

Aportación del neuropatólogo al diagnóstico de las enfermedades musculares

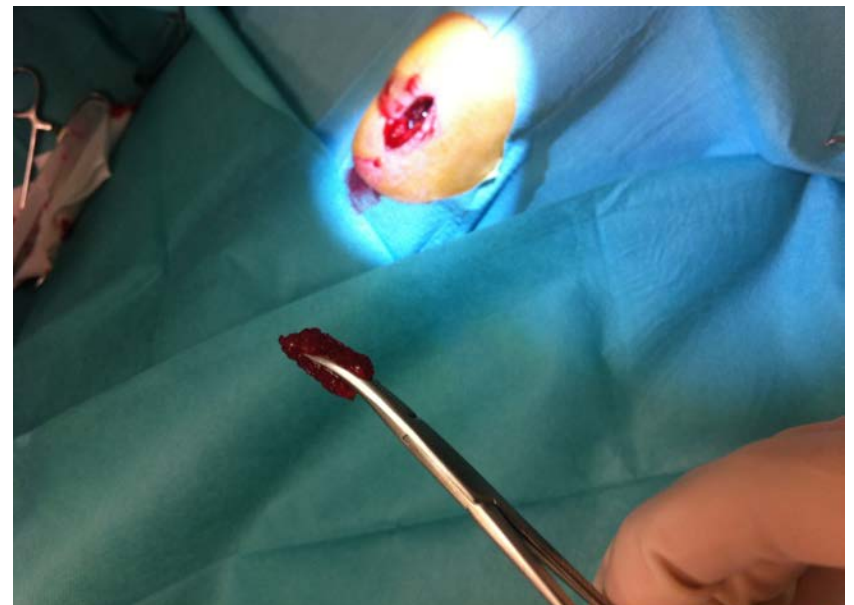
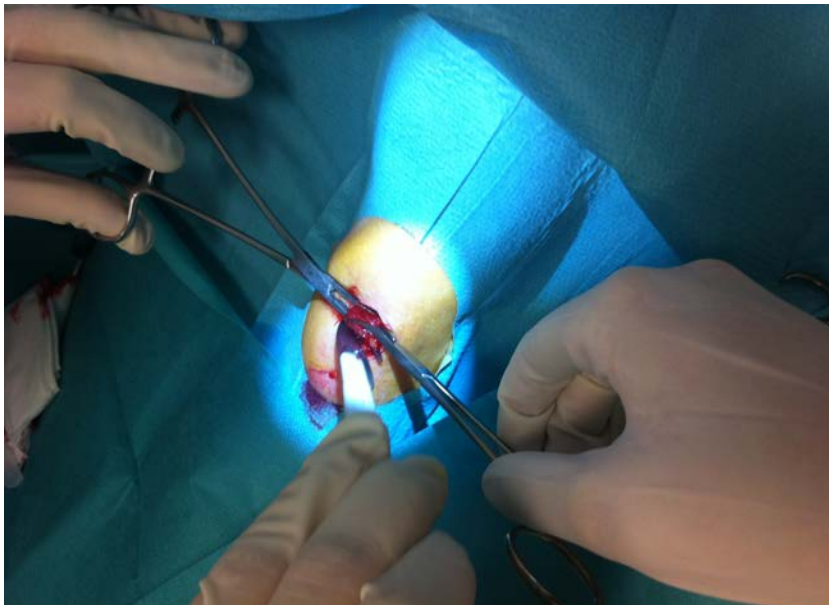
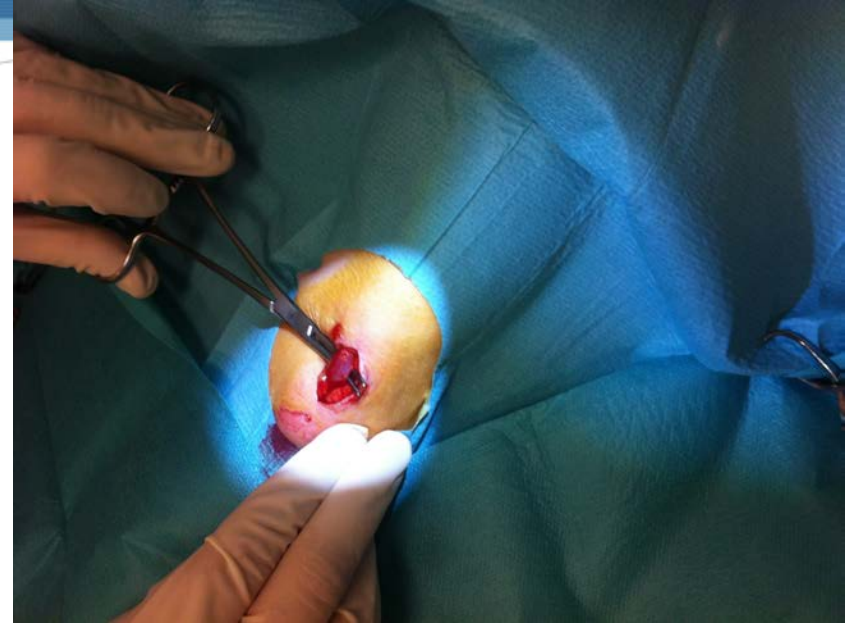


Hospital Universitario
12 de Octubre

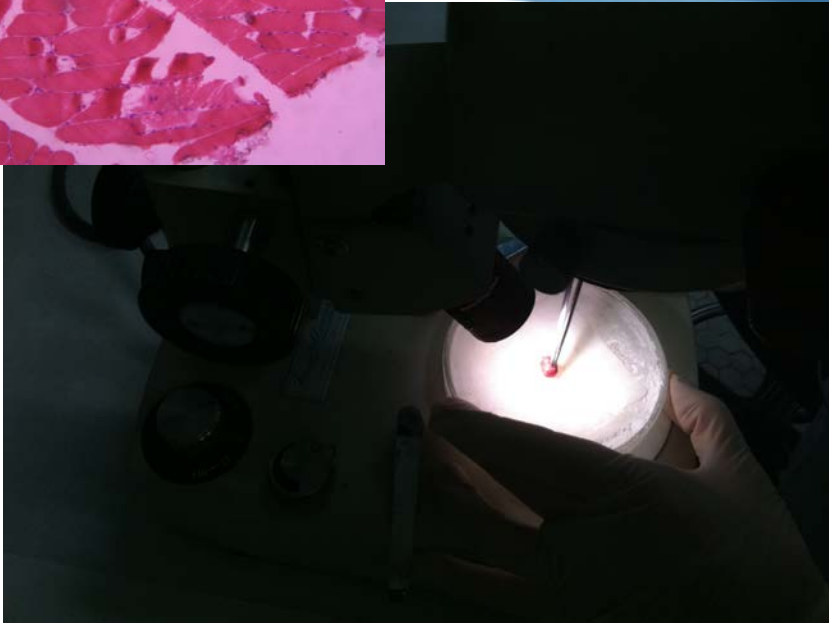


Dr. Aurelio Hernández Laín
Sección Neuropatología 
Hospital Universitario 12 Octubre

