Introduction to Myopathies and Muscular Dystrophy

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OBJECTIVES

1)
-Histology
- Muscle fibers:
Type I
Type II

2) Causes of muscle atrophy…

3) Inherited disorders of skeletal muscle

3) Muscle Dystrophy

Duchenne muscle dystrophy (DMD)

Becker muscle dystrophy (BMD)

4) Myotonic dystrophy

4) Acquired disorders of skeletal muscle

5) Inflammatory myopathy

Infectious

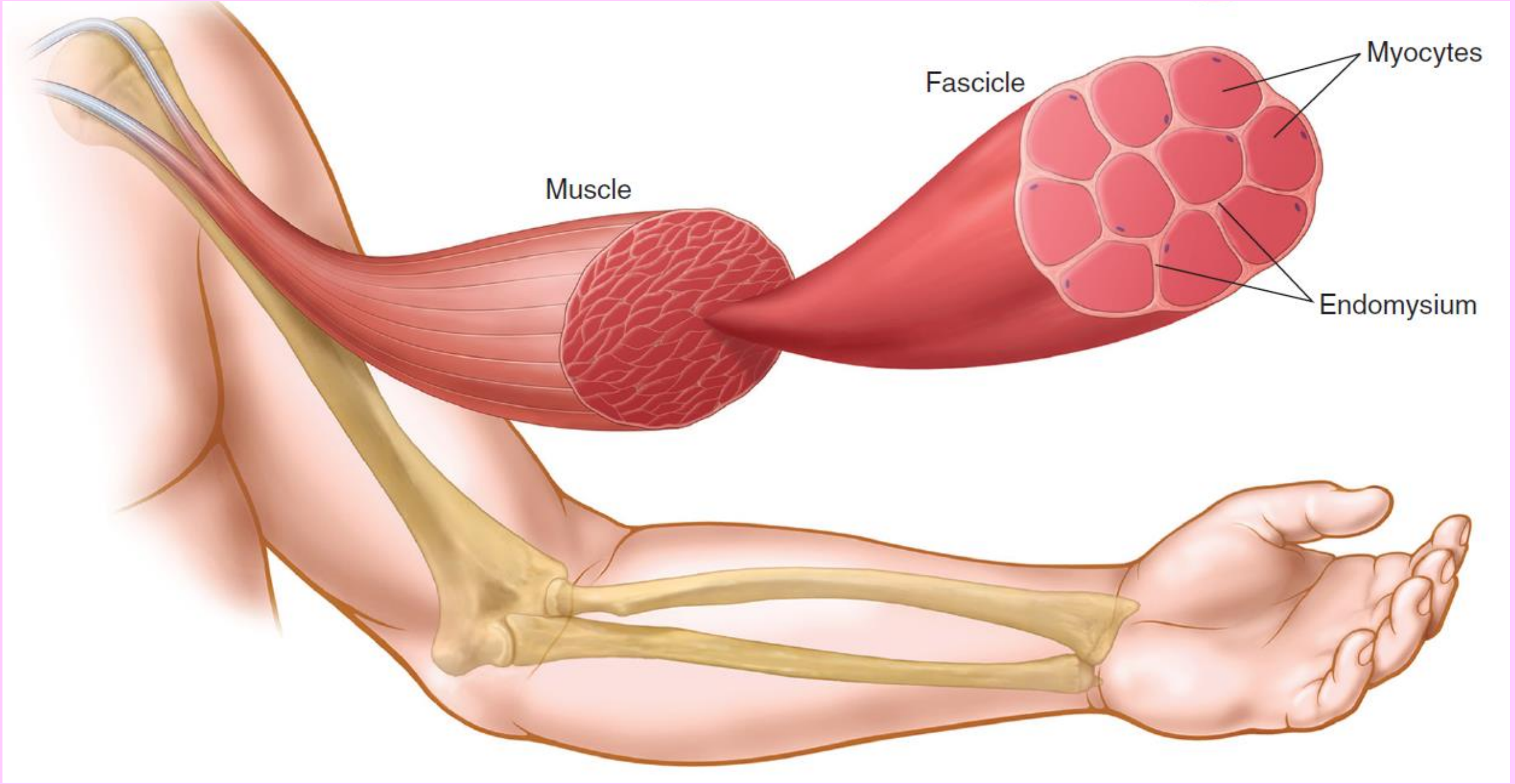
Non-infectious (immune)

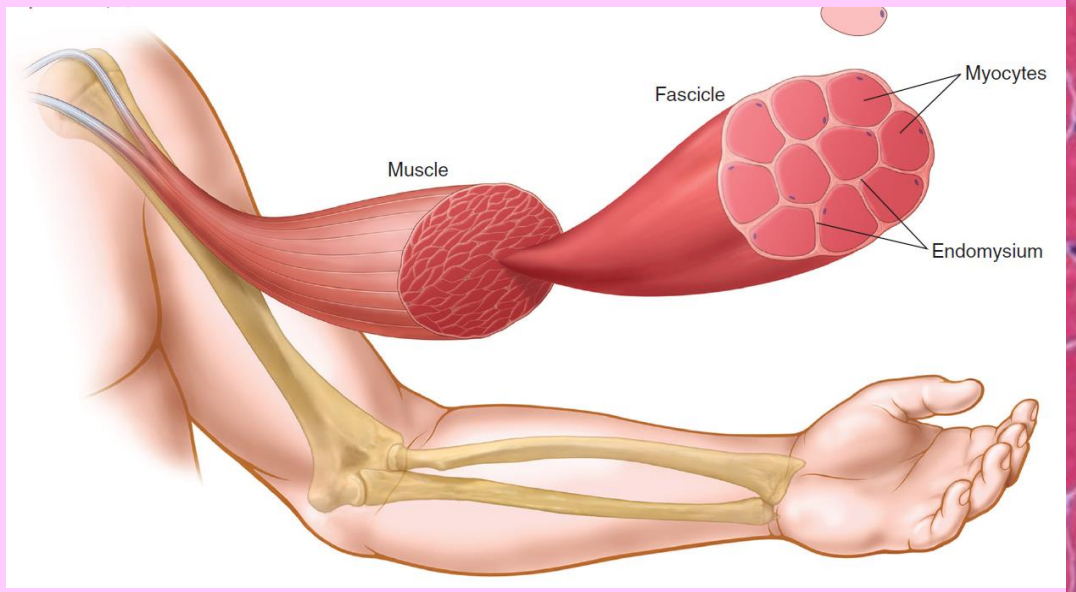
dermatomyositis

polymyositis

Inclusion body myositis

1) Histology and muscle fiber types


Myocytes
Fascicle
Muscle
Endomysium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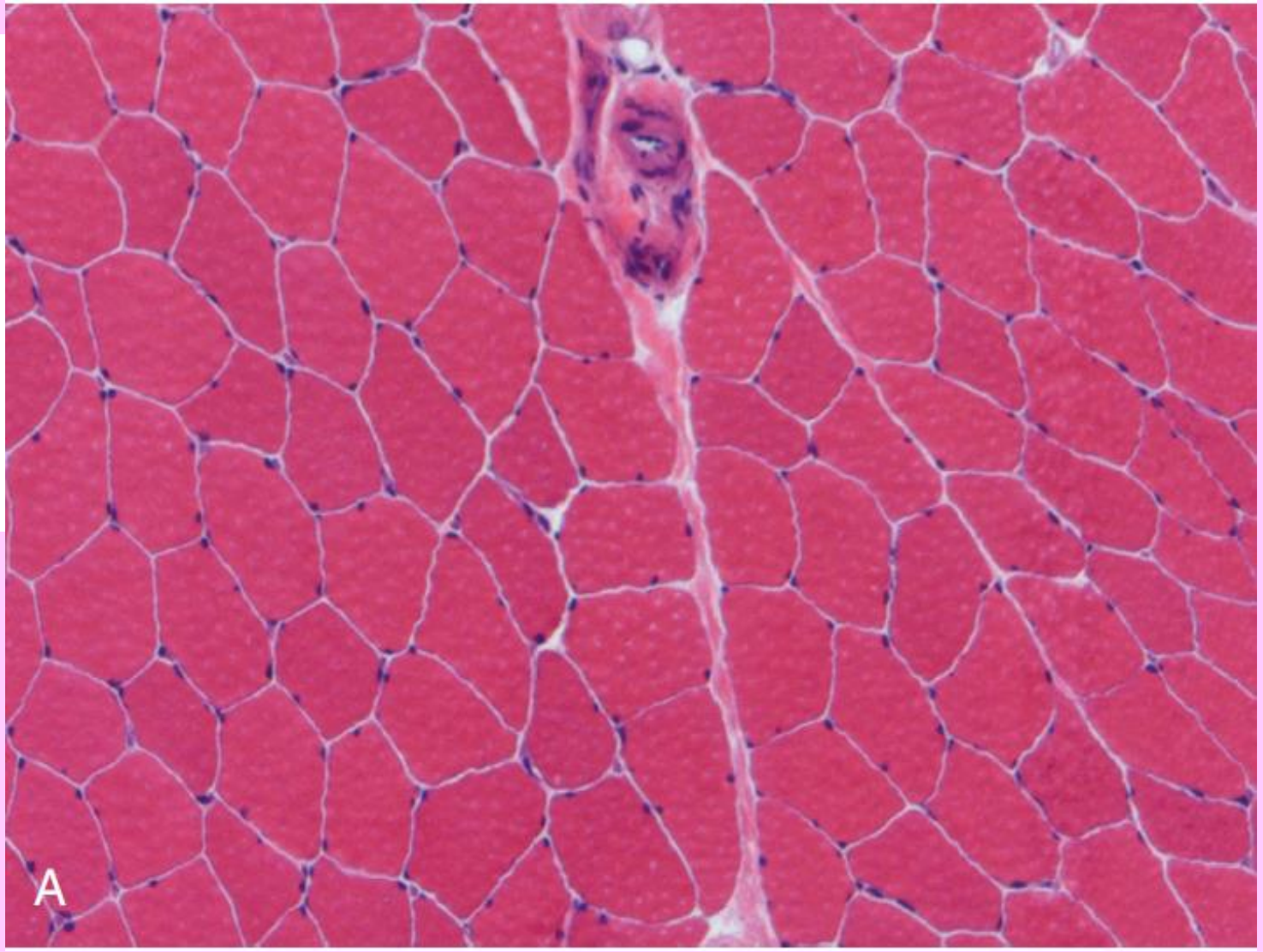
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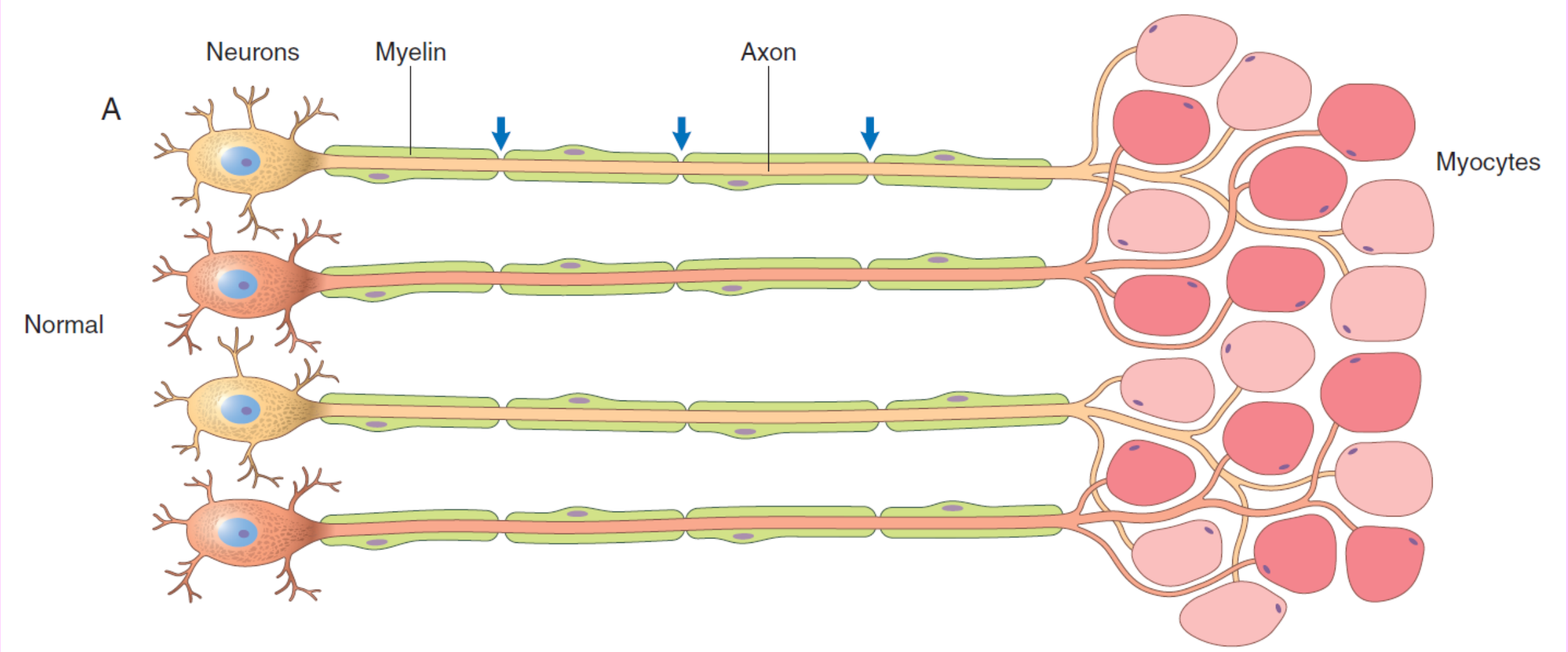
Normal motor unit:

