*
- The fibers of a single motor unit are distributed across the muscle, giving rise to a checkerboard pattern of alternating fiber types





- 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*)

MYOPATHY

- Myopathy as a term may encompass 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

- A non-specific response
- Characterized by abnormally small myofibers
- *Muscle fiber atrophy* is shared by both neuropathic and myopathic processes. However, certain disorders are associated with particular patterns of atrophy.

MUSCLE ATROPHY

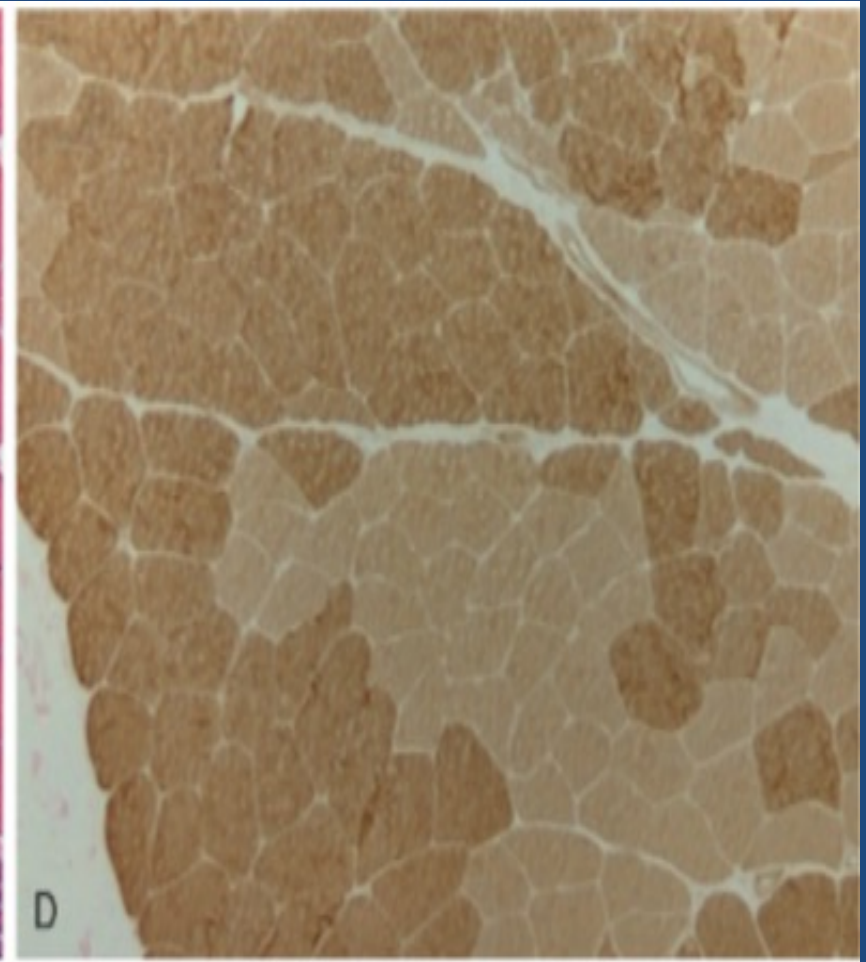
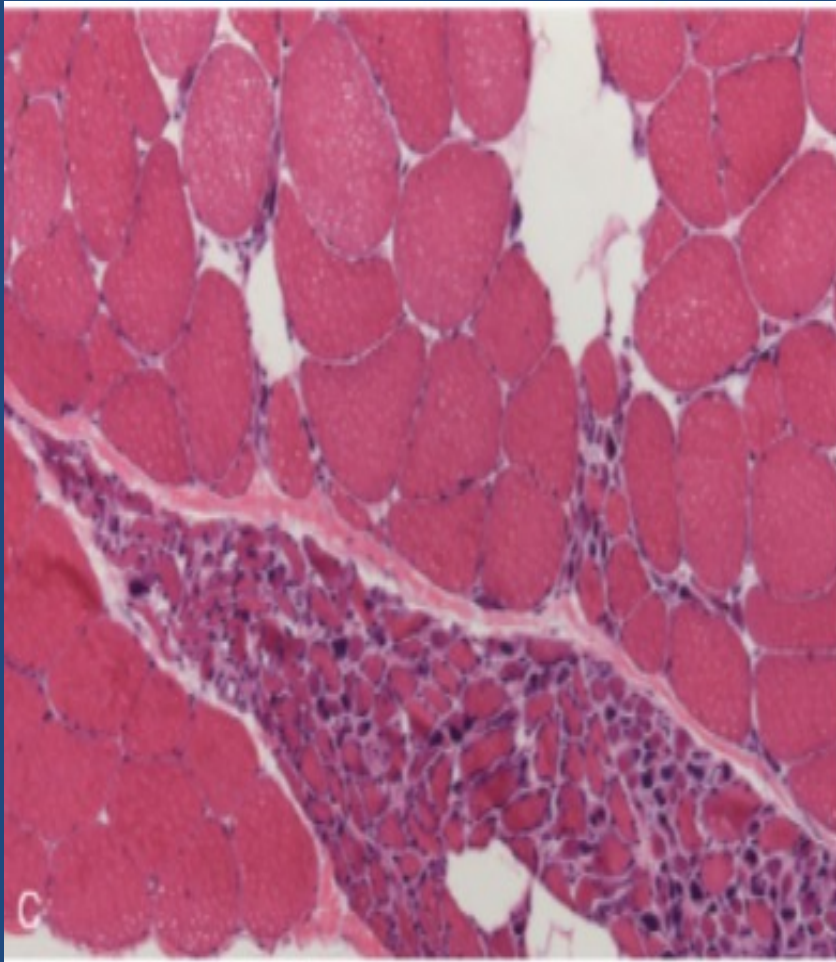
- Causes:
 - Simple disuse, type II fibers
 - Exogenous glucocorticoids or endogenous hypercortisolism (proximal weakness)
 - Myopathies
 - Neurogenic atrophy