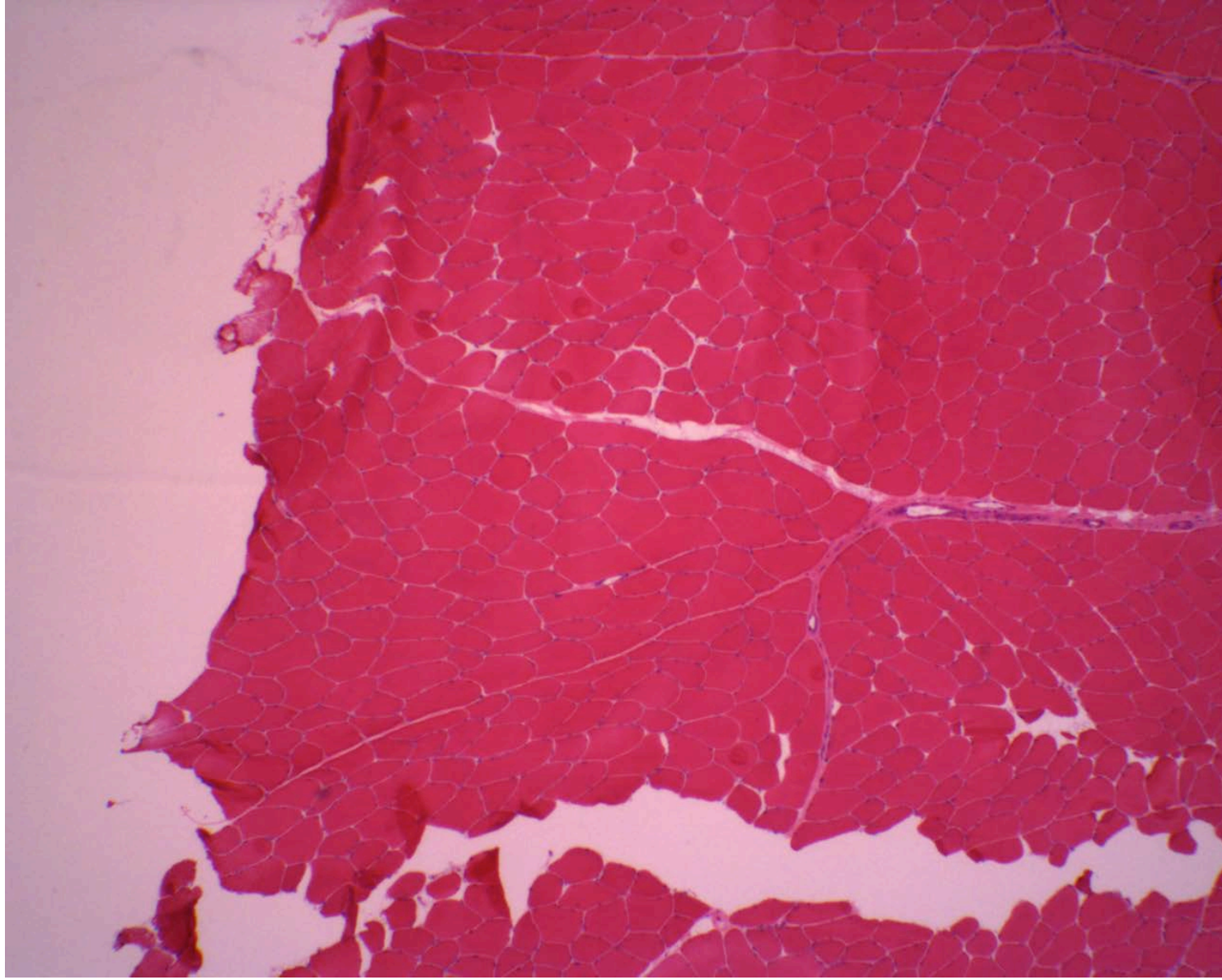
Técnica biopsia



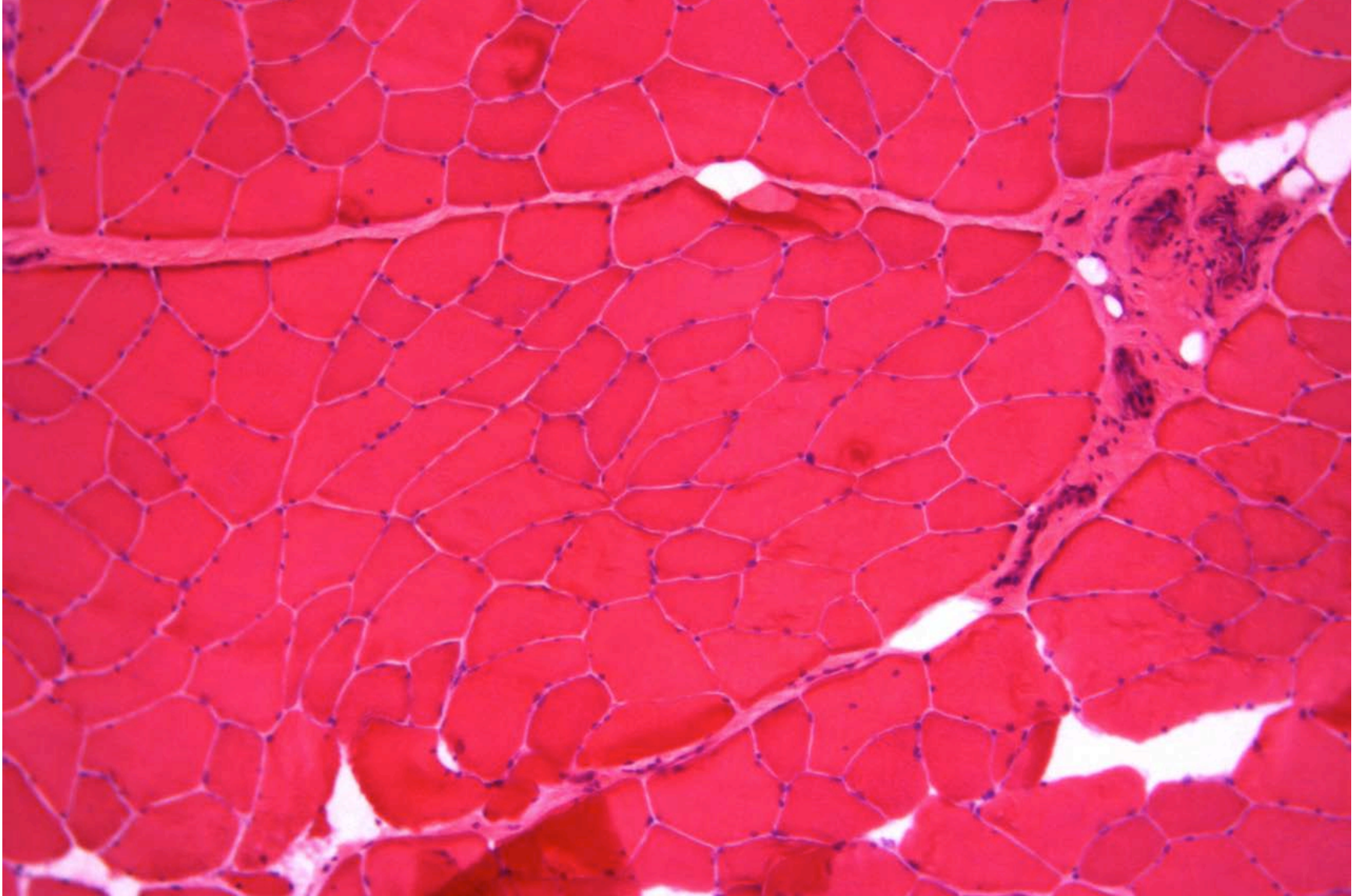
Procesamiento



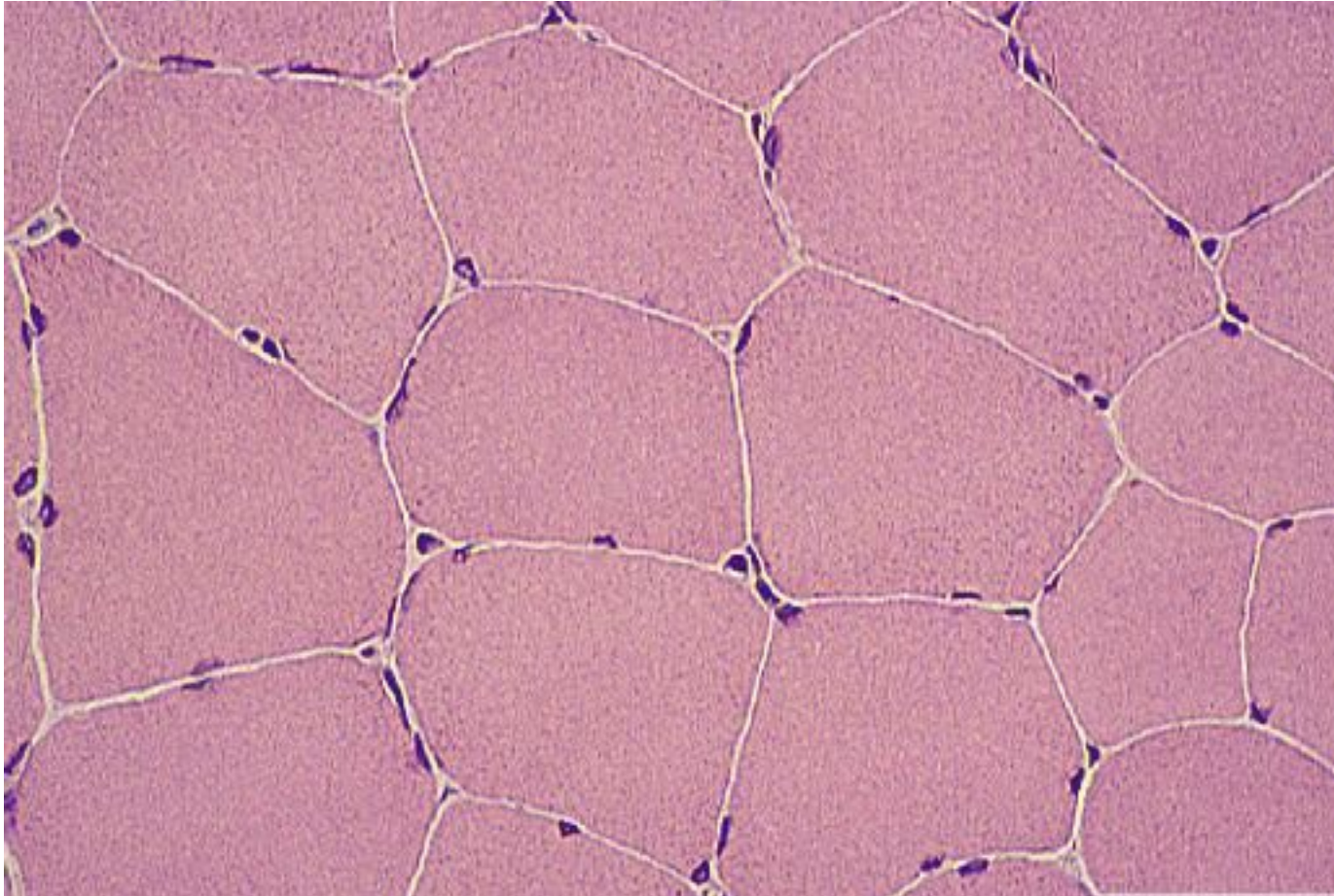
Músculo normal



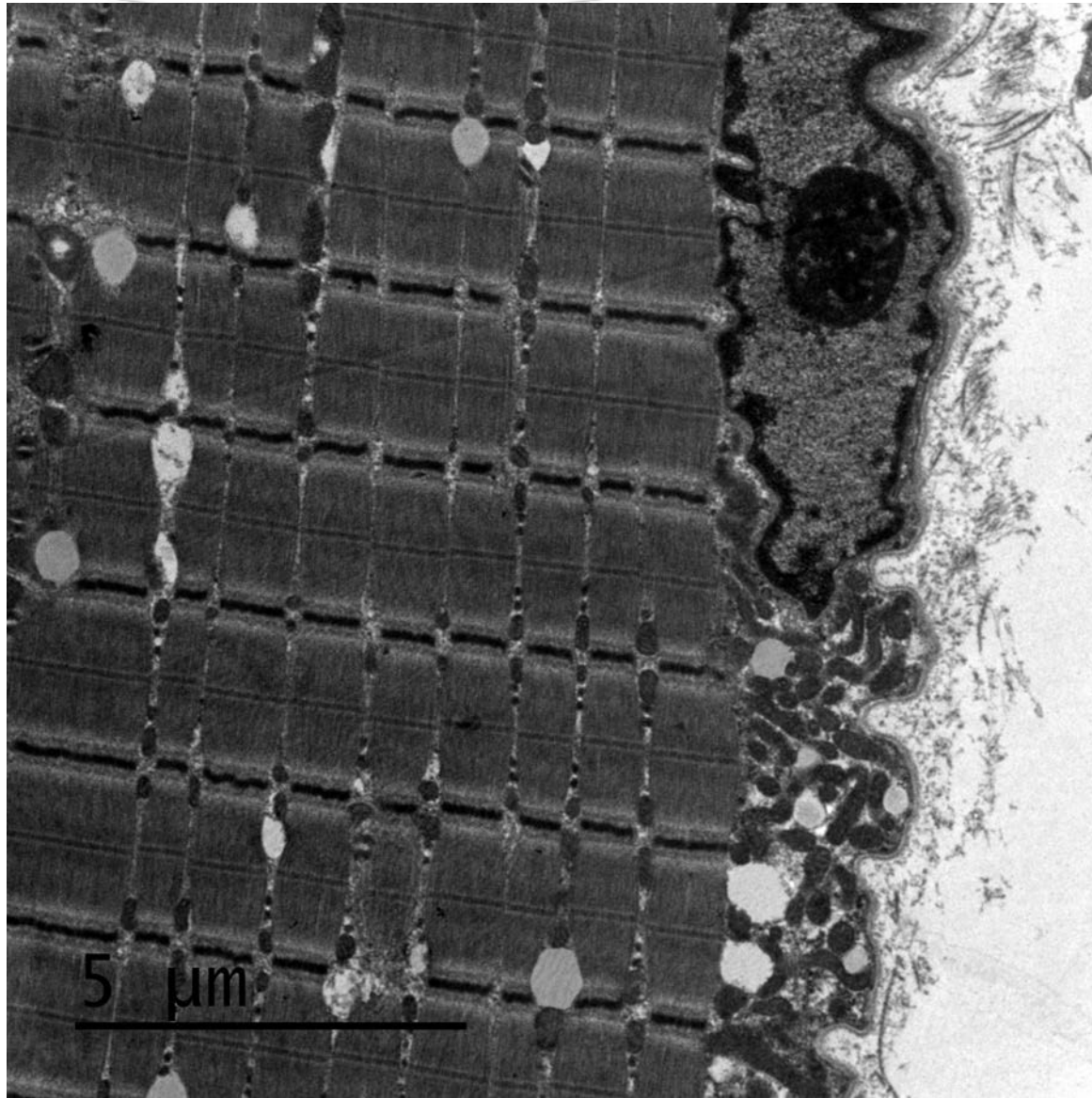