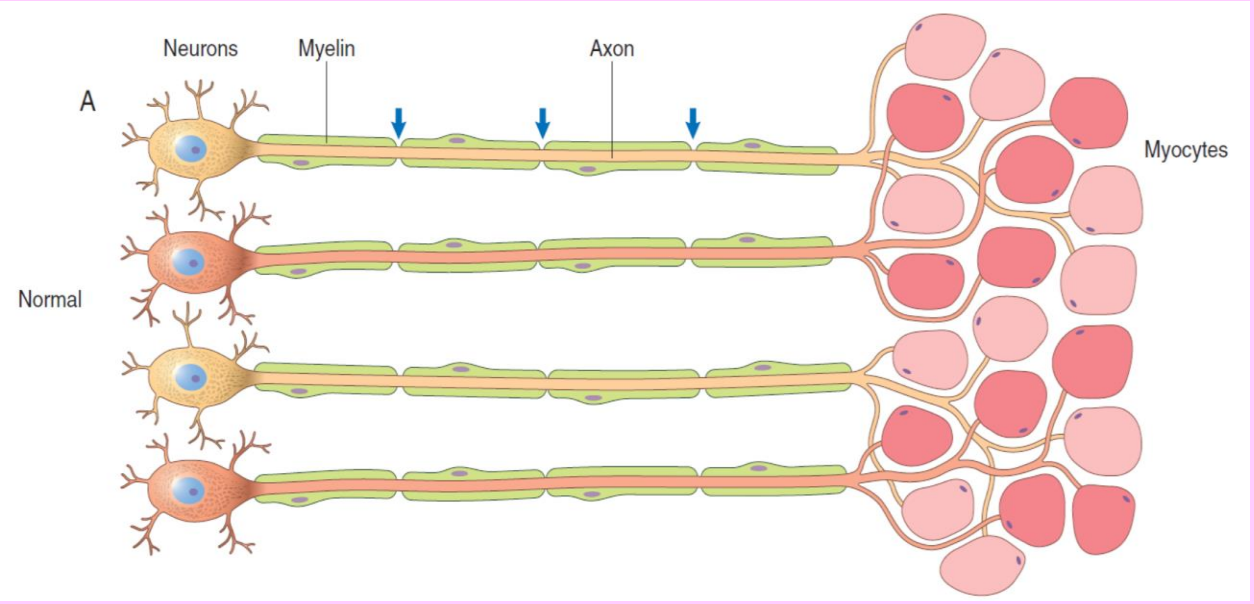


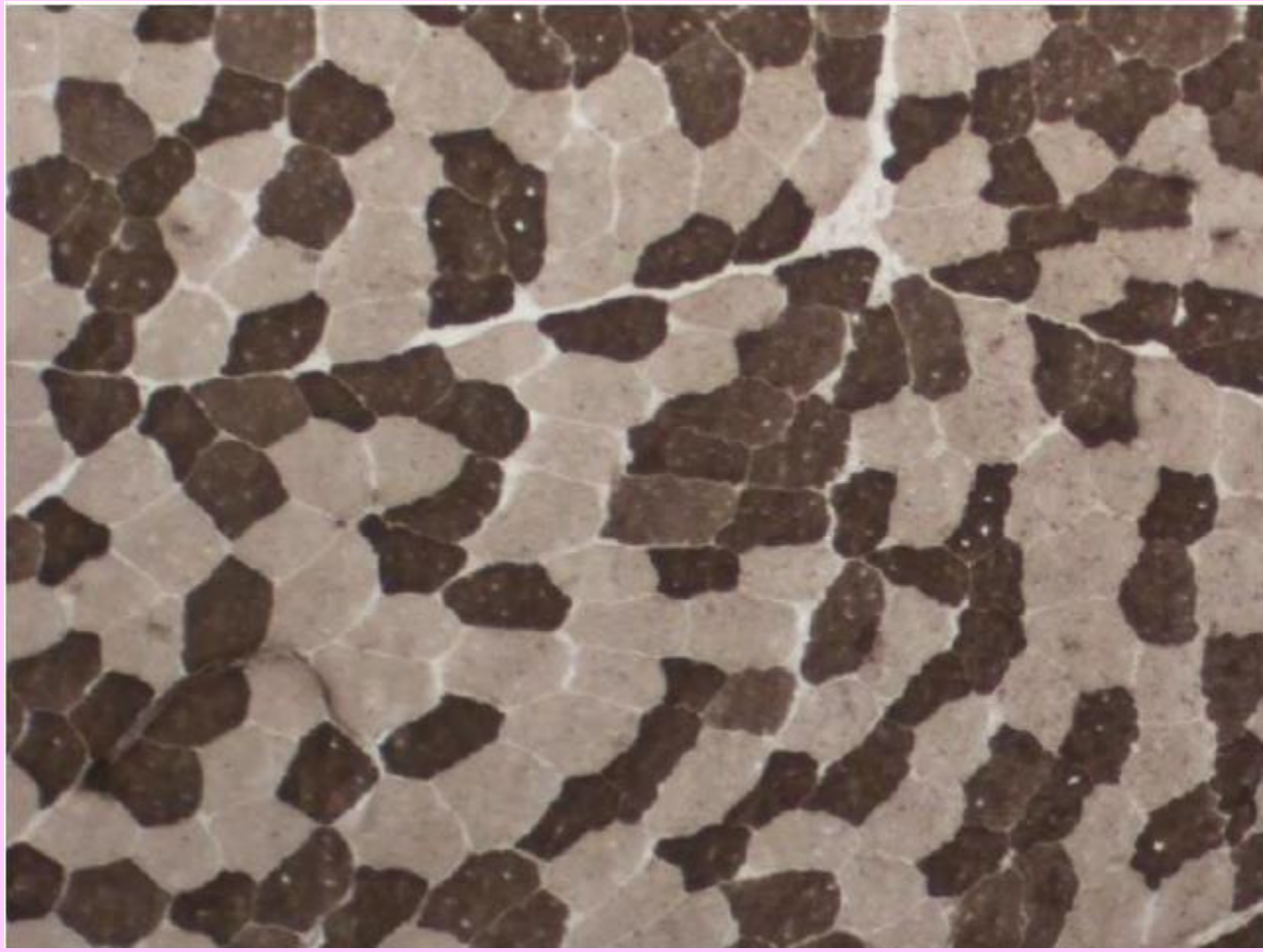
Muscle fiber types:

Table 22.2 Muscle Fiber Types

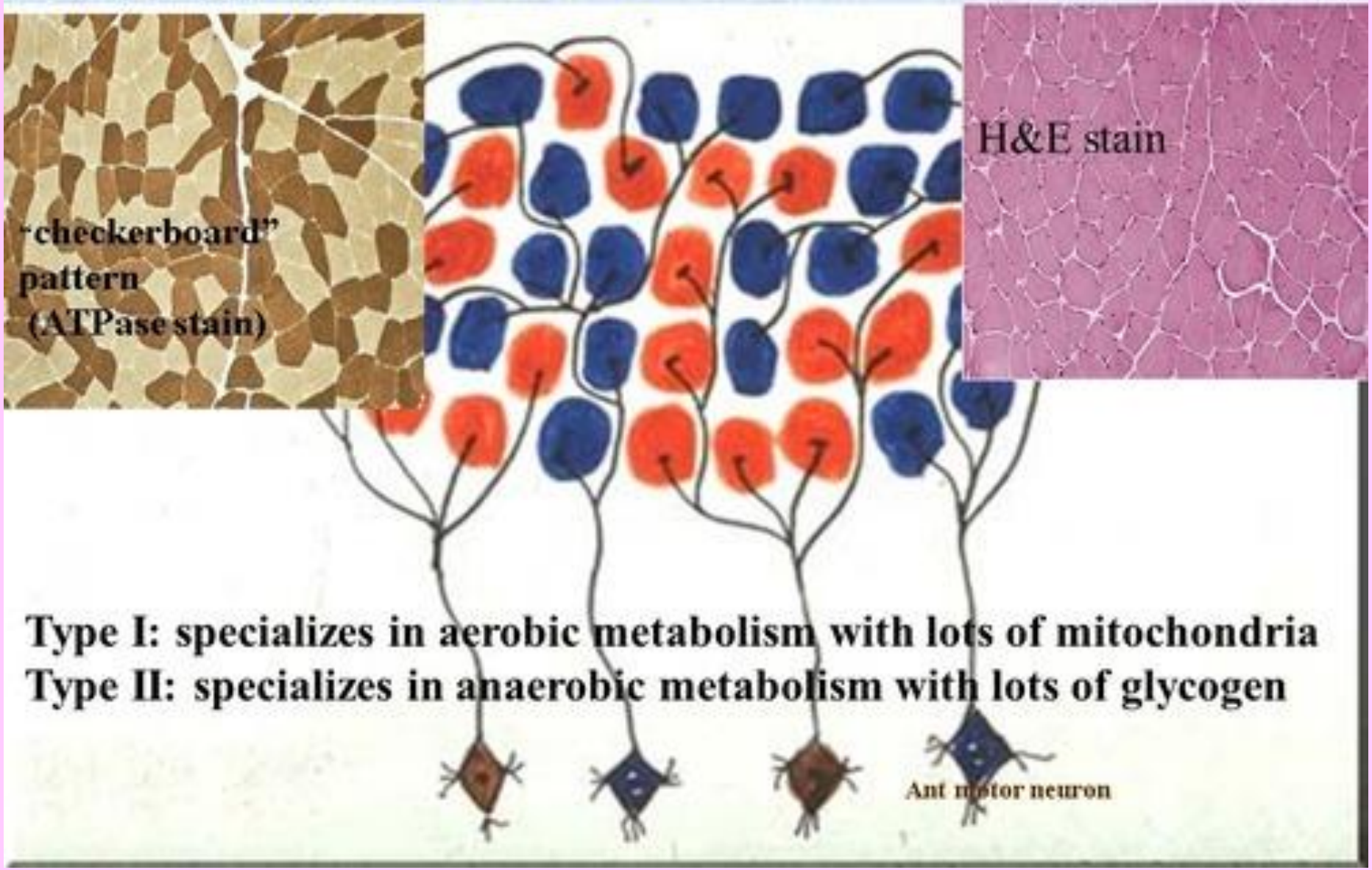
	Type I	Type II
Action	Sustained force	Fast movement
Activity type	Aerobic exercise	Anaerobic exercise
Power produced	Low	High
Resistance to fatigue	High	Low
Lipid content	High	Low
Glycogen content	Low	High
Energy metabolism	Low glycolytic capacity, high oxidative capacity	High glycolytic capacity, low oxidative capacity
Mitochondrial density	High	Low
Myosin heavy chain gene expressed	*MYH7*	*MYH2*, *MYH4*, *MYH1*
Color	Red (high myoglobin content)	Pale red / tan (low myoglobin content)