MUSCLE ATROPHY

Neurogenic Atrophy

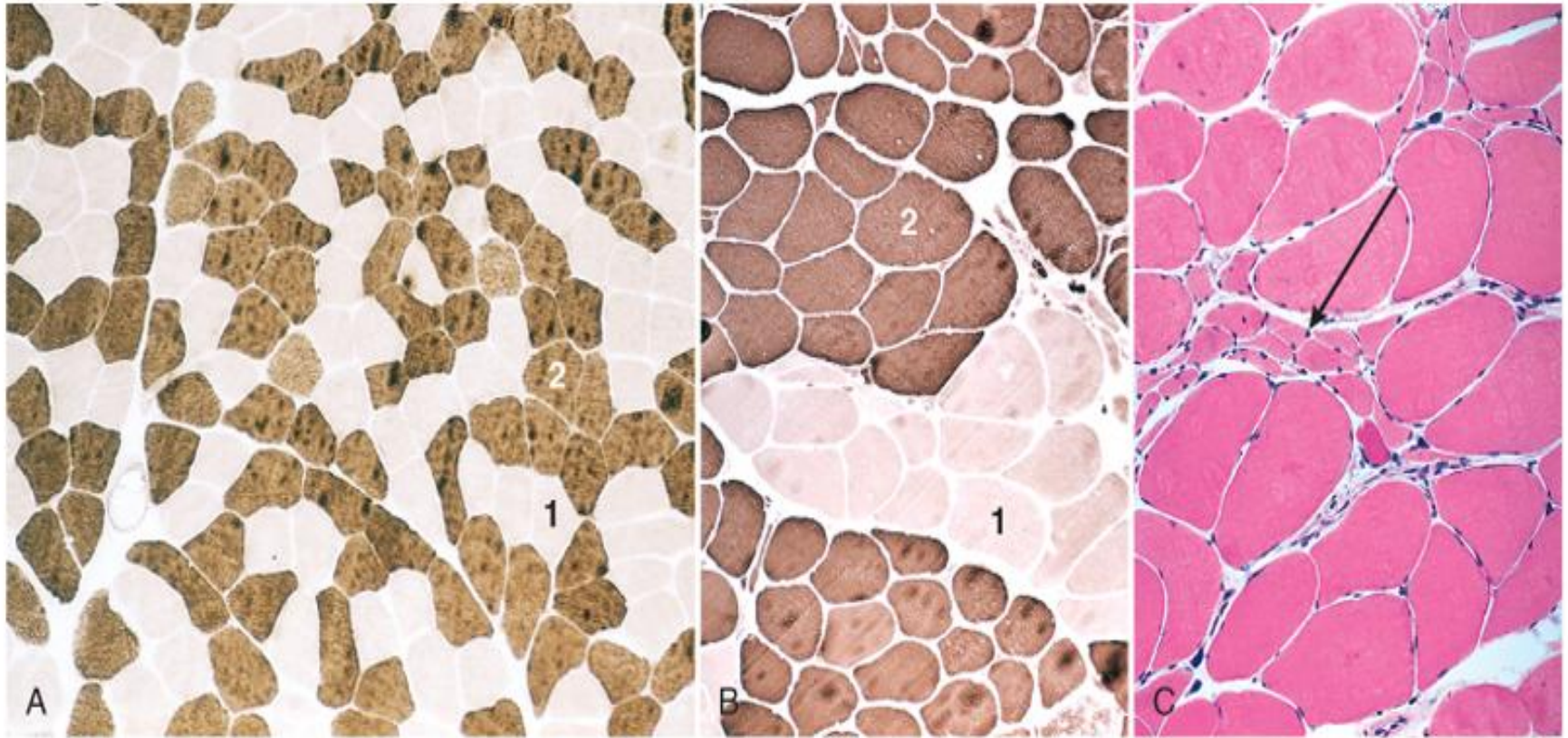
- Neurogenic Atrophy :
 - Both fiber types
 - Characterized **by fiber type grouping and grouped atrophy**
 - Deprived of their normal enervation, skeletal fibers undergo progressive atrophy
 - injury and regeneration of peripheral nerves alters muscle innervation, it will change the distribution of type I and type II myofibers.

Clusters of both atrophic myofibers (**C**) (grouped atrophy) and fiber-type grouping (**D**), patchy areas in which myofibers share the same fiber type, are features of neurogenic remodeling. The ATPase reaction shown in **D** is one method of distinguishing between fiber types, as type I fibers stain more lightly than type II fibers. Note loss of the “checkerboard” pattern



MUSCLE ATROPHY

Neurogenic Atrophy



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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*).