Músculo normal



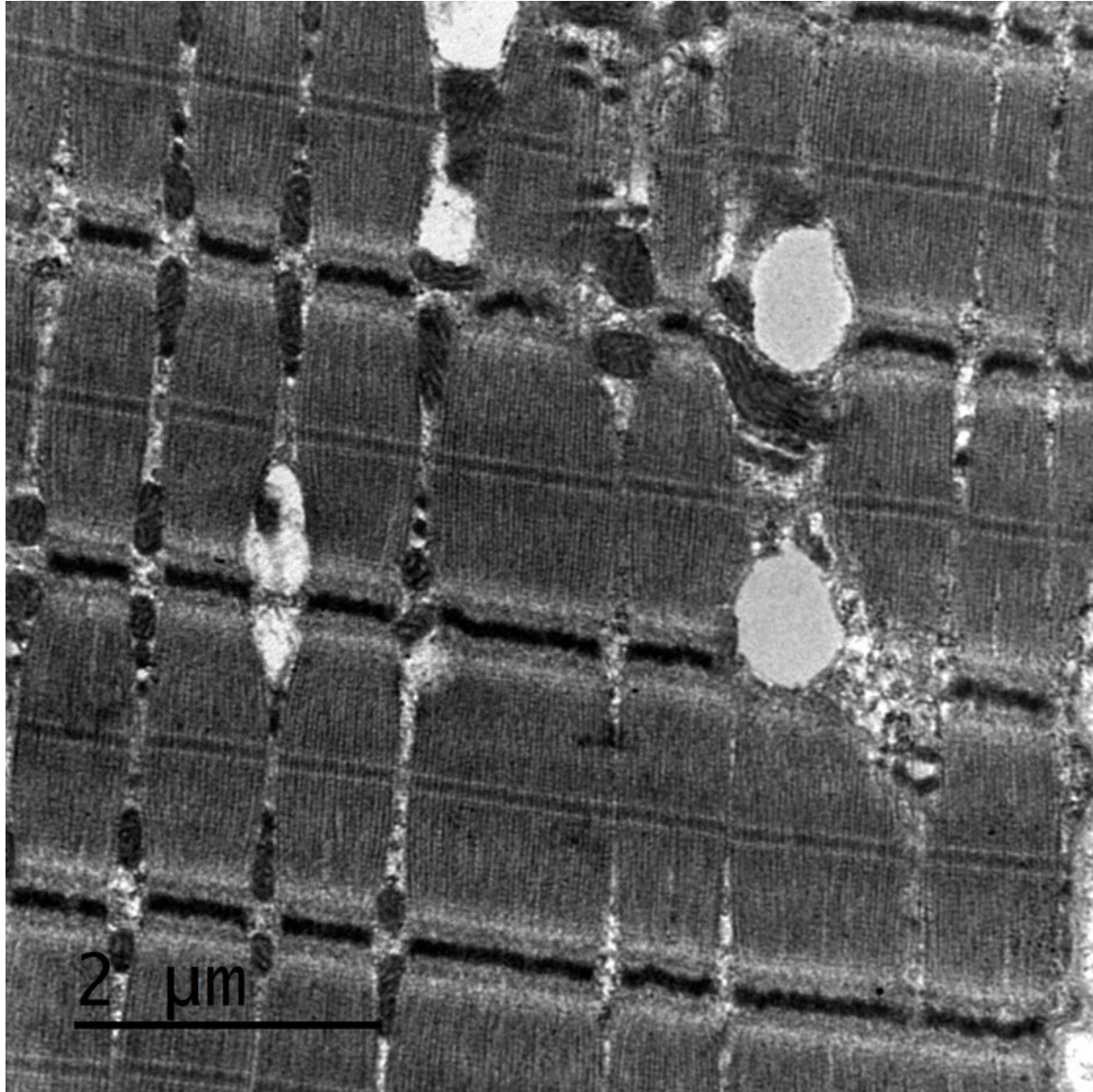
Músculo normal



Microscopia Electrónica

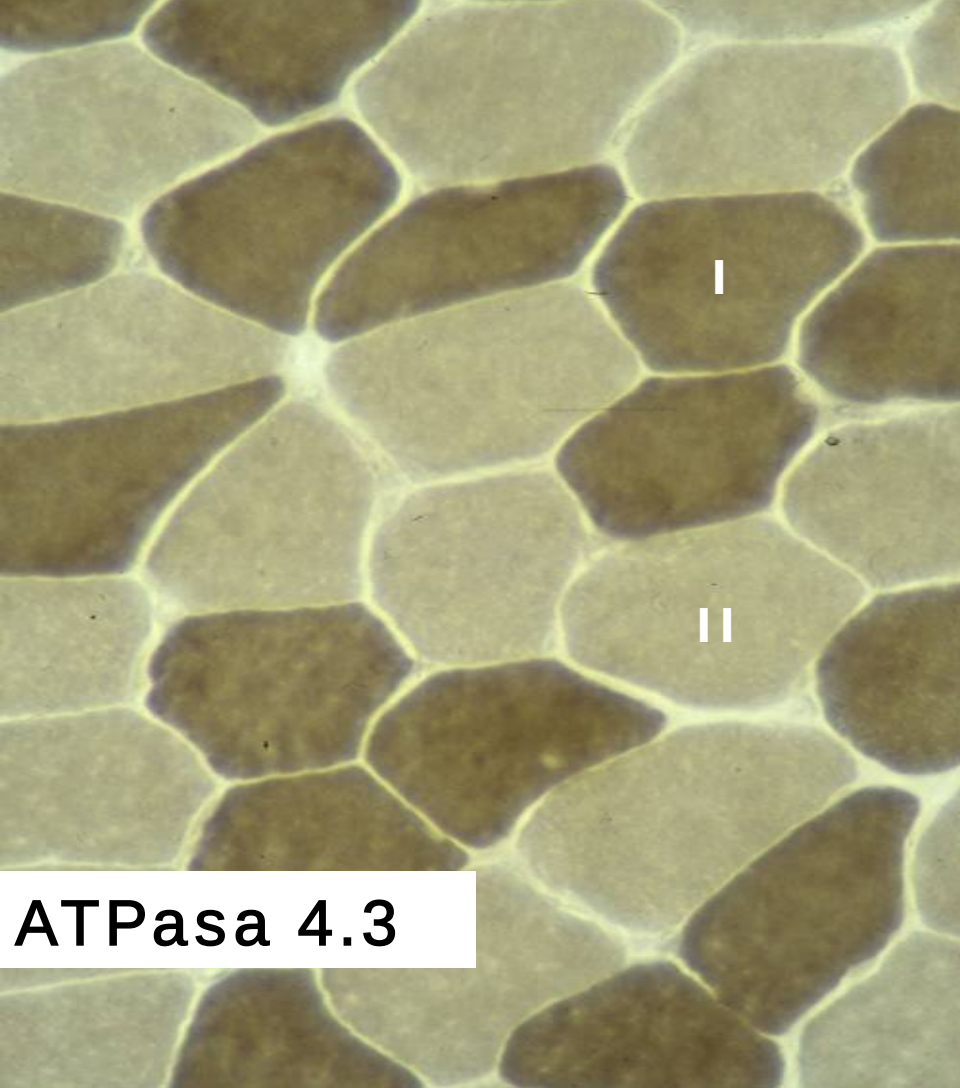


Microscopia Electrónica

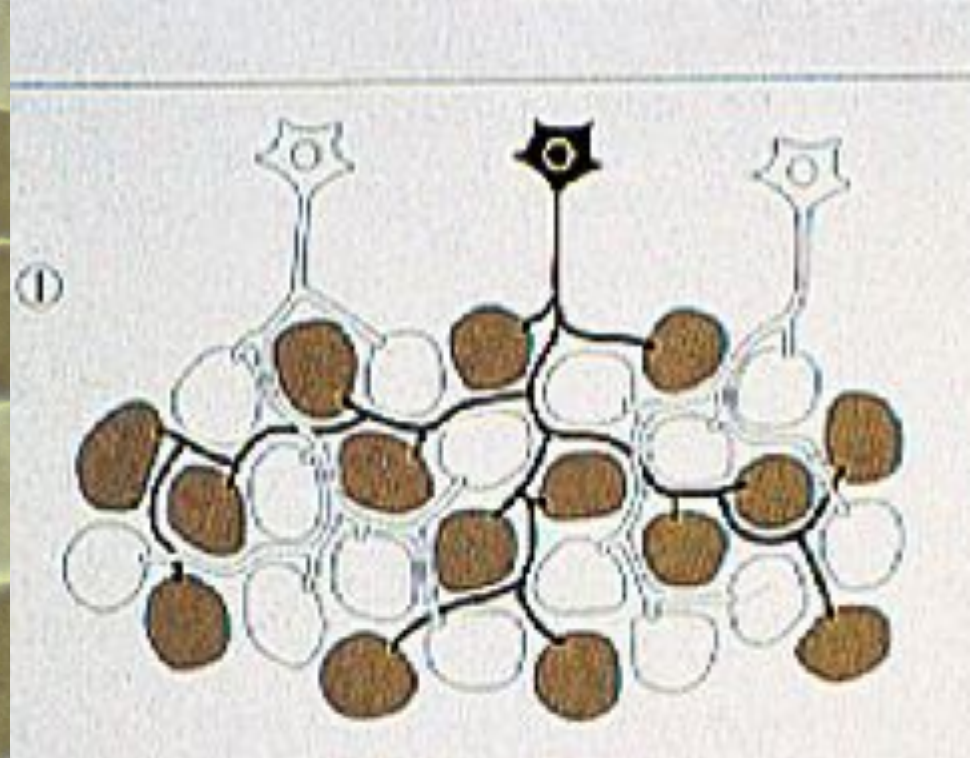