Normally the fibers of different types are distributed in checkerboard patterns (ATPase stain)



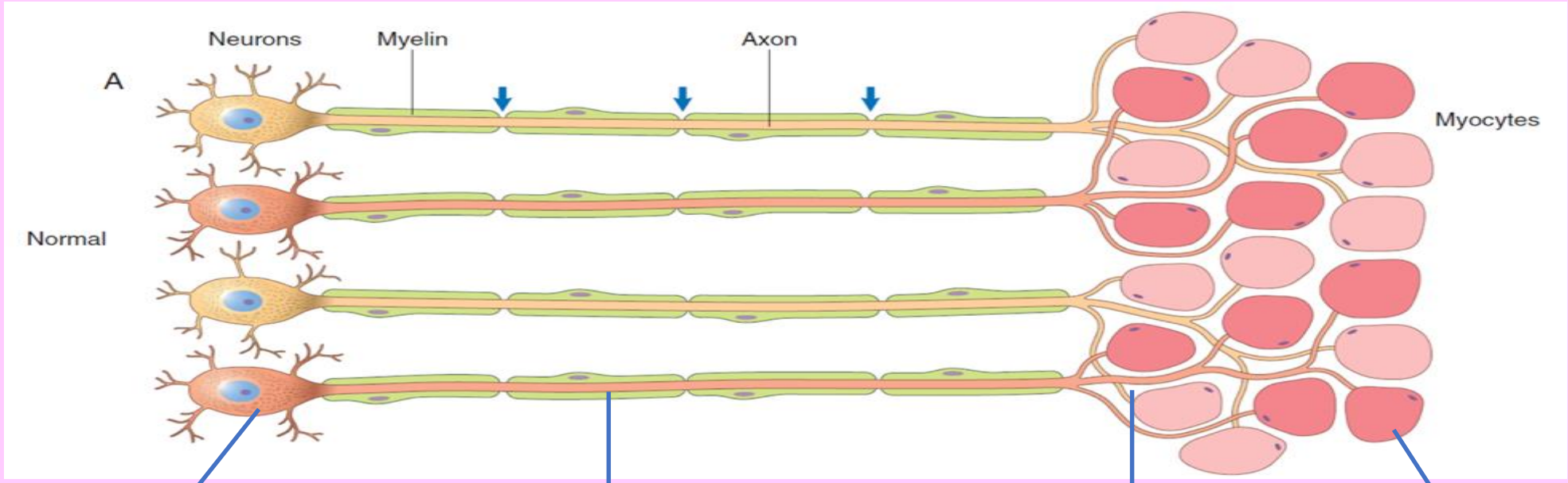


Neuronal trophic effects of each motor neuron determines the muscle fiber type: I or II



2) Myopathy and muscle atrophy

Diseases affecting skeletal muscles..



Lower motor neuron

axon

NM junction

Muscle (enzymes and proteins) MYOPATHY

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

Causes of muscle atrophy

1) Myopathy

2) Neuropathy

3) Prolonged disuse of muscle:

- Prolonged bedrest in the sick.
- Casting of a broken bone.

- Affect type II fibers more than type I.

4) Glucocorticoid exposure (hypercortisolism):

1) exogenous.
2) Endogenous (?? Syndrome).

- Affect proximal muscles and type II fibers.

1) PRIMARY MUSCLE DISEASE (MYOPATHY)

- **Altered muscle function and morphology.**
- Segmental necrosis and regeneration of individual muscle fibers.
- Inflammatory infiltrate.
- Intracellular inclusions.
- **Endomysial fibrosis and fatty replacemeny (chronic)**

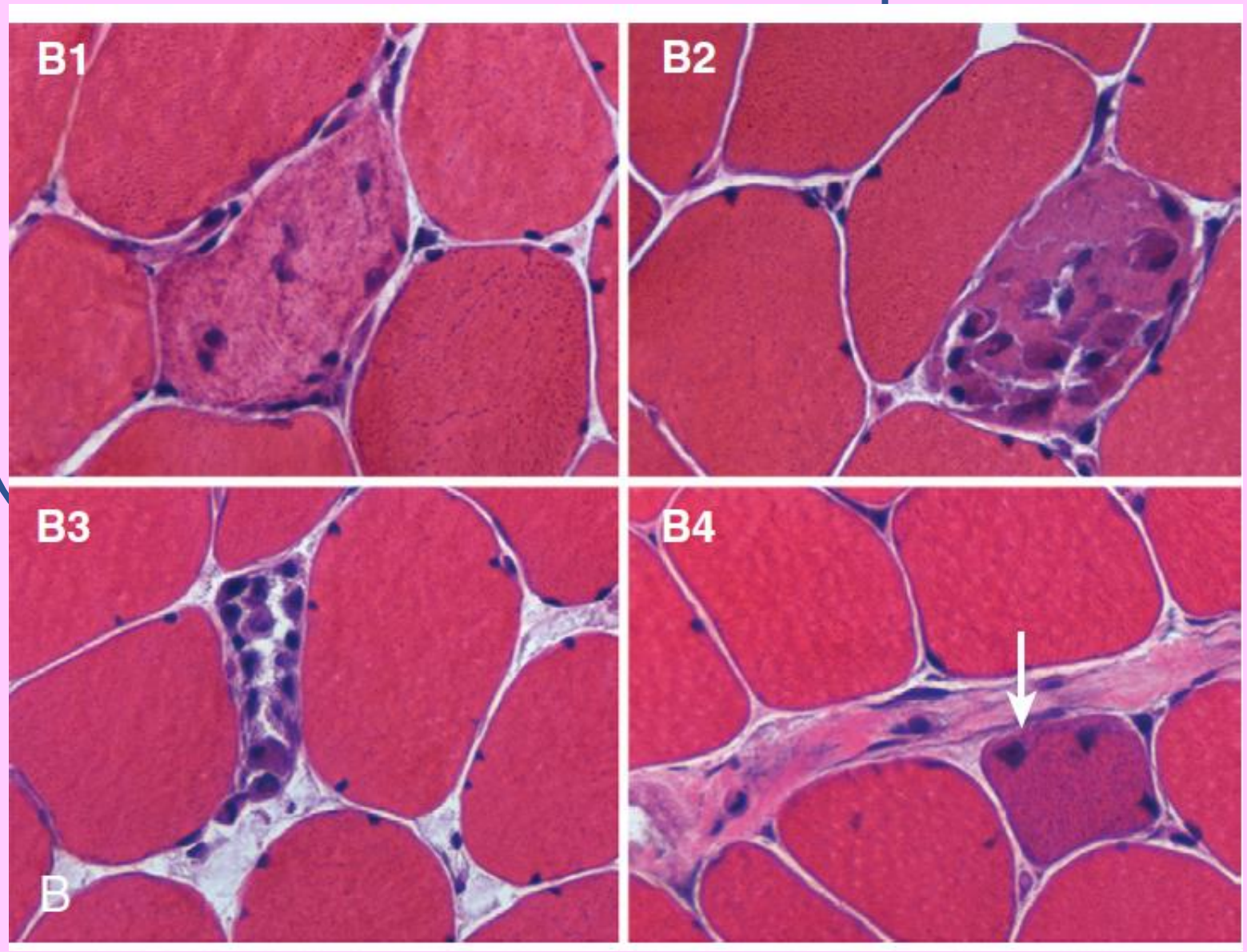
2) NEUROPATHIC CHANGES:

- Altered muscle function and morphology.

1) Group atrophy.
2) Fiber type grouping.

- Endomysial fibrosis and fatty replacement (chronic).

PRIMARY MUSCLE DISEASE (MYOPATHY)



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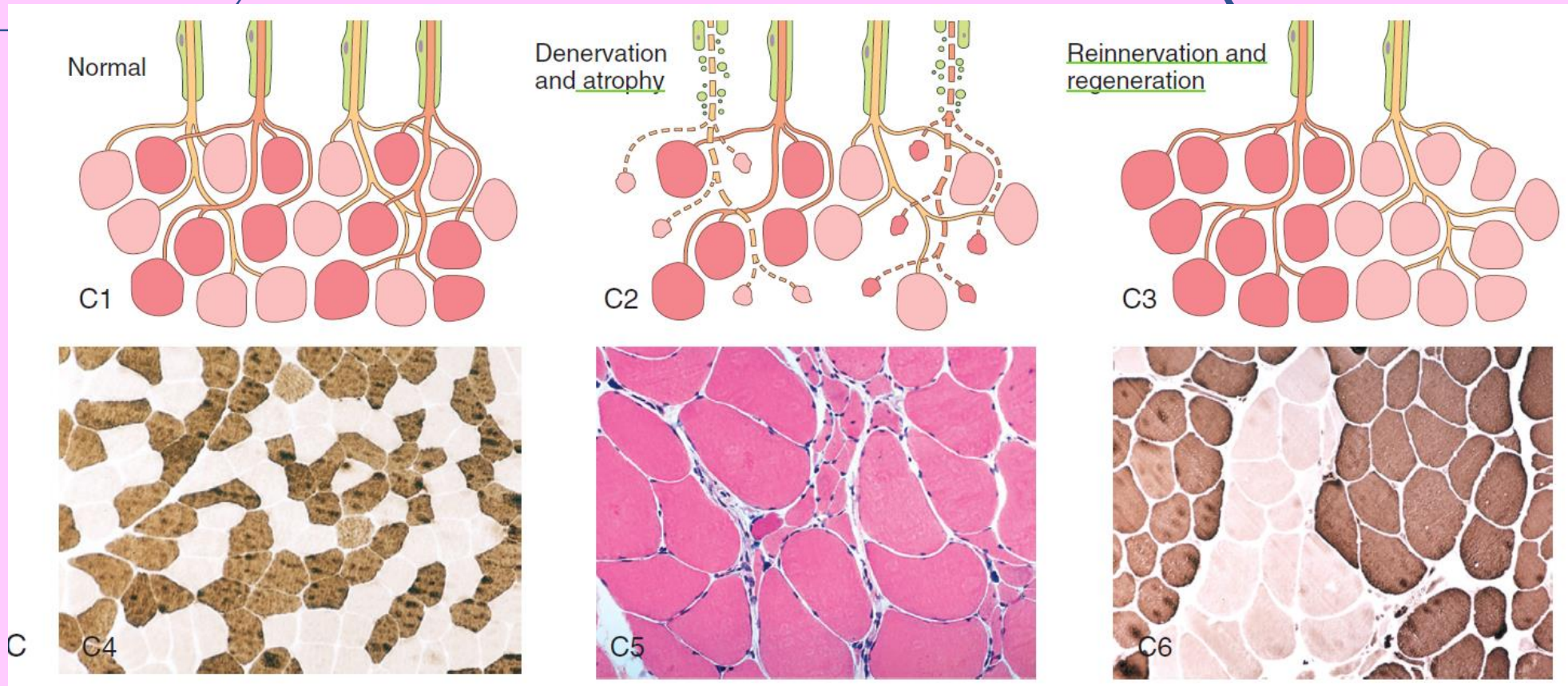


3) Inherited disorders of skeletal muscles..

- Diverse collection of disorders.
- Skeletal muscle, heart, nerves…
- Different classification systems.