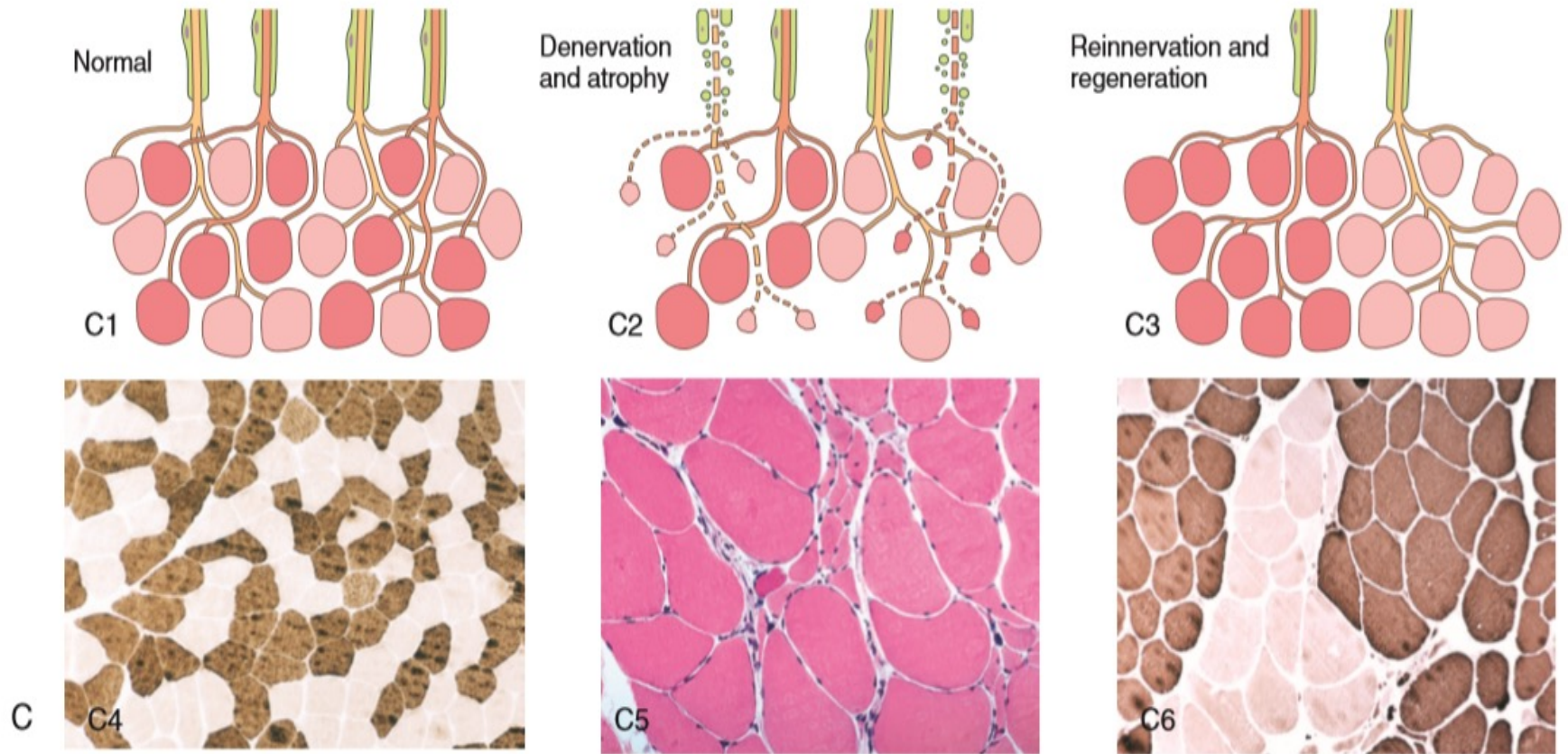


Fig. 22.4 Patterns of skeletal muscle injury. (A) Normal skeletal muscle has relatively uniform polygonal myofibers with peripherally placed nuclei that are tightly packed together into fascicles separated by scant connective tissue. A perimysial interfascicular septum containing a blood vessel is present (*top center*). (B) Myopathic conditions often are associated with segmental necrosis and regeneration of individual myofibers. Necrotic cells (B1–B3) are infiltrated by variable numbers of inflammatory cells. Regenerative myofibers (B4, *arrow*) are characterized by cytoplasmic basophilia and enlarged nucleoli (not visible at this power). (C) Neurogenic changes. (C1) This diagrammatic representation of four normal motor units shows a checkerboard-type admixture of light and dark stained fibers of opposite type. (C2) Damage to innervating axons leads to a loss of trophic input and the atrophy of myofibers. (C3) Reinnervation of myofibers can result in a switch in fiber type and segregation of fibers of like type. As illustrated here, reinnervation is also often associated with an increase in motor unit size, with more myofibers innervated by an individual axon. (C4) Normal muscle has a checkerboard distribution of type I (*light*) and type II (*dark*) fibers on this ATPase reaction (pH9.4), corresponding to findings in (A). (C5) Clustered flattened “angulated” atrophic fibers (*grouped atrophy*) are a typical finding associated with disrupted innervation. (C6) With ongoing denervation and reinnervation, large clusters of fibers appear that all share the same fiber type (*fiber type grouping*).

- inflammatory infiltrates usually are absent in skeletal muscle disorders caused by abnormal innervation.
- Prolonged disuse of muscles due to any cause (e.g., prolonged bed rest in the sick, casting of a broken bone) can cause focal or generalized muscle atrophy, which tends to affect **type II fibers** more than type I fibers.
- Glucocorticoid exposure, whether exogenous or endogenous (e.g., in Cushing syndrome), also can cause muscle atrophy. **Proximal muscles and type II myofibers** are affected preferentially by these agents.

MUSCULAR DYSTROPHIES

- 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

Duchenne Muscular dystrophy (DMD) and Becker Muscular Dystrophy (BMD)

- **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 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

Pathogenesis

- Both DMD and BMD are caused by mutations in the dystrophin gene located on the short arm of the X chromosome (Xp21).
- Dystrophin is a very large protein found in skeletal and cardiac muscle, brain, and peripheral nerves

- It is part of the dystrophin-glycoprotein complex . This complex stabilizes the muscle cell during contraction and may be involved in cell signaling through interaction with other proteins.
- Dystrophin-glycoprotein complex defects are thought to make muscle cells vulnerable to transient membrane tears during contraction that lead to calcium influx.
- The result is myofiber degeneration that with time outpaces the capacity for repair.
- The dystrophin-glycoprotein complex also is important for cardiac muscle function; this explains why cardiomyopathy eventually develops in many patients

Pathogenesis

- In the affected families females are carriers; they are clinically asymptomatic but often have elevated serum creatine kinase and show minimal histologic abnormalities on muscle biopsy.
- Female carriers and affected males who survive into adulthood are also at risk for developing dilated cardiomyopathy

- Muscle biopsy specimens from individuals with DMD show little or no dystrophin by both staining and western blot analysis
- People with **BMD**, who also have mutations in the dystrophin gene, have diminished amounts of dystrophin, usually of an abnormal molecular weight, reflecting mutations that allow synthesis of an **abnormal protein of smaller size**

Morphology

The histologic alterations in skeletal muscles affected by DMD and BMD are similar except that the changes are milder in BMD

1- The hallmarks are ongoing myofiber necrosis and regeneration.