Técnicas Histoquímicas

- ◆ Hematoxilina-eosina
- ◆ Tricrómico
- ◆ PAS
- ◆ Oil Red O
- ◆ ATPasas pH 9.4, 4.6 y 4.3
- ◆ Técnicas enzimas oxidativos:
 - ◆ -DPNH
 - ◆ -SDH (Succínico Deshidrogenasa)
 - ◆ -COX (Citocromo oxidasa)



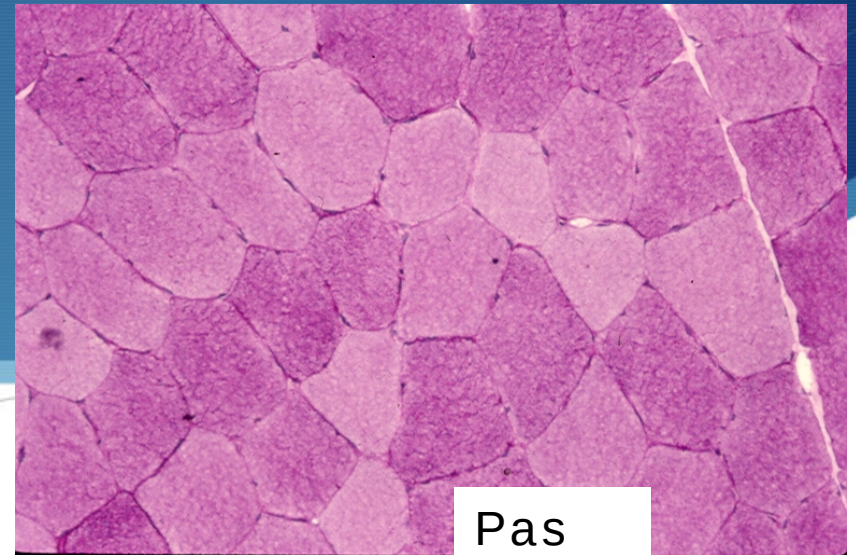
Tipo I: Contracción lenta, sostenida
 Ejercicio de resistencia
 Ac.grasos, ciclo Krebs
 Ricas en lípidos y mitocondrias