OBJECTIVES

Dystrophinopathies (Dystrophin gene)

3) Inherited disorders of skeletal muscle

3) Muscle Dystrophy

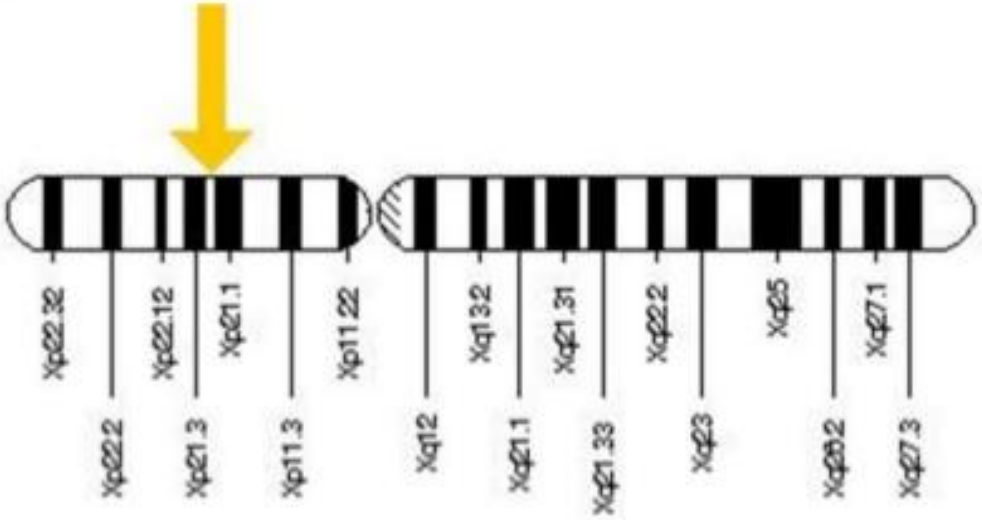
Duchenne muscle dystrophy (DMD)

Becker muscle dystrophy (BMD)

4) Myotonic dystrophy

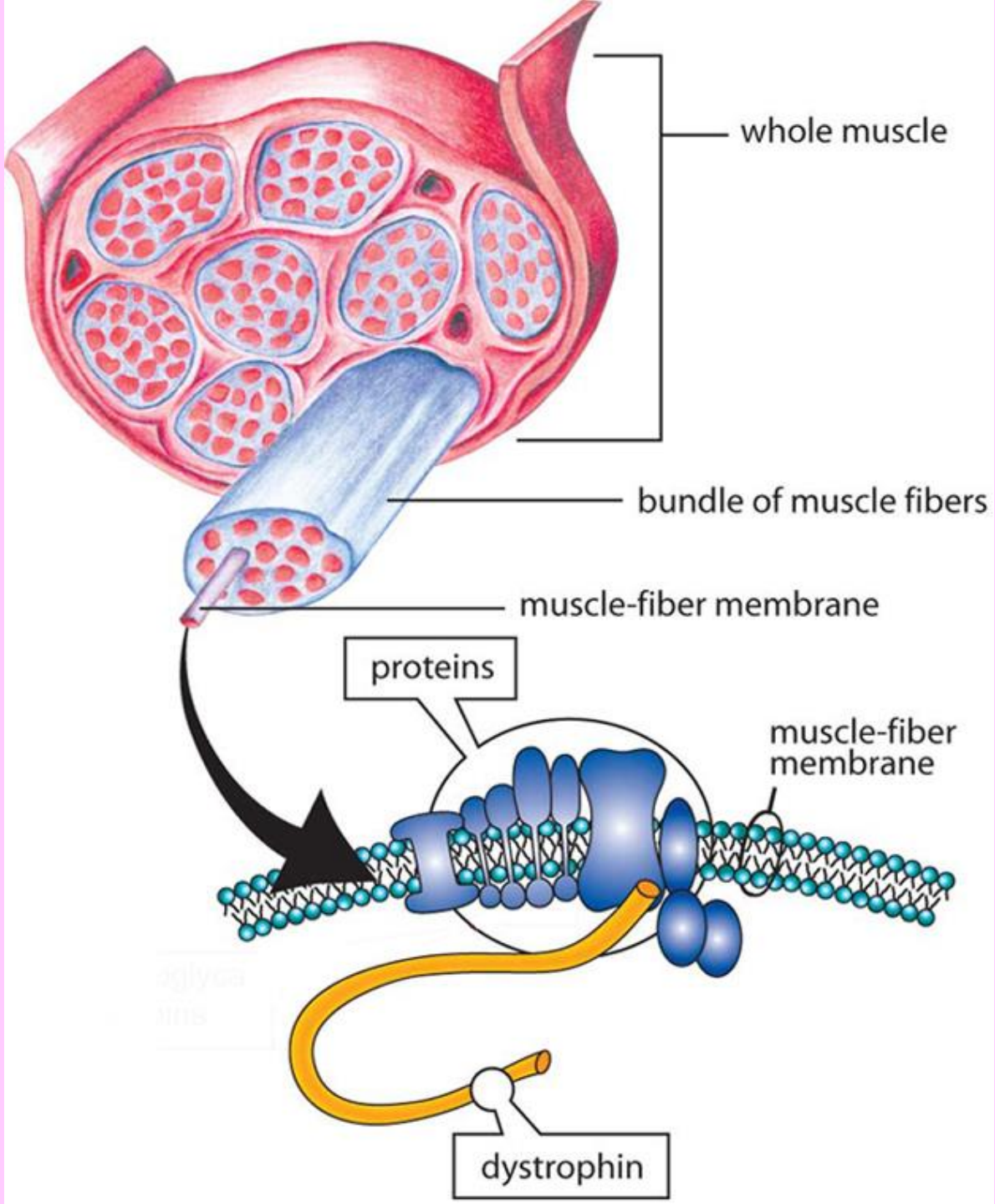
Dystrophin Gene

- The largest known human gene (vulnerable to mutation)
- Provides instructions for making a protein called ***Dystrophin.***
- **LOCATION:**
  - (i) Short (p) arm of the X chromosome at position 21.2. (Xp21.2)
  - (ii) Primarily in muscles used for movement (skeletal muscles) and in heart (cardiac) muscle. Small amounts of dystrophin are present in nerve cells in the brain.



Function

- Part of dystrphin-glycoprotein complex.
- Stabilizes muscle during contraction.
- Defect..Muscle cells vulnerable to transient membrane tears during contraction that lead to calcium influx.. Degeneration outpacing repair.
- Cardiac myopathy.