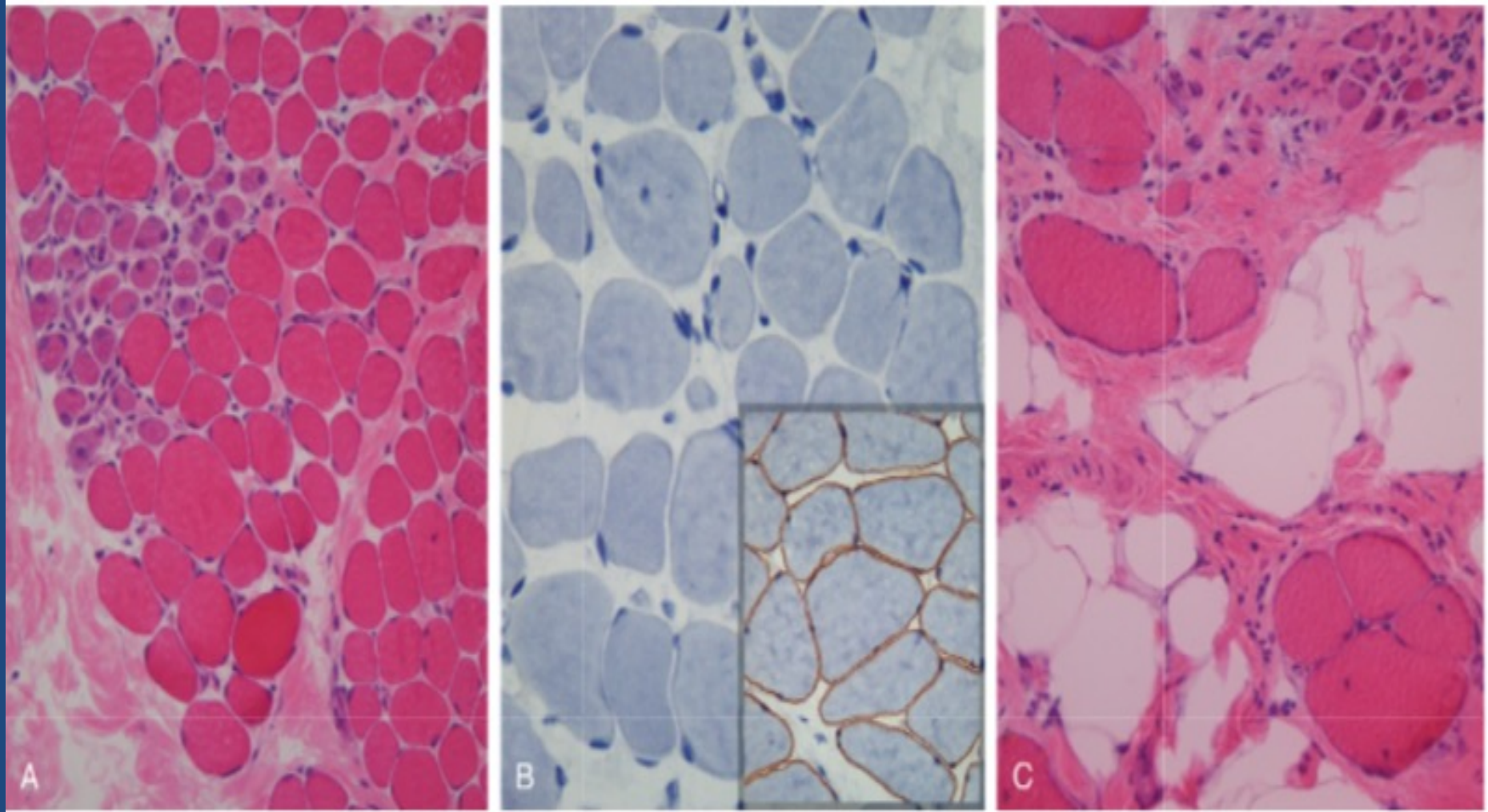
2- Progressive replacement of muscle tissue by fibrosis and fat is the result of degeneration outpacing repair.

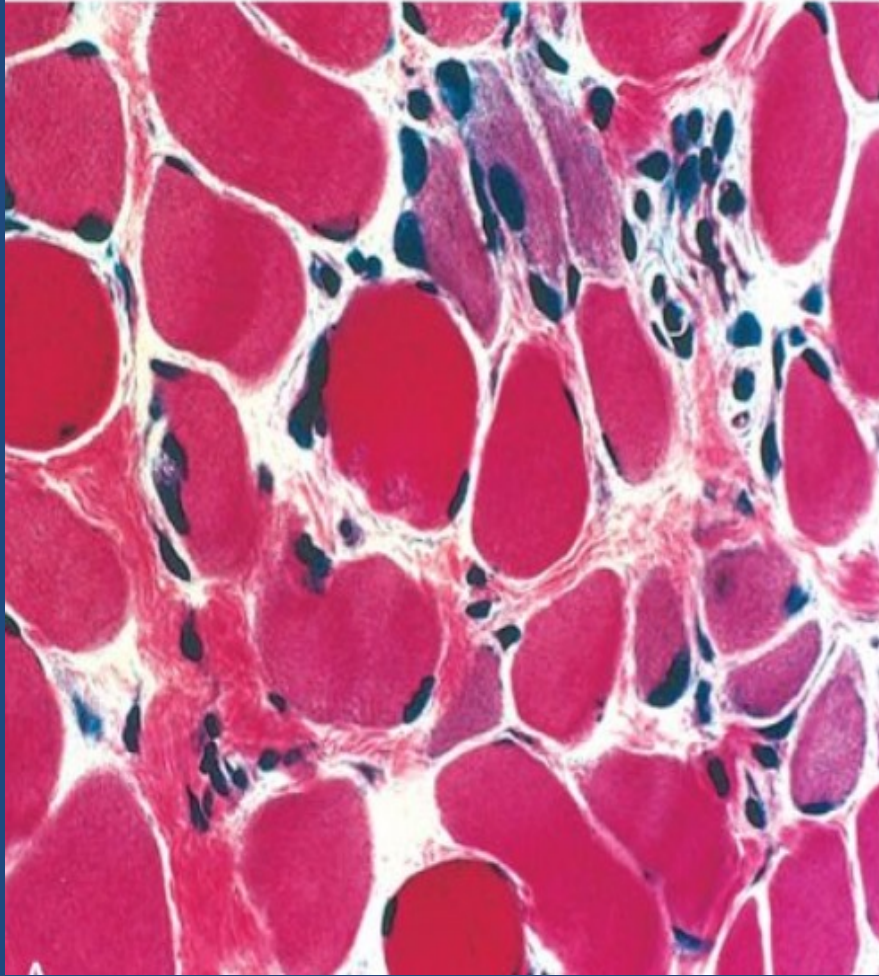
3- marked variation in myofiber size and

4- abnormal internally placed nuclei.