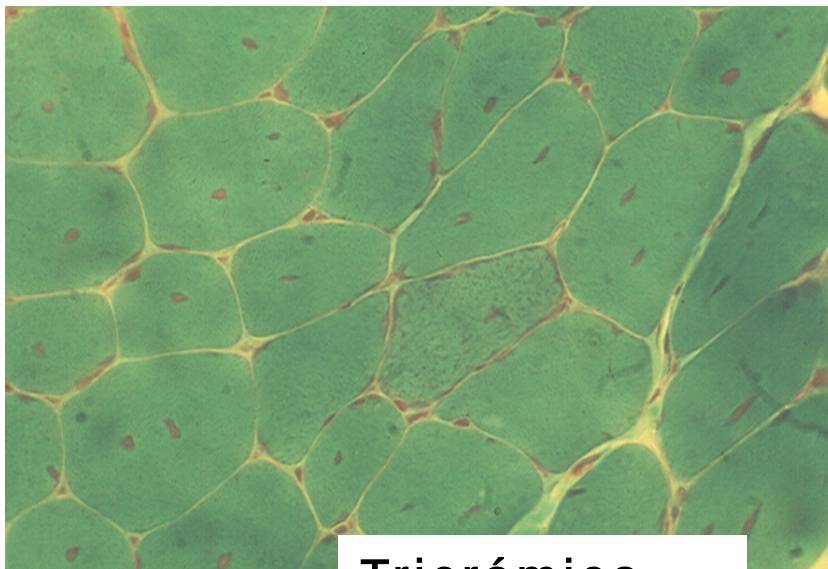
Tipo II: Contracción rápida
 Ejercicio de fuerza
 Glicolisis anaerobia
 Ricas en glucógeno