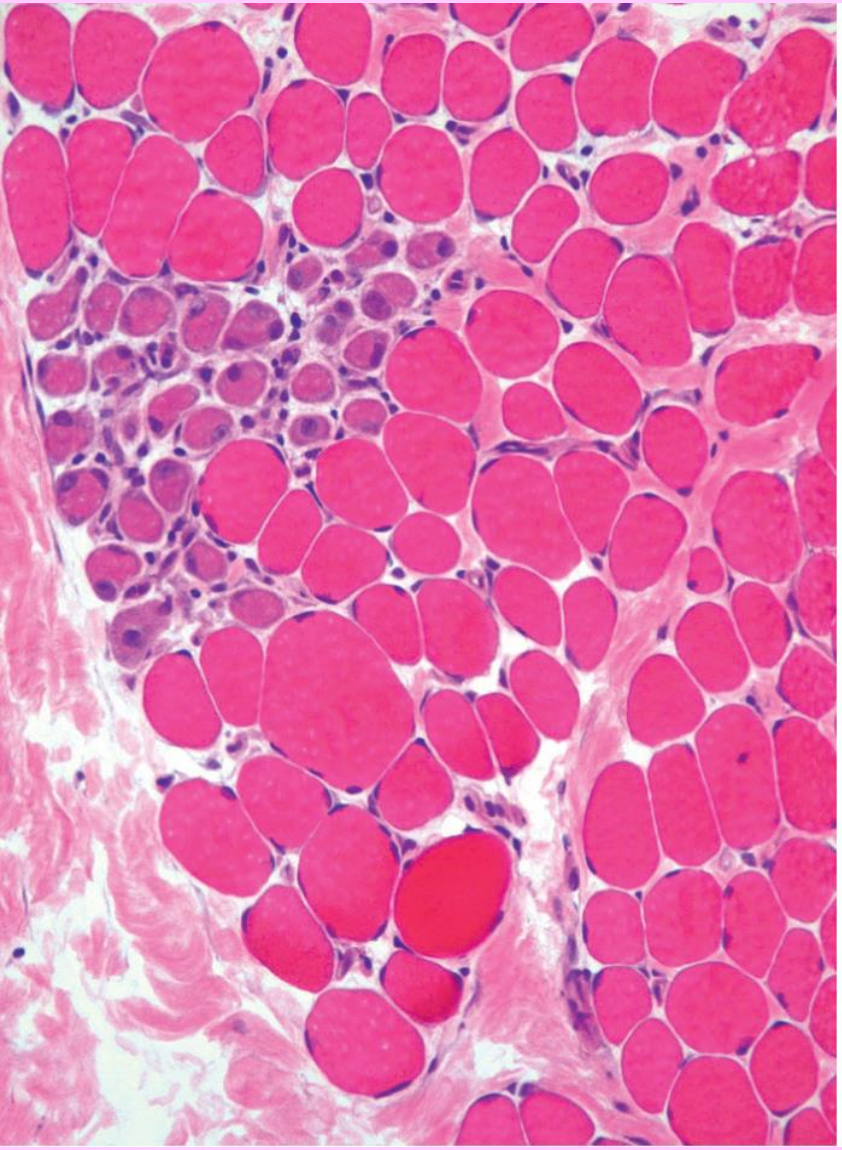


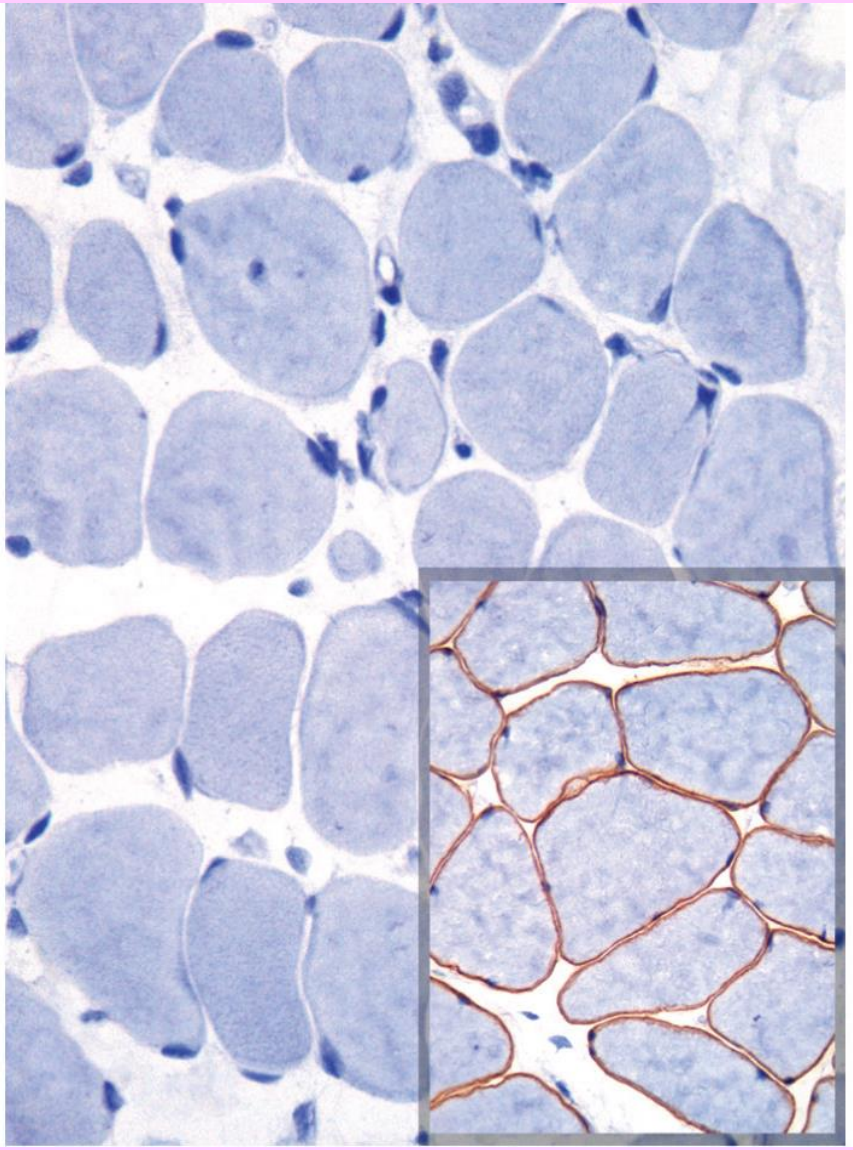
DMD

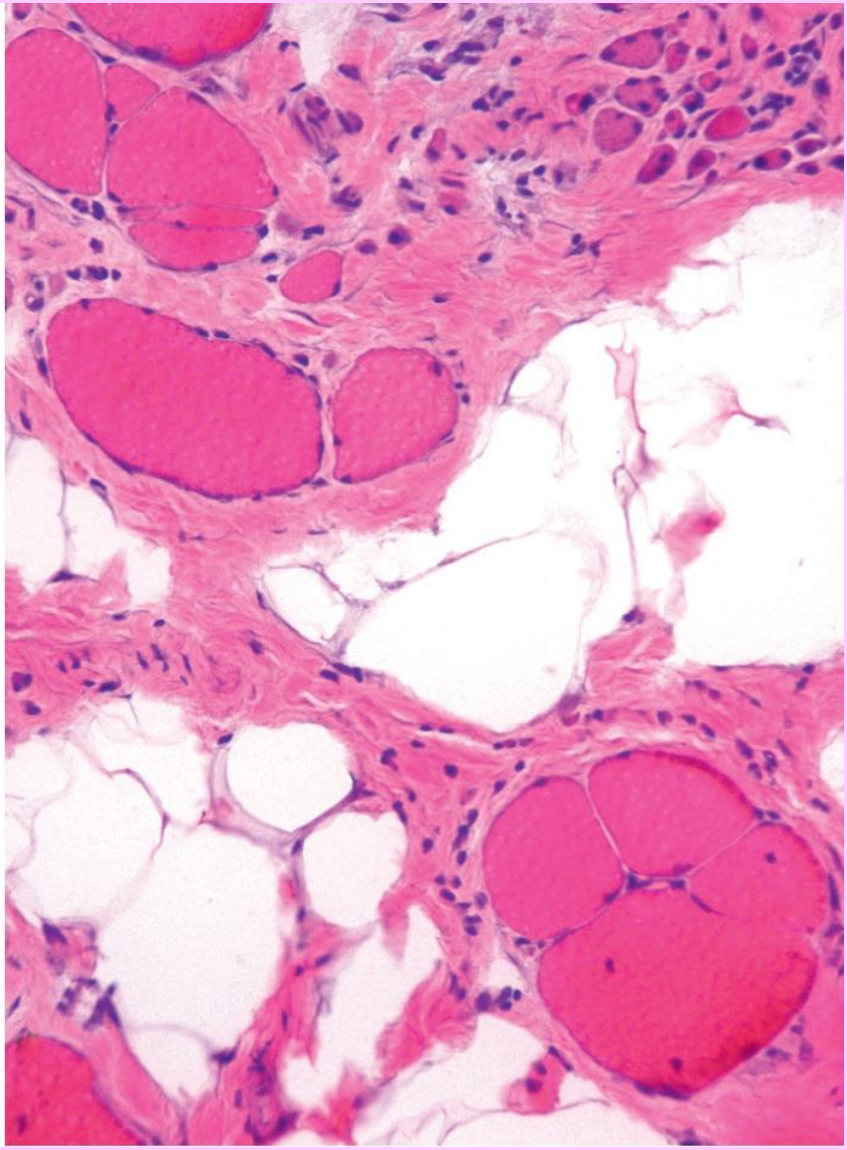
- Incidence: 1 per 3500 live **male** births.
- Invariably fatal course.
- Early childhood (clumsiness).
- Wheelchair-bound: teenagers
- DOD: early adulthood.

DMD and BMD…morphology

- Ongoing myofiber necrosis and regeneration.
- Variation in myofiber size and abnormal internally placed nuclei.
- Progressive replacement of muscle tissue by fibrosis and fat is the result of degeneration outpacing repair.
- Cardiac muscle: myocyte hypertrophy and interstitial fibrosis.







DMD.. Clinical features

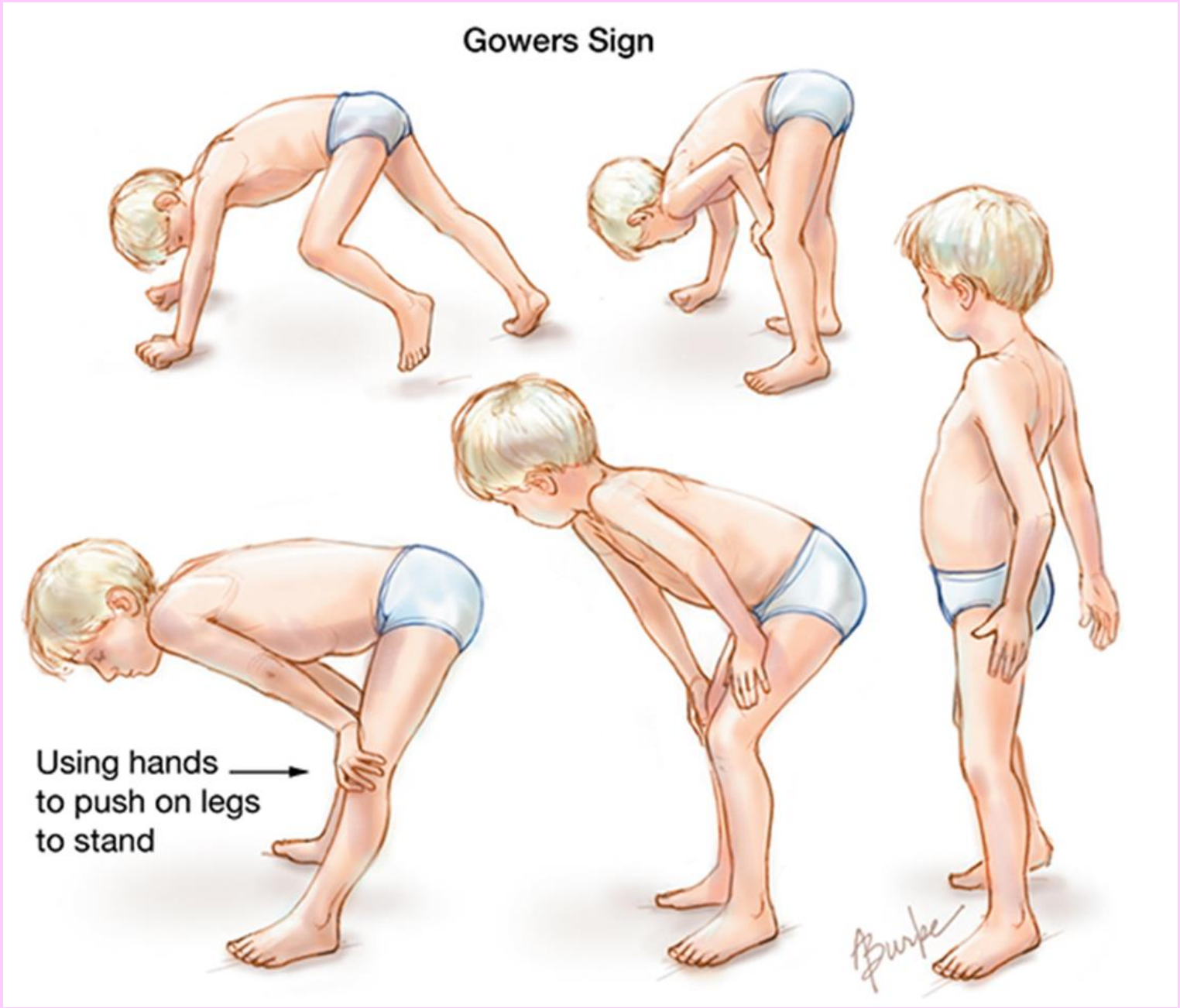
- Early: Clumsiness
- Muscle weakness first in pelvic girdle then shoulder girdle.
- Early: Enlargement of calves (pseudohypertrophy): myofiber hypertrophy..progressive degeneration (high serum creatinine kinase).. fatty replacement and endomysial fibrosis.
- Cardiac muscle: arrhythmia and heart failure (dilated cardiomyopathy).
- CNS: cognitive impairment.. Mental retardation.
- High serum creatinine kinase at birth (as ongoing muscle degeneration) till first decade of life (when muscle mass is lost).
- **DEATH:** respiratory insufficiency, pneumonia, and cardiac decompensation.

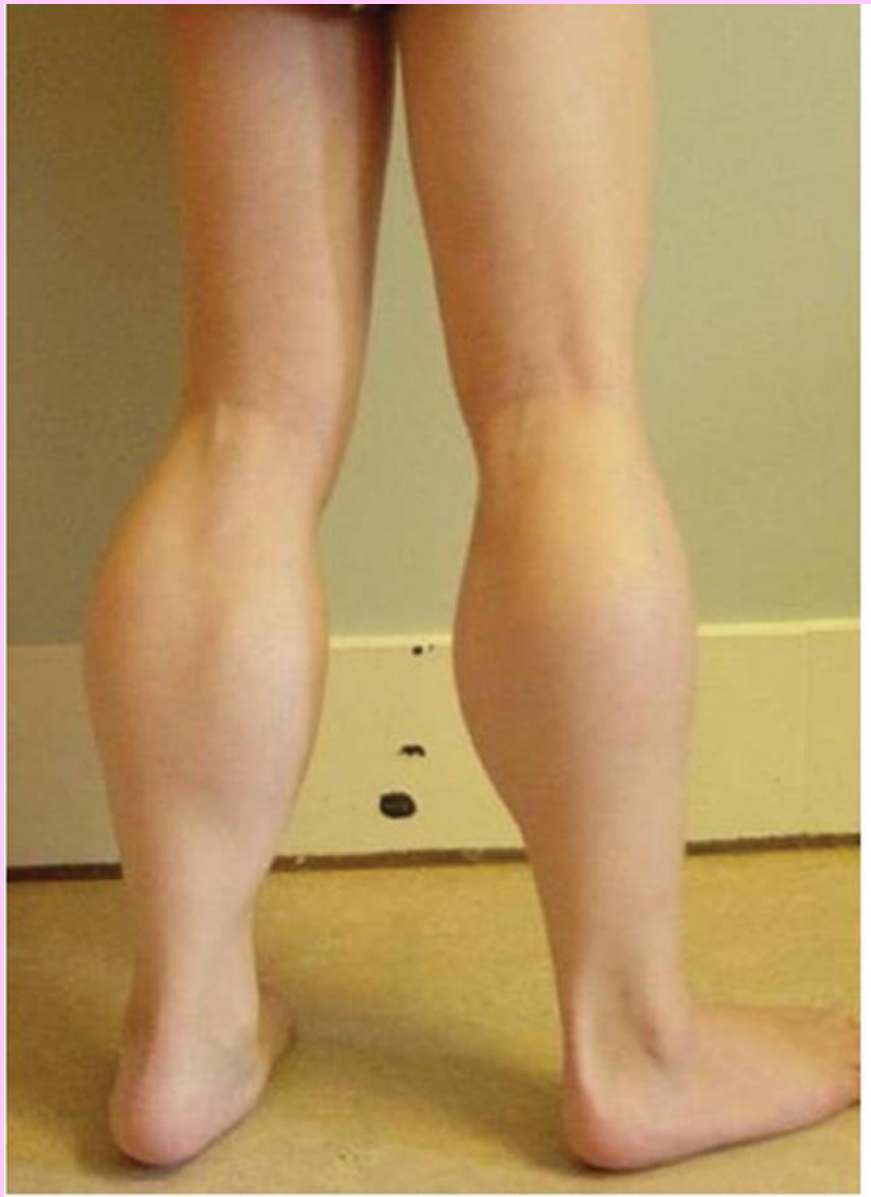
BMD... Clinical features

- Symptoms.. Later in childhood or early adulthood.
- Progress at slower and more variable rate.
- Many patients live well with normal life span.
- Cardiac involvement may be the dominant feature.. And result in death even in absence of significant skeletal muscle weakness.