Both DMD and BMD also affect cardiac muscles, which show variable degrees of interstitial fibrosis

Duchenne muscular dystrophy. Histologic images of muscle biopsy specimens from two brothers. A and B, Specimens from a 3-year-old boy. C, Specimen from his brother, 9 years of age. As seen in A, at a younger age fascicular muscle architecture is maintained, but myofibers show variation in size. Additionally, there is a cluster of basophilic regenerating myofibers (left side) and slight endomysial fibrosis, seen as focal pink-staining connective tissue between myofibers. In B, immunohistochemical staining shows a complete absence of membrane-associated dystrophin, seen as a brown stain in normal muscle (inset). In C, the biopsy from the older brother illustrates disease progression, which is marked by extensive variation in myofiber size, fatty replacement, and endomysial fibrosis.





Clinical Features

- Boys with DMD:
 - Normal at birth, and early motor milestones are met on time
 - first symptoms of DMD are clumsiness and an inability to keep up with peers due to muscle weakness
 - 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

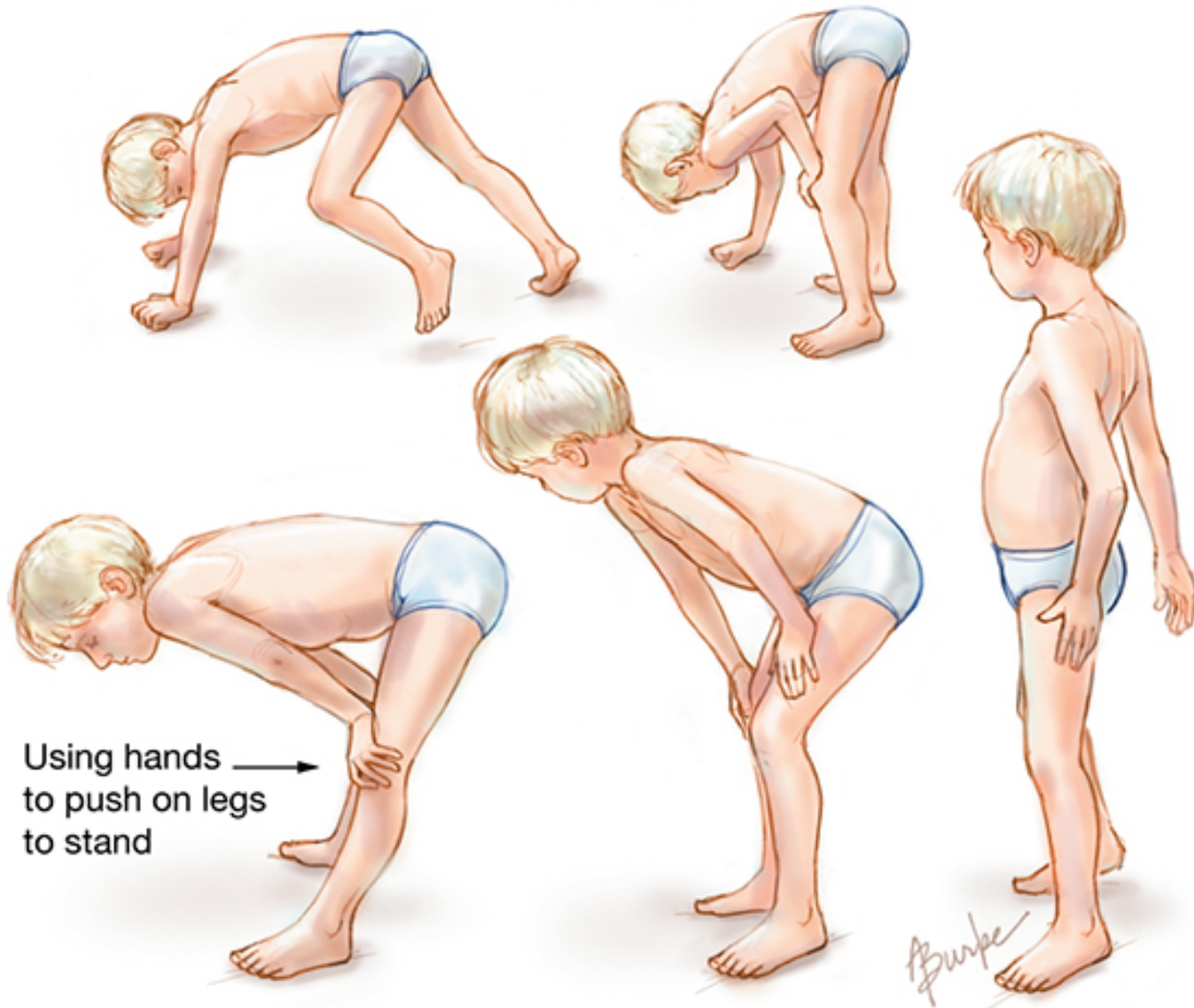
Clinical Features

- Cognitive impairment seems to be a component of the disease and is severe enough in some patients to be considered mental retardation
- Serum creatinine 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



Source: Richard P. Usatine, Mindy Ann Smith, Heidi S. Chumley, Camille Sabella, E.J. Mayeaux, Jr., Elumalai Appachi: *The Color Atlas of Pediatrics*:
www.accesspediatrics.com
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Gowers Sign



BMD

- BMD becomes symptomatic later in childhood or adolescence and progresses at a slower and more variable rate.
- Many patients live well into adulthood and have a nearly normal life span.
- Cardiac involvement can be the dominant clinical feature and may result in death in the absence of significant skeletal muscle weakness.