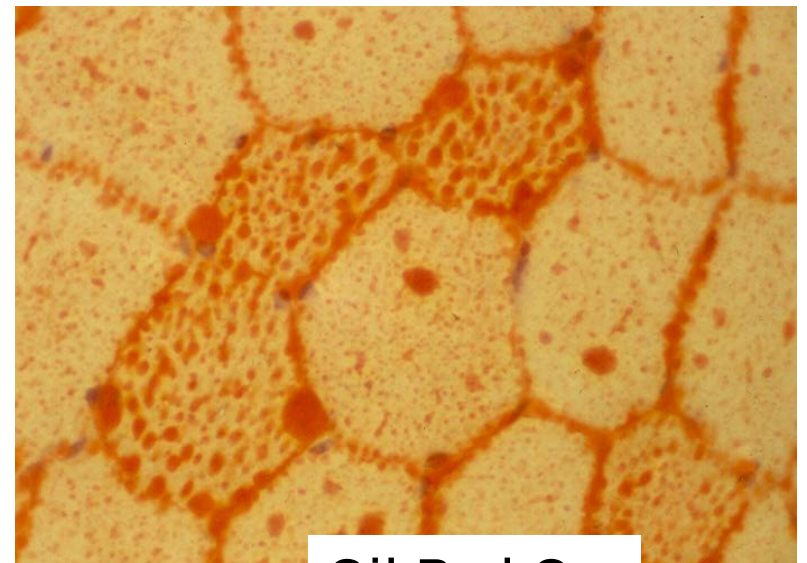
**Hematox
-eosina**



Pas

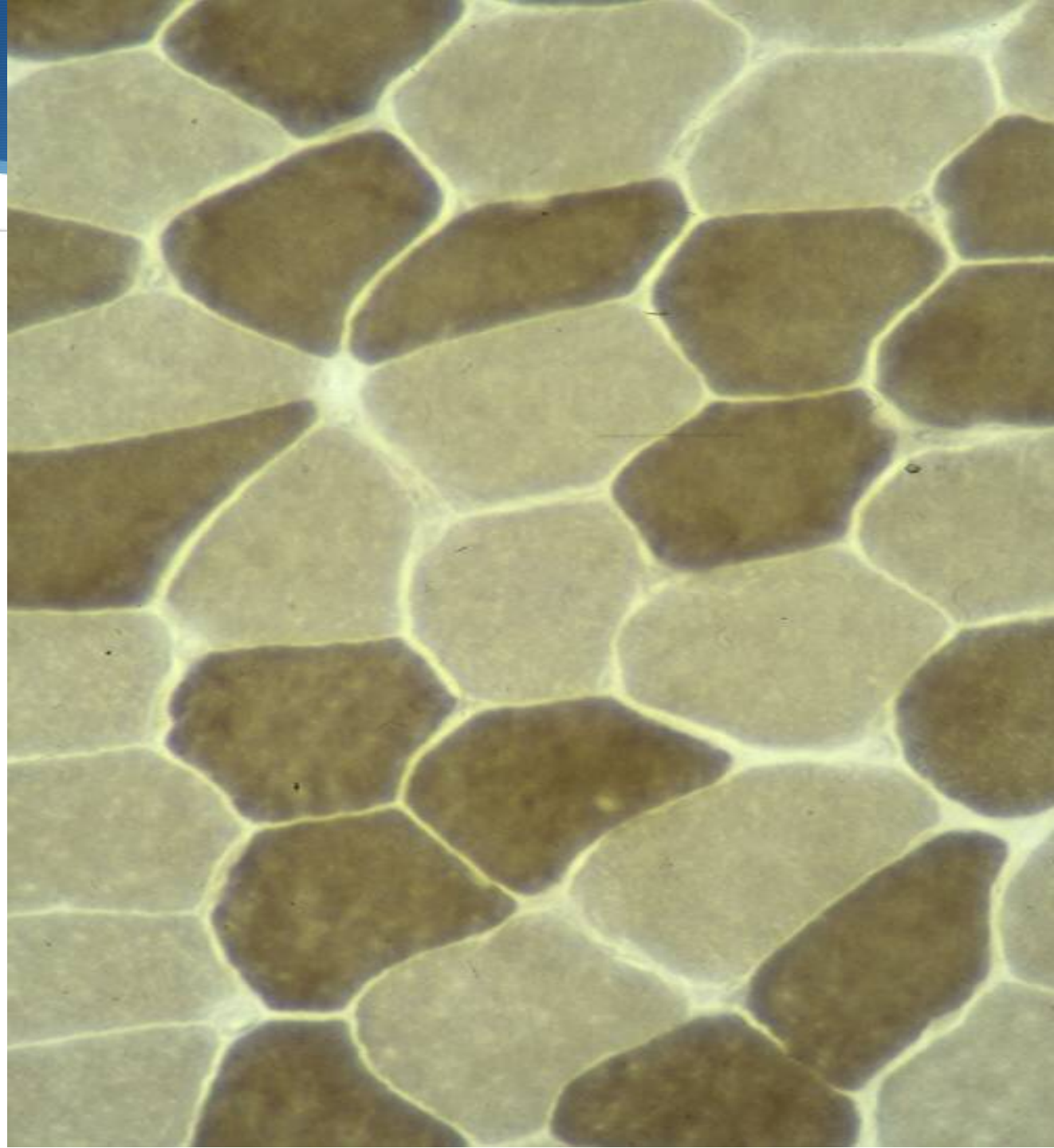


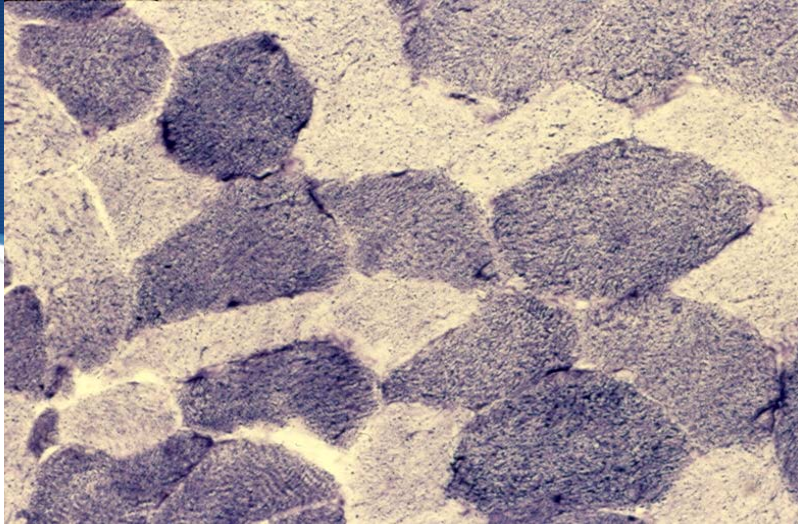
Tricrómico



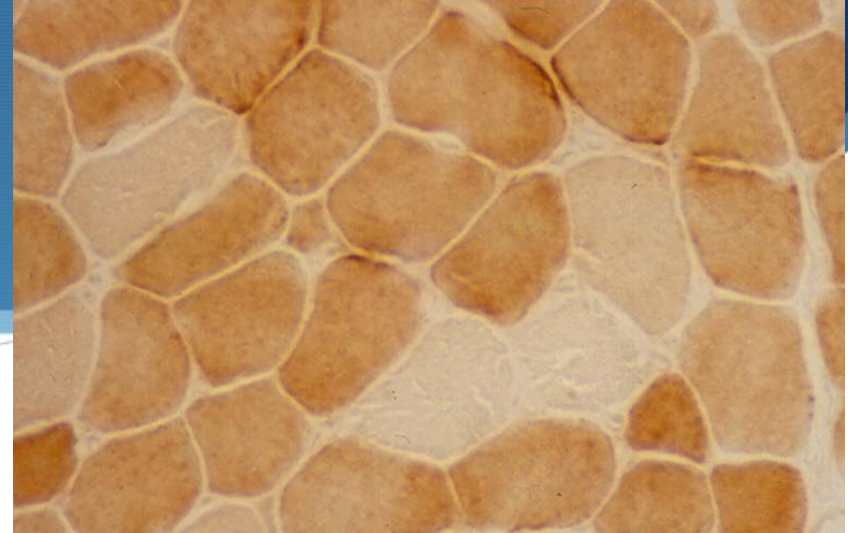
Oil Red O

ATPasa pH 4.6

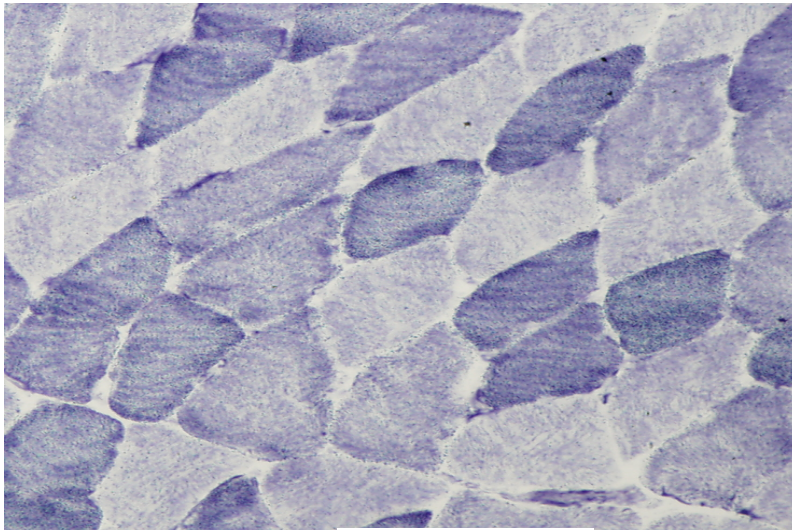




NADH

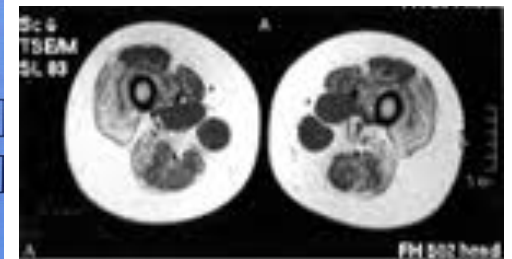
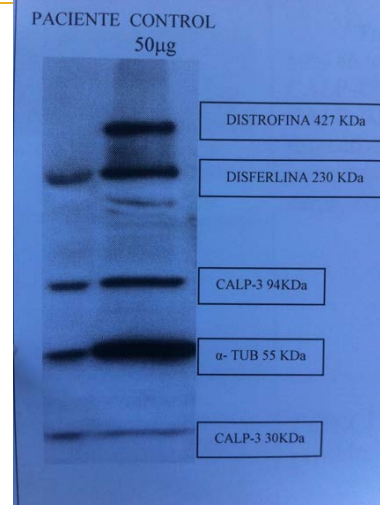
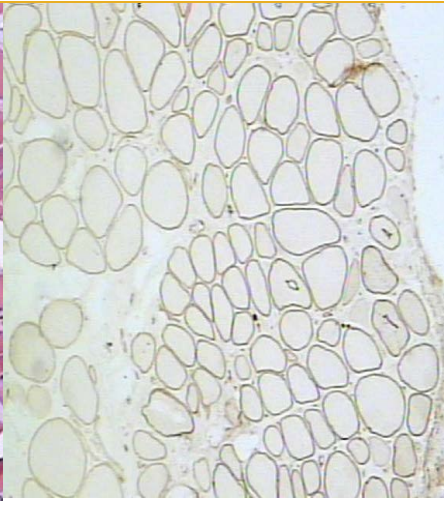
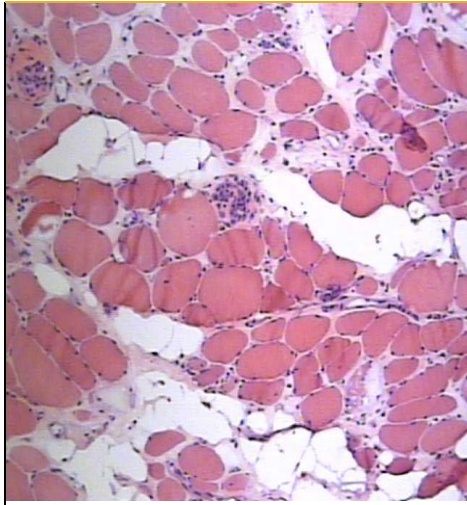