TREATMENT of dystrphinopathies

- Challenging
- No cure
- Supportive care
- Definitive therapy: restoration of dystrophin level (trials of gene therapy)





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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3) Inherited disorders of skeletal muscle

3) Muscle Dystrophy

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4) Myotonic dystrophy

Myotonic Dystrophy

- Myotonia:

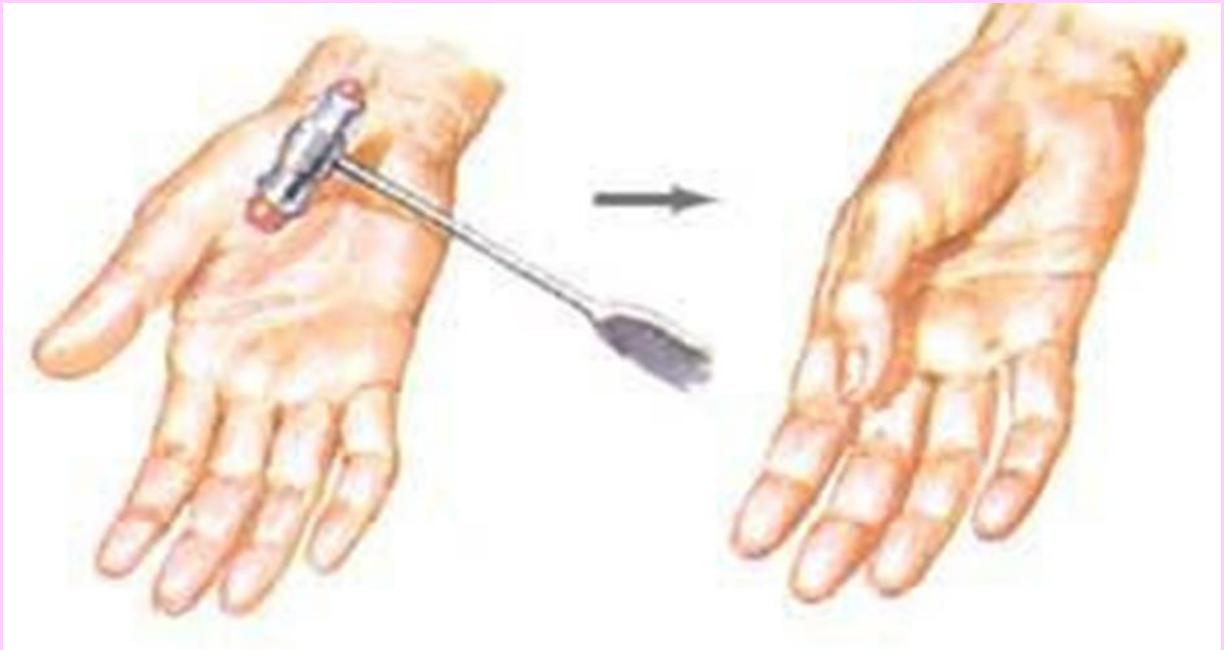
The sustained involuntary contraction of a group of muscles.

- Stiffness and difficulty in relaxing their grip (e.g. after a handshake).

Clinical features

- The disease often presents in late childhood with abnormalities in gait (weakness in foot dorsiflexors).
- 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

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.

Pathogenesis

- Nucleotide repeat expansion disease (anticipation).
- Autosomal dominant.
- More than 95%..mutation in the gene encoding dystrophia myotonica protein kinase (DMPK)

NORMAL:
- The gene contains 5-37 CTG repeats.

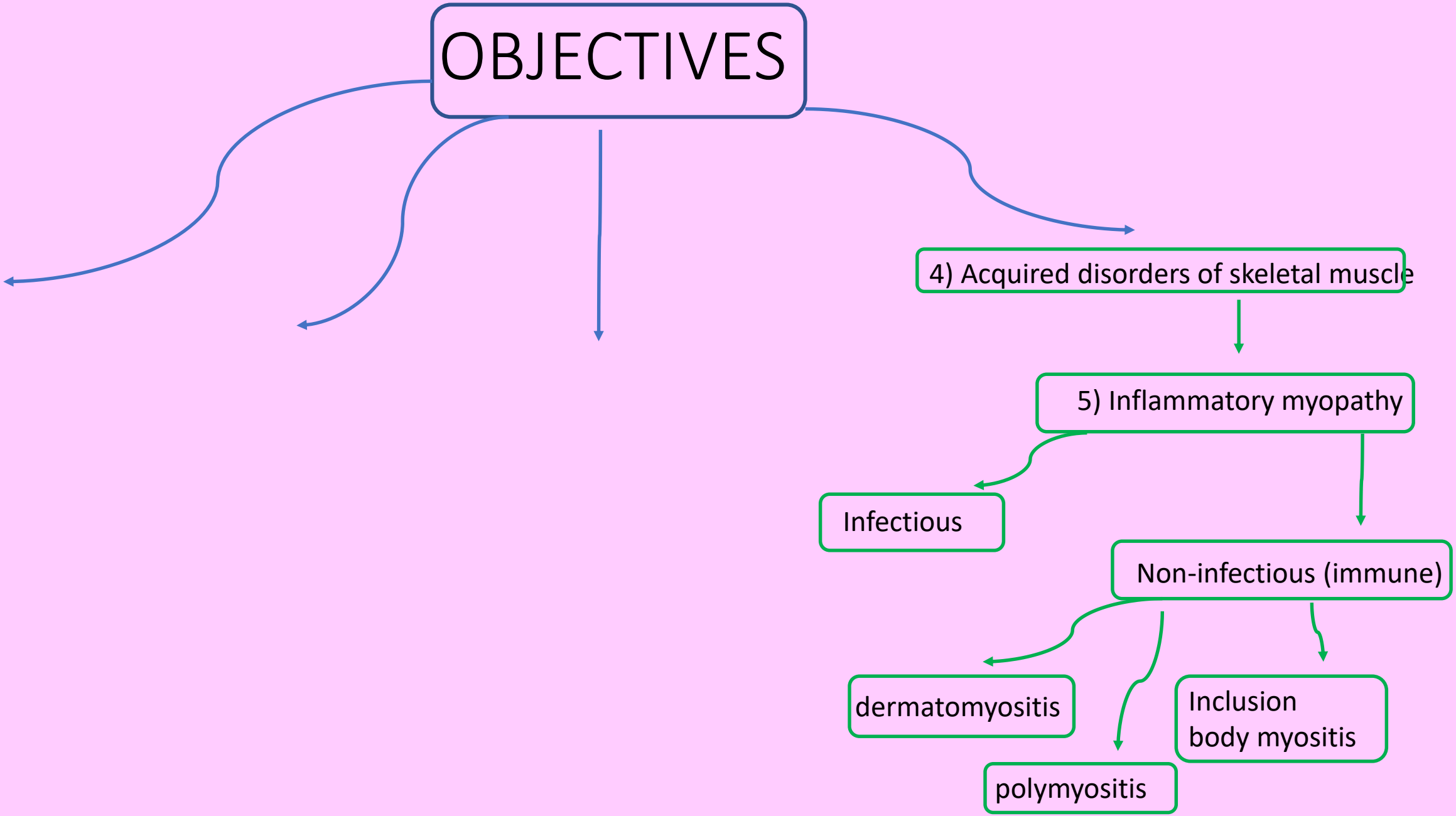
Myotonic dystrophy:
- The gene contains 45-several thousands of CTG repeats.

Morphology

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

? Mitochondrial…

OBJECTIVES


4) Acquired disorders of skeletal muscle
5) Inflammatory myopathy
Infectious
Non-infectious (immune)
dermatomyositis
polymyositis
Inclusion body myositis

4) Acquired disorders of skeletal muscles

Inflammatory myopathies:
- Dermatomyositis.
- Polymyositis.
- Inclusion body myositis.

* immune-mediated muscle injury and inflammation

Toxic muscle injury

Post-infectious rhabdomyolysis

Muscle infarction in diabetics

Dermatomyositis

- Most common inflammatory myopathy in children.
- In adult: Paraneoplastic disorder (20-25% have cancer).
- SKIN RASH: 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).

Dermatomyositis

SKIN RASH:

- May accompany or precede the onset of muscle disease.
- The classic rash takes the form of : 1) discoloration of the upper eyelids associated with periorbital edema,
  2) Scaling erythematous eruption over the knuckles.

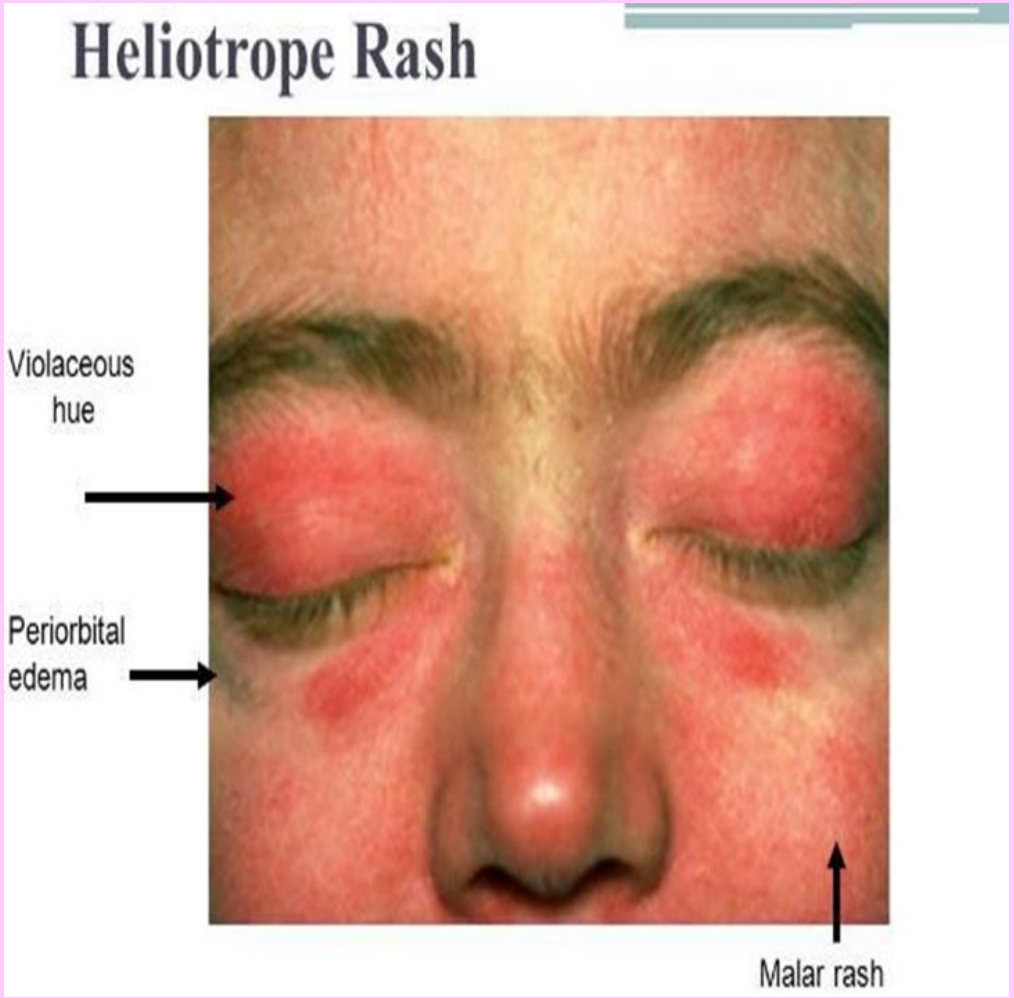
MUSCLE WEAKNESS:

- 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

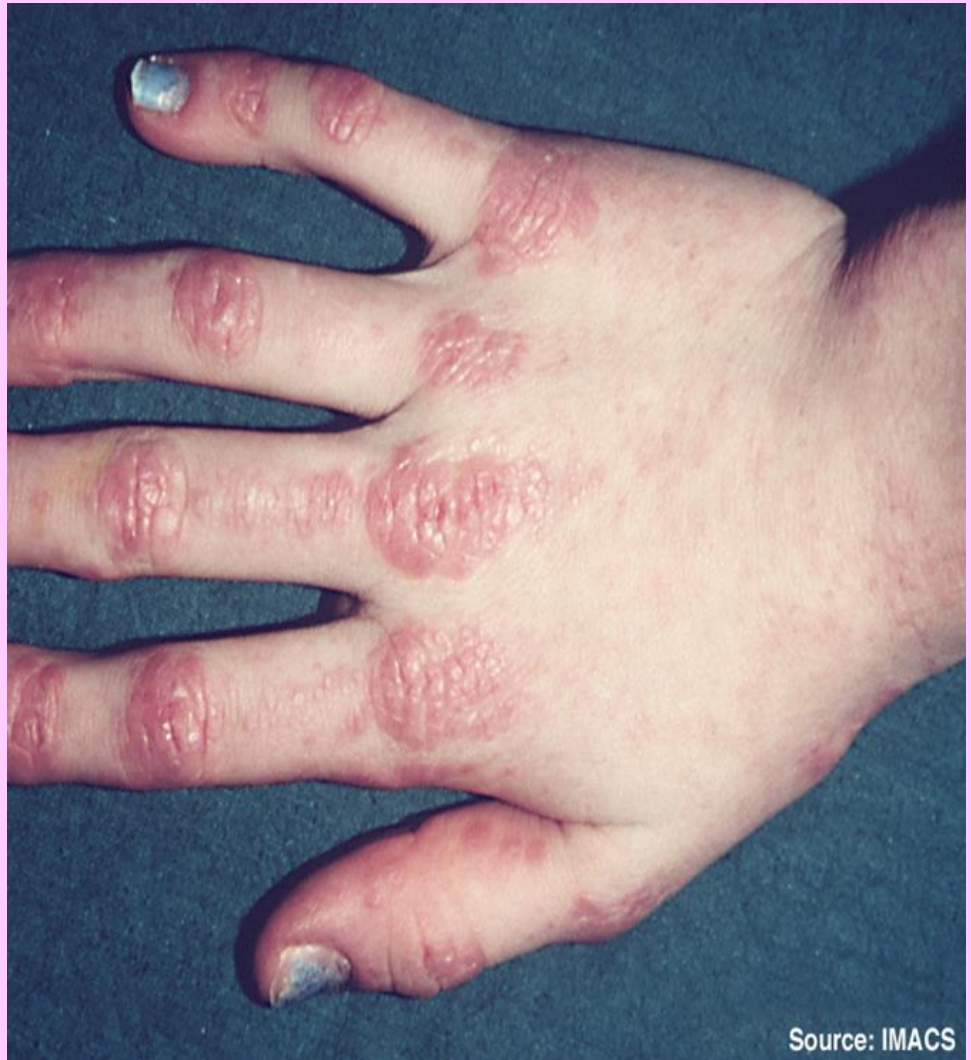
OTHER:

- Interstitial lung disease
- Vasculitis,
- Myocarditis, may be present in some cases

Heliotrope rash



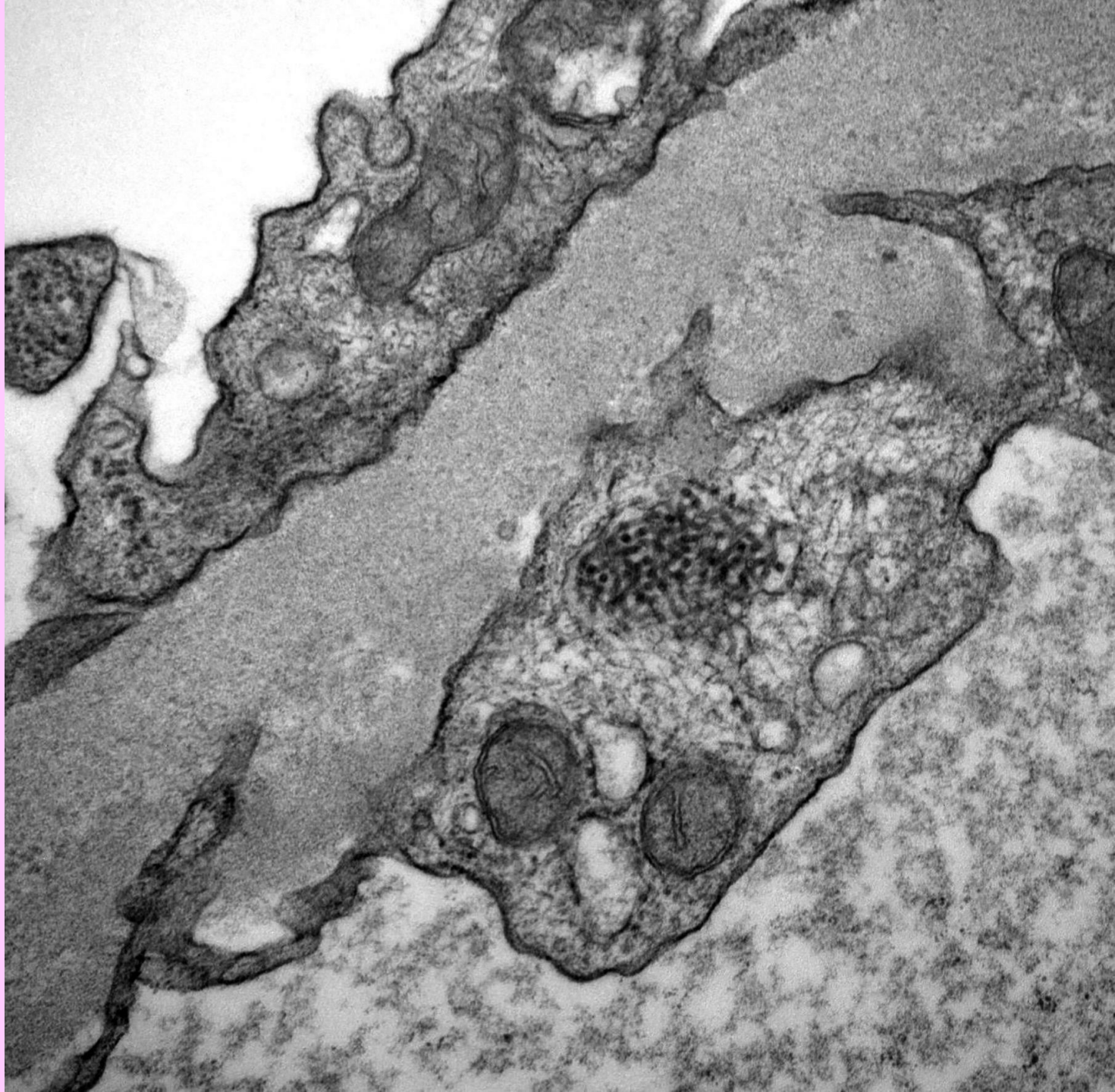
Gottron's lesions

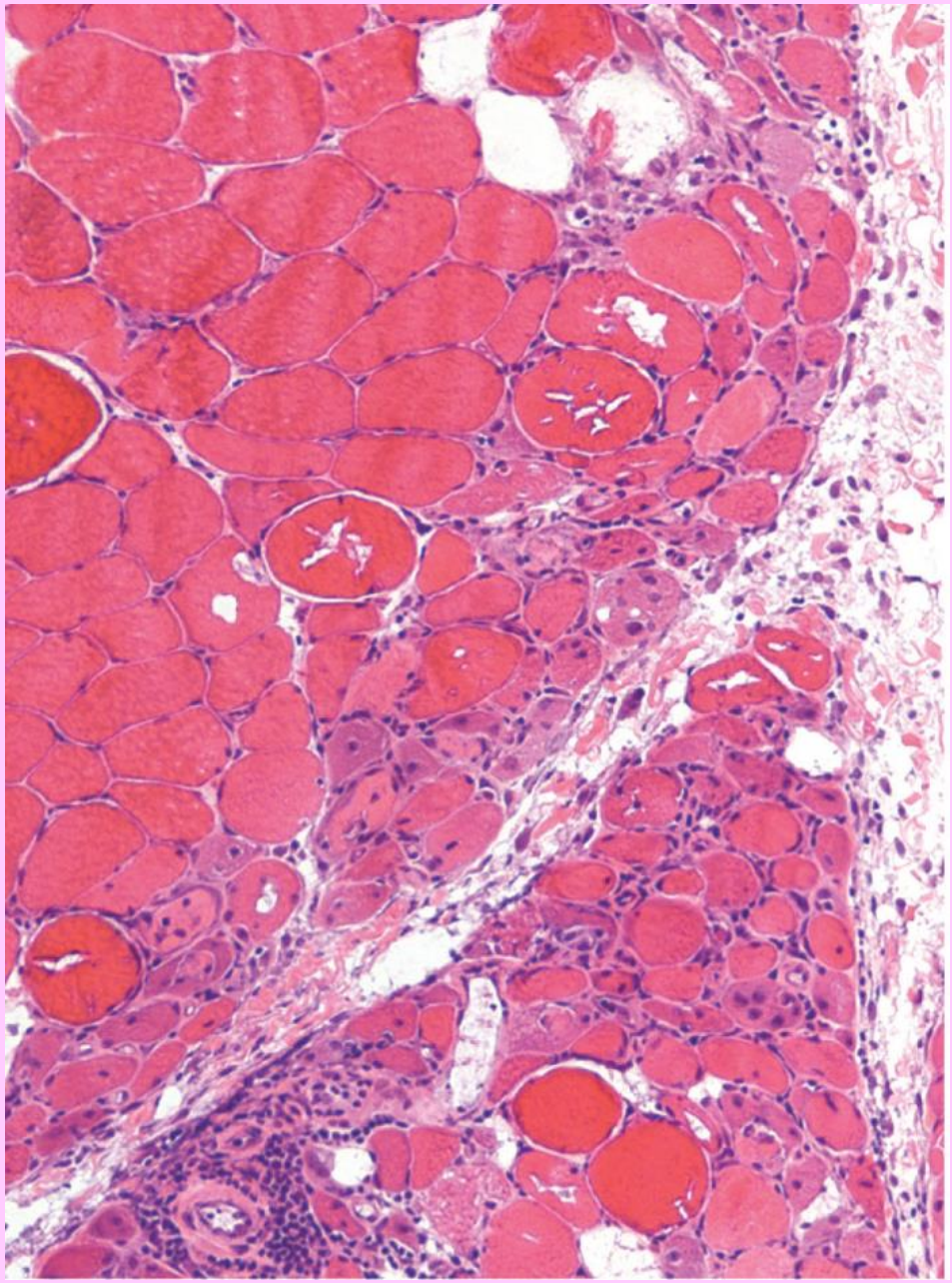


Dermatomyositis.. morphology

- 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 “dropout”