Myotonic Dystrophy

- ***Myotonia***, the sustained involuntary contraction of a group of muscles, is the cardinal symptom in this disease.
- Patients often complain of “stiffness” and have difficulty in releasing their grip, for instance, after a handshake.
- Myotonia can often be elicited by percussion of the thenar eminence.



On percussion of thenar muscles, the thumb moves sharply into opposition and adduction and slowly returns to initial position in individuals exhibiting a myotonic response.

Pathogeneis

- Mutations in the gene that encodes the dystrophia myotonica protein kinase (**DMPK**).
- In normal subjects, this gene contains fewer than 30 repeats of the sequence CTG, whereas in severely affected persons, several thousand repeats may be present.
- Myotonic dystrophy thus falls into the group of disorders associated with **trinucleotide repeat expansions**
- Myotonic dystrophy exhibits the phenomenon of *anticipation*, characterized by worsening of the disease manifestations with each passing generation due to further trinucleotide repeat expansion.

Morphology

- **Skeletal muscle may show variation in fiber size.**
- **Increase in the number of internal nuclei.**
- **Another well-recognized abnormality is the ring fiber**

Clinical Course.

- **The disease often presents in late childhood with abnormalities in gait**
- **weakness of the hand intrinsic muscles and wrist extensors.**
- **Atrophy of muscles of the face and ptosis .**
- **Cataracts**
- **Other associated abnormalities include frontal balding, gonadal atrophy, cardiomyopathy, smooth muscle involvement, decreased plasma IgG, and abnormal glucose tolerance.**
- **Dementia has been reported in some cases**

Inflammatory myopathies

1- Infectious

2 - Noninfectious inflammatory

Noninfectious Inflammatory Myopathies

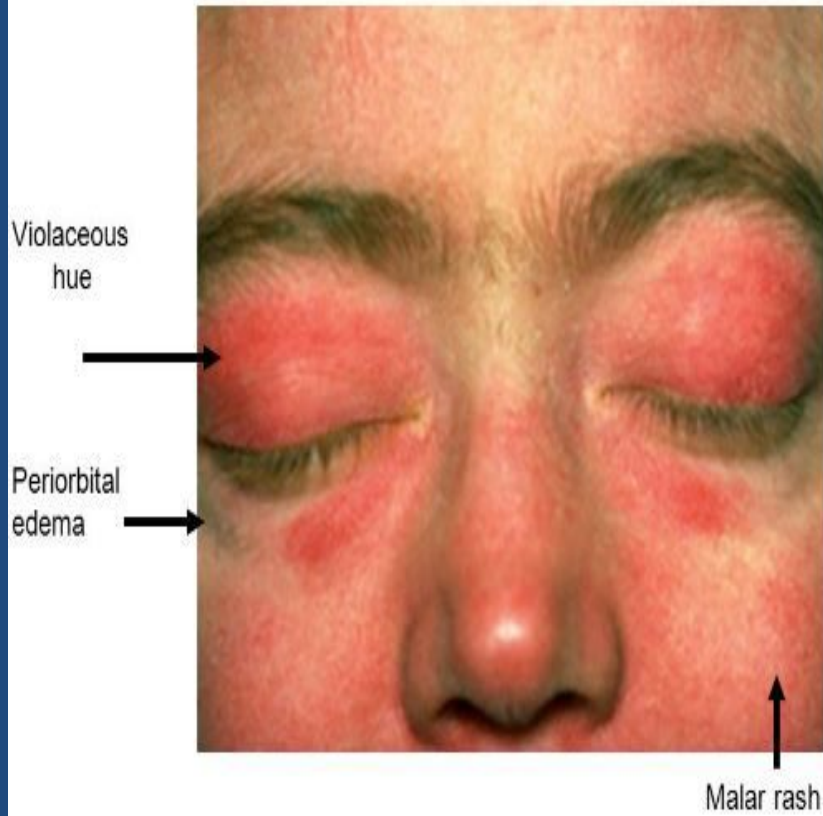
- Inflammatory myopathies make up a heterogeneous group of rare disorders characterized by immune-mediated muscle injury and inflammation

- Based on the clinical, morphologic, and immunologic features, three disorders:
 - *Polymyositis*
 - *Dermatomyositis*
 - *Inclusion body myositis*