Tubuloreticular inclusions





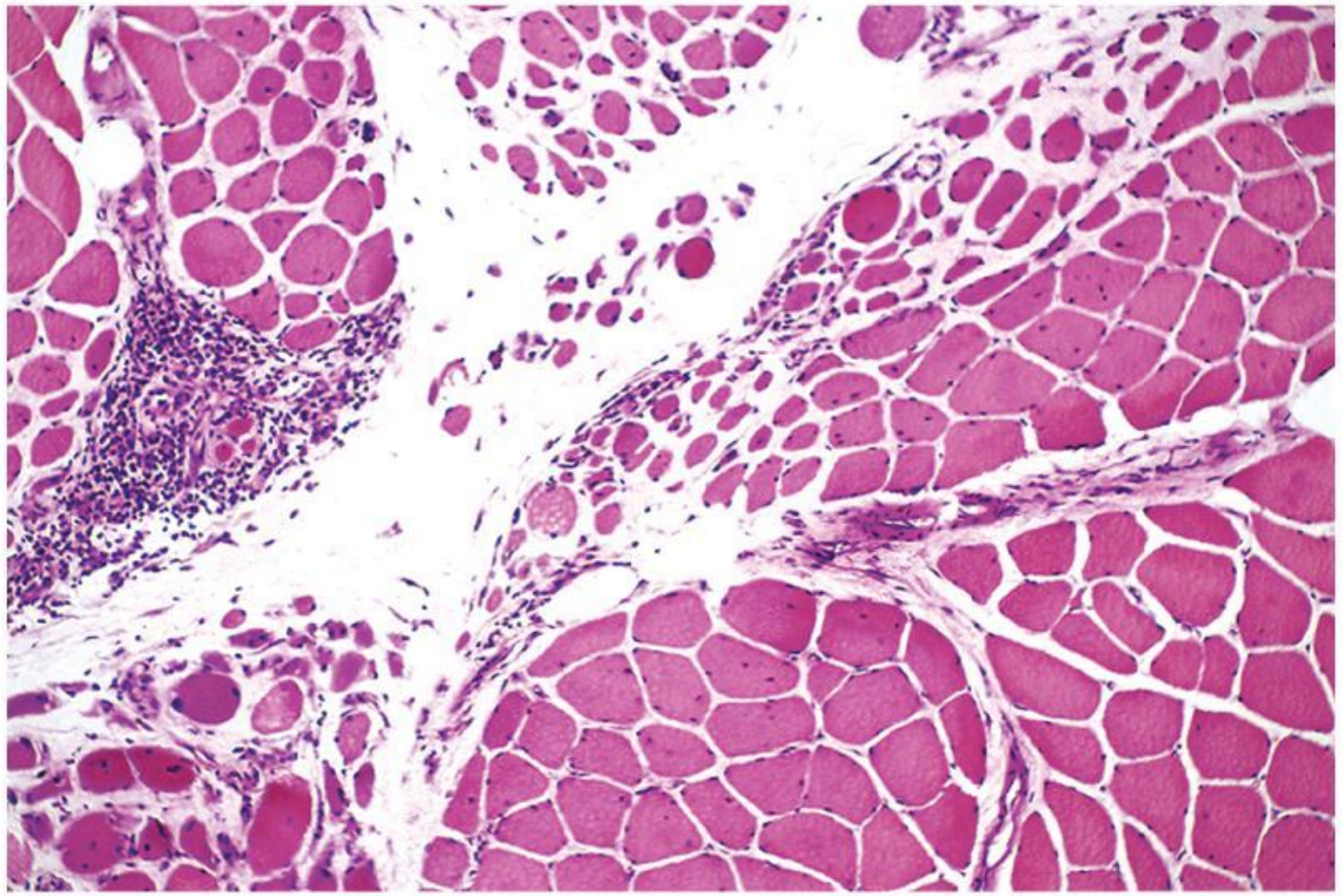
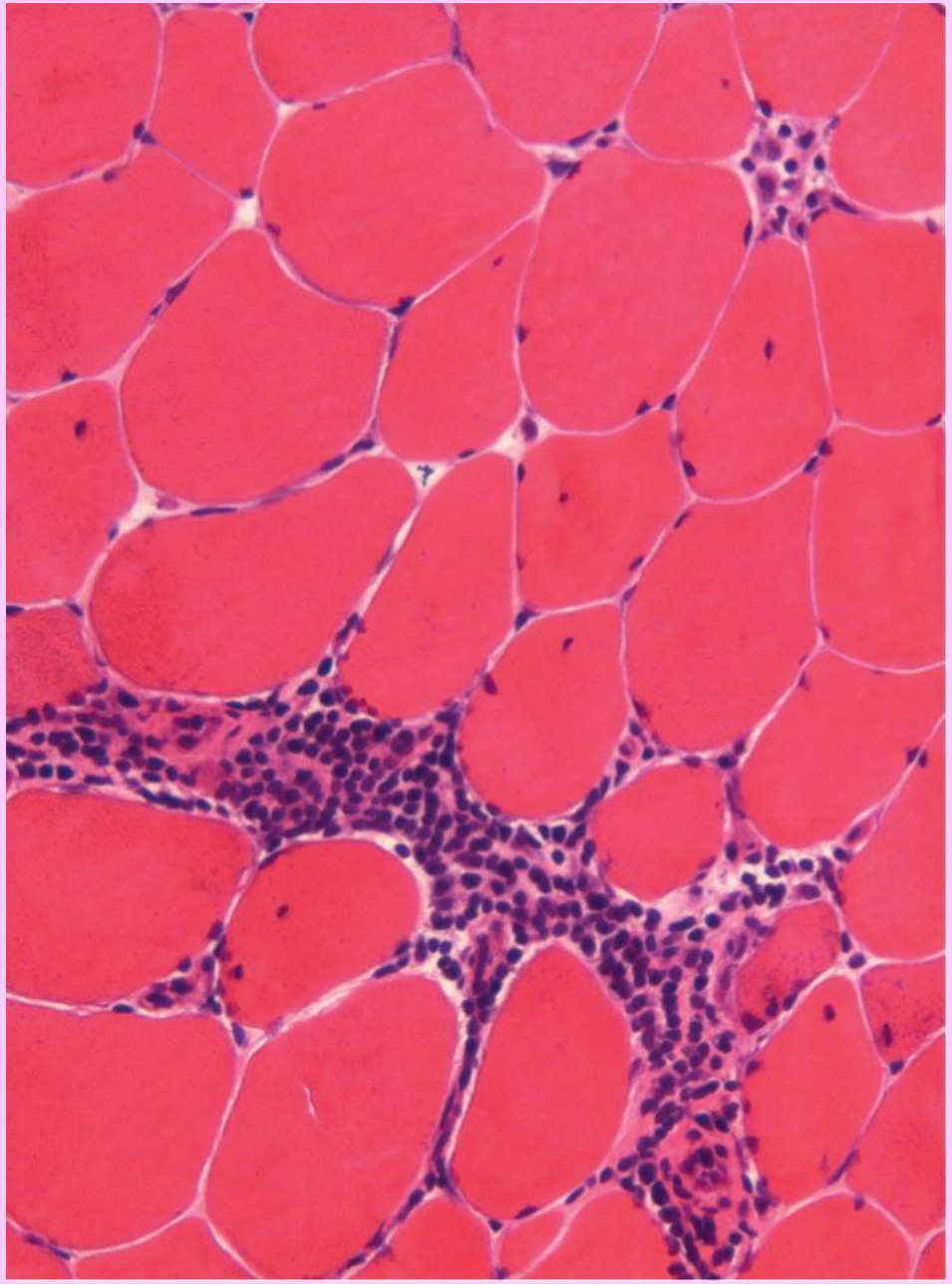


Figure 5-28 Dermatomyositis. Perifascicular inflammation and atrophy in a skeletal muscle. (Courtesy of Dr. Dennis Burns, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

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.
- Increased expression of MHC class I molecule. Endomysial inflammatory infiltrate by CD8+ cytotoxic T- lymphocytes

- 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.

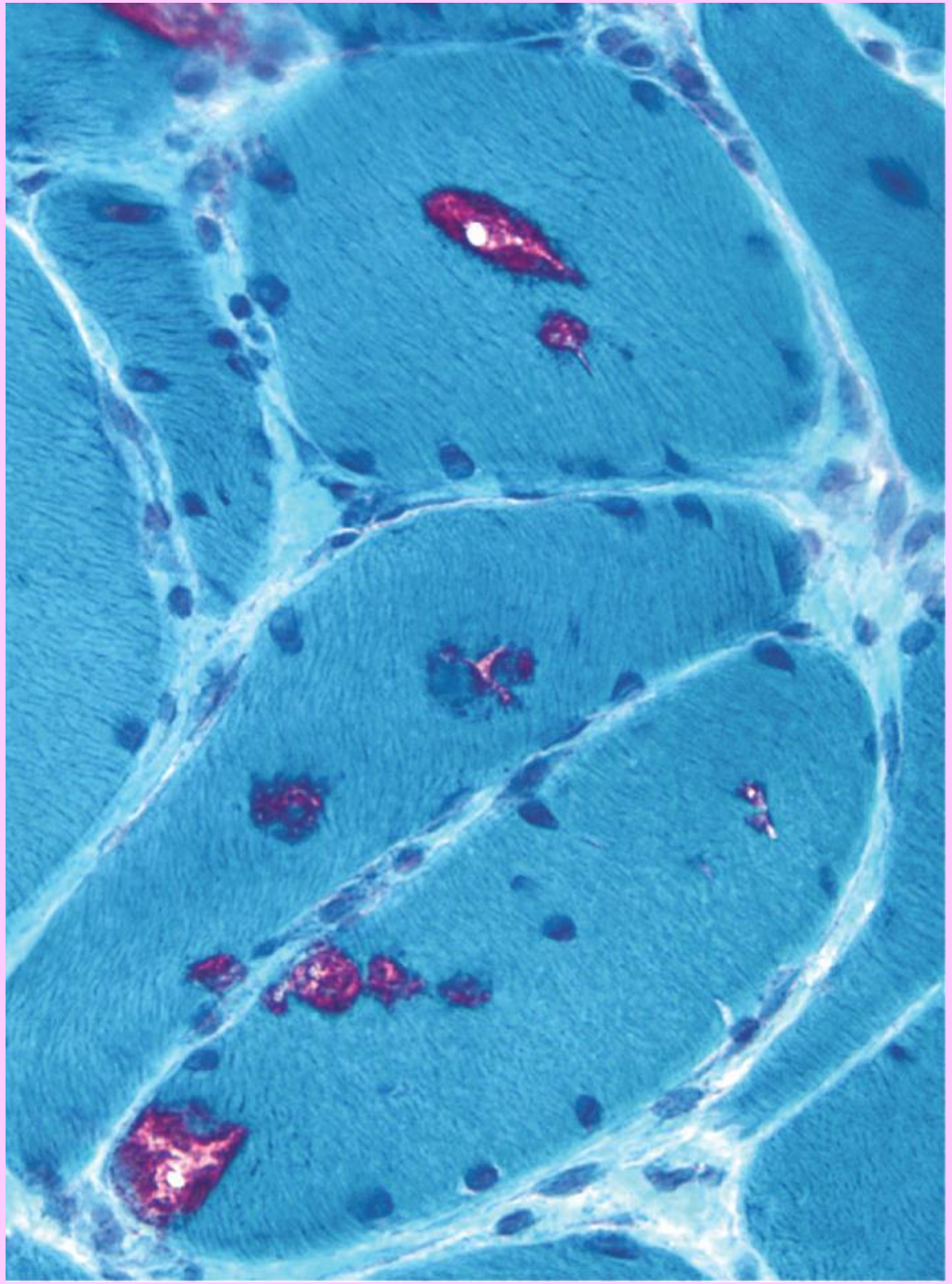


Inclusion body myositis

- the most common inflammatory myopathy in patients older than 60.
- 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.



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Infectious

Non-infectious (immune)

dermatomyositis

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Reference

Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 10th ed. Elsevier; 2017. Philadelphia, PA.
p. 840-845.

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