Dermatomyositis

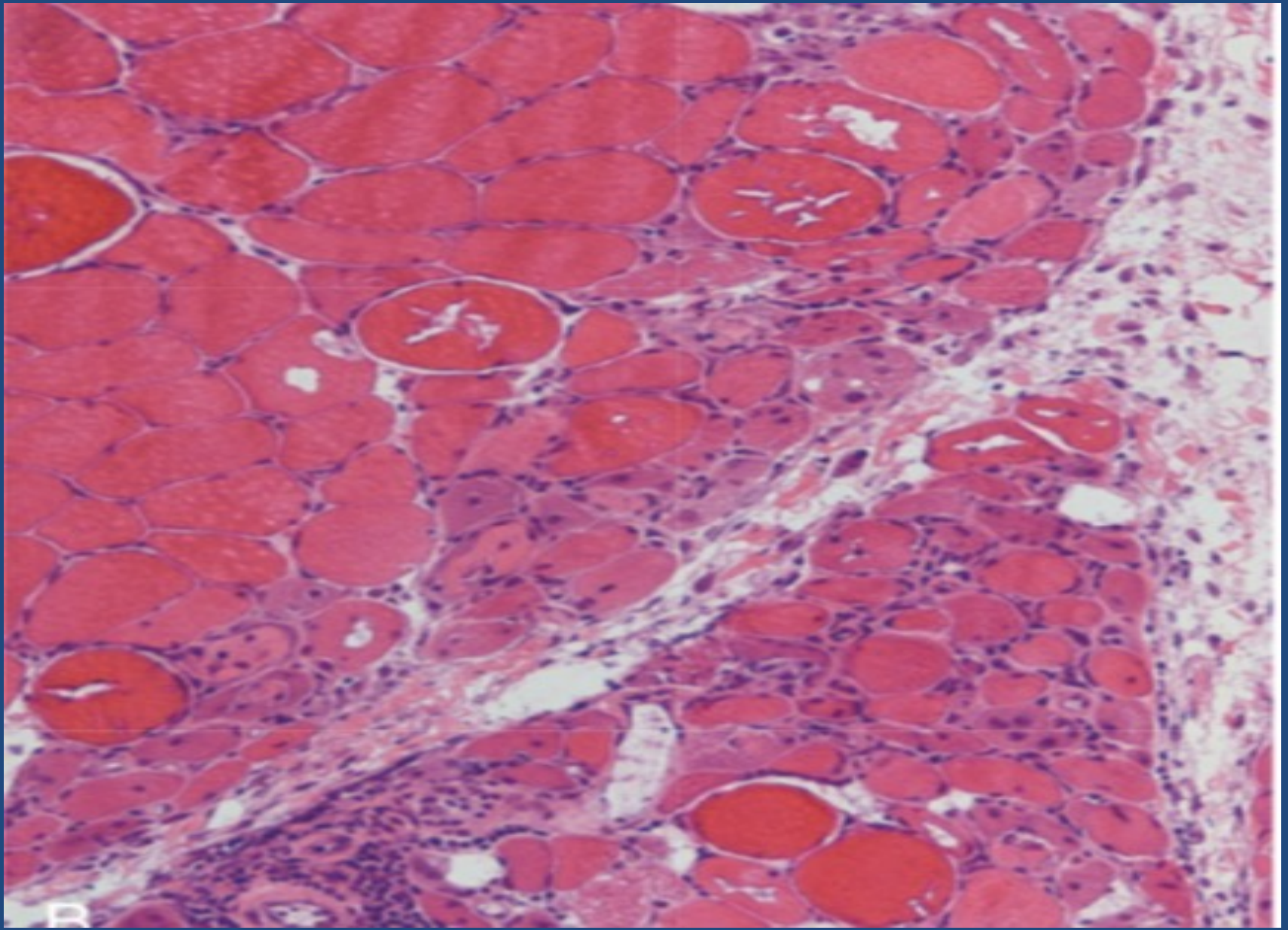
- inflammatory disorder of the skin as well as skeletal muscle.
- **skin rash** that may accompany or precede the onset of muscle disease. The *classic rash takes the form of ** a discoloration of the upper eyelids associated with periorbital edema ** scaling erythematous eruption over the knuckles(Gottron's lesions).*
- **Muscle weakness** is slow in onset, bilaterally symmetric
It typically affects the proximal muscles first. As a result, tasks such as getting up from a chair become increasingly difficult.
- Dysphagia
- Extramuscular manifestations, including interstitial lung disease, vasculitis, and myocarditis, may be present in some cases
- According to several studies, 20% to 25% of adults with dermatomyositis have cancer (paraneoplastic)

Heliotrope Rash

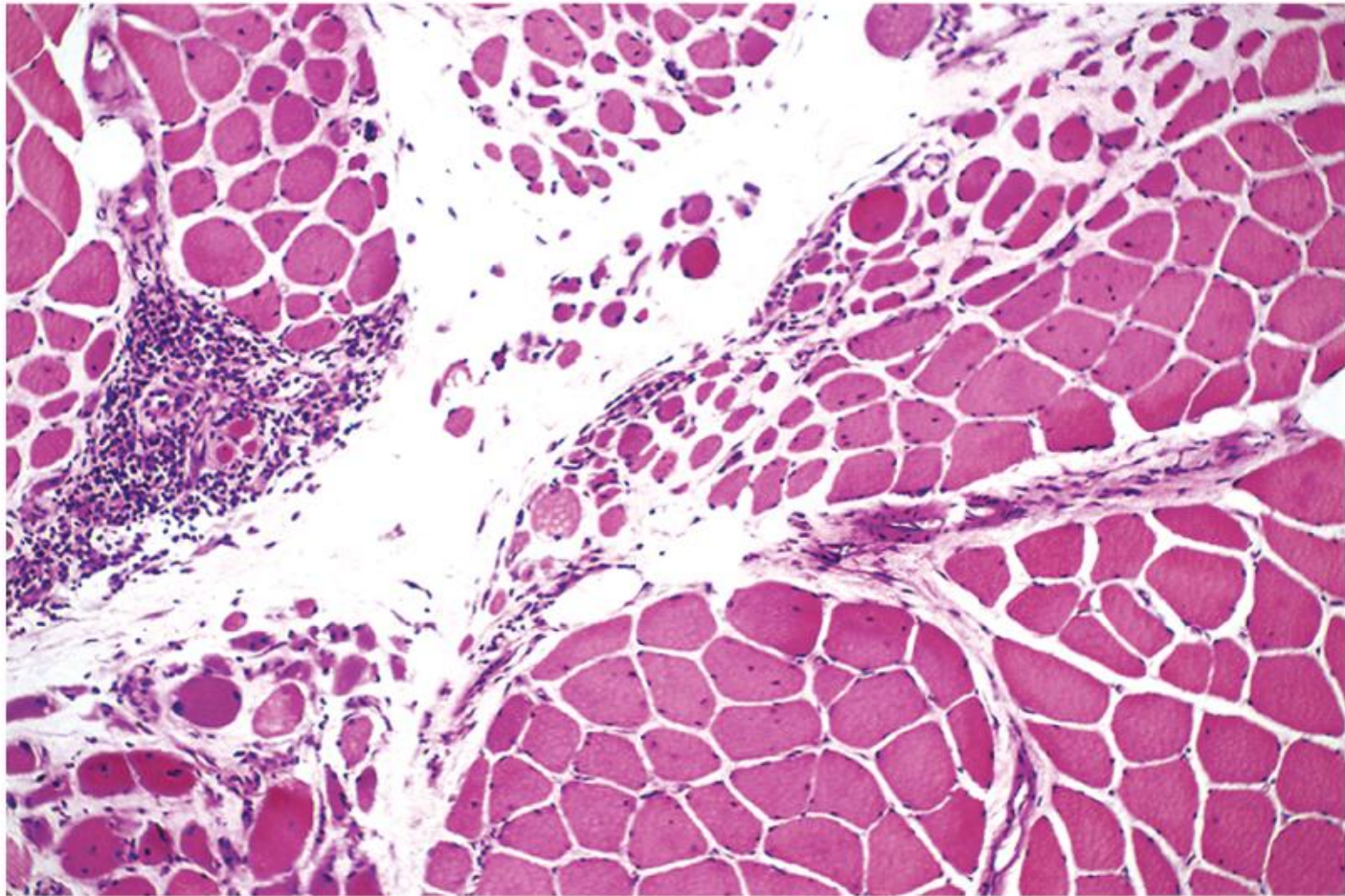


Morphology

- **Mononuclear inflammatory infiltrate** located predominantly around small blood vessels.
- Groups of atrophic fibers are particularly prominent at the periphery of fascicles. This “**perifascicular atrophy**” is sufficient for diagnosis, even if the inflammation is mild or absent.
- marked reduction in the intramuscular capillaries



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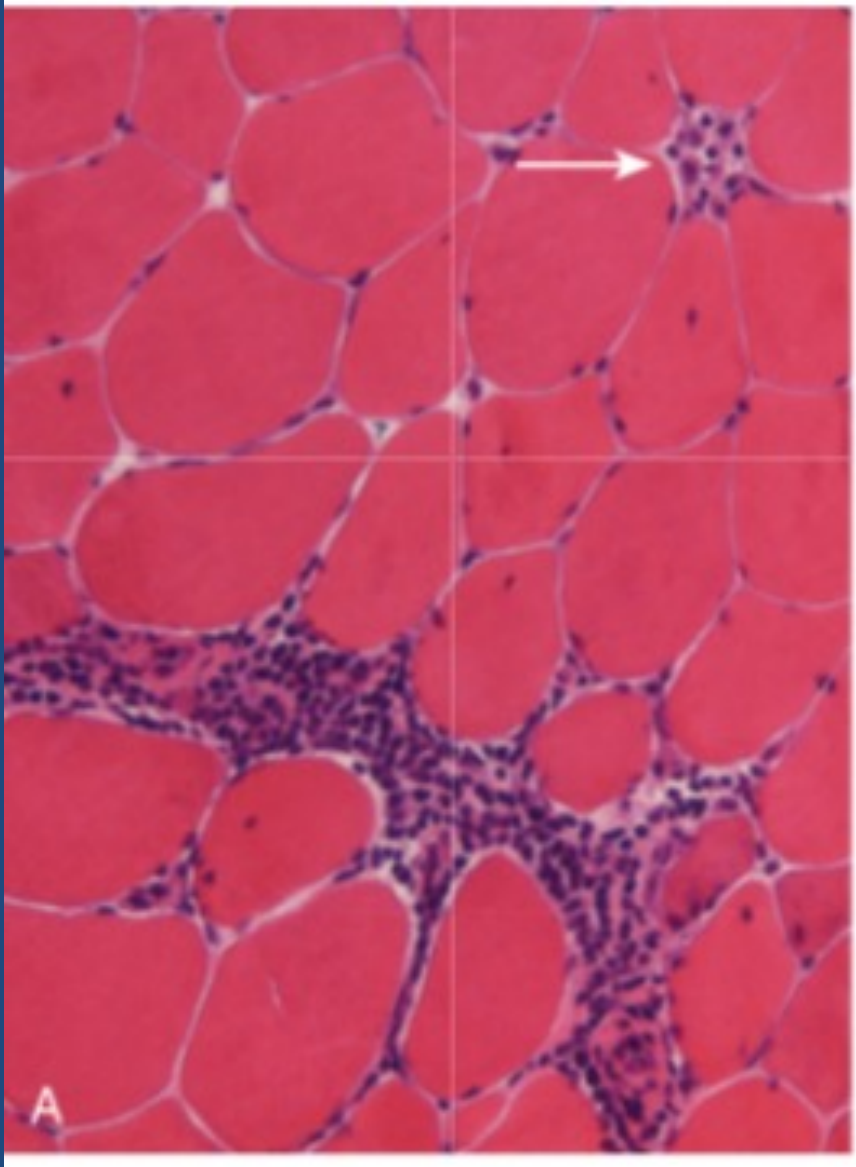
Figure 5-28 Dermatomyositis. Perifascicular inflammation and atrophy in a skeletal muscle. (Courtesy of Dr. Dennis Burns, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Polymyositis.

- This inflammatory myopathy is characterized by symmetric proximal muscle involvement, similar to that seen in dermatomyositis.
- *It differs from dermatomyositis by the lack of cutaneous involvement and its occurrence mainly in adults.*
- Similar to dermatomyositis, there may be inflammatory involvement of heart, lungs, and blood vessels.

Morphology

- lymphocytes surround and invade healthy muscle fibers.
- Both necrotic and regenerating muscle fibers are scattered throughout the fascicle, without the perifascicular atrophy seen in dermatomyositis.
- There is no evidence of vascular injury in polymyositis.



Inclusion body myositis

- the most common inflammatory myopathy in patients older than 60 years of age.
- The morphologic hallmark of inclusion body myositis is the presence of rimmed vacuoles that contain aggregates of the same proteins that accumulate in the brains of patients with neurodegenerative **diseases—hyperphosphorylated tau, amyloid derived from β -amyloid precursor protein, and TDP-43**—leading some to speculate that this is a degenerative disorder of aging.
- Other features typical of chronic inflammatory myopathies, including myopathic changes, mononuclear cell infiltrates, endomysial fibrosis, and fatty replacement, also are evident.
- The disease follows a chronic, progressive course and generally does not respond well to immunosuppressive agents.

) Inclusion body myositis, showing myofibers containing rimmed vacuoles (arrows). Modified Gomori trichrome stain.