COX

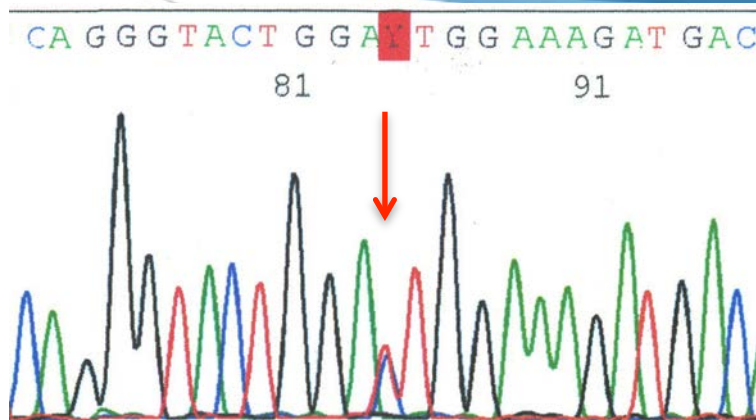


SDH

Diagnóstico



Estudio genético



Sanger



NGS (Next Generation Sequencing)

Paneles, Exoma y Transcriptoma, Genoma

Unidad Motora

Diseases of motor neurons

Spinal muscular atrophies
Motor neuron disease (ALS)
Local damage: trauma,
ischaemia, tumours, infections

Diseases of peripheral nerves

Axonal degeneration
Segmental demyelination

Diseases of neuromuscular transmission

Myasthenis gravis
Eaton–Lambert
Syndrome

Primary muscle disease – Myopathies and dystrophies

(a) Destructive myopathies

Dystrophies
Polymyositis
Dermatomyositis
Local damage:
Infections,
trauma,
tumours

(b) Disorders of intracellular organelles, structural proteins and enzymes

e.g. mitochondria, glycogen,
lipids, ion channels, desmin-
related proteins

(c) Myopathies associated with systemic disorders

Endocrine and metabolic
diseases

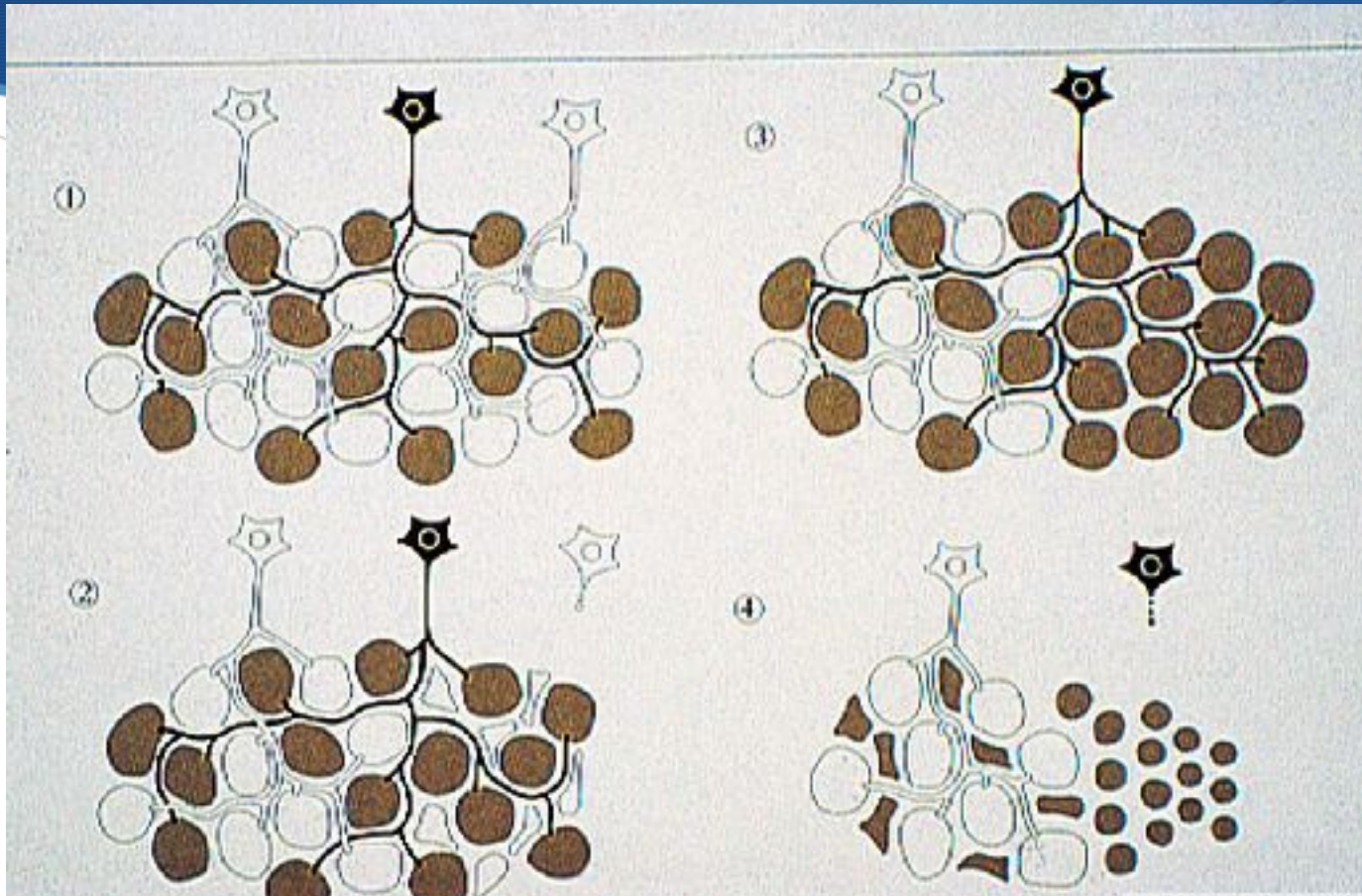
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**ATROFIA
NEURÓGENA**

Alteración en la
Transmisión neuromuscular
MIASTENIA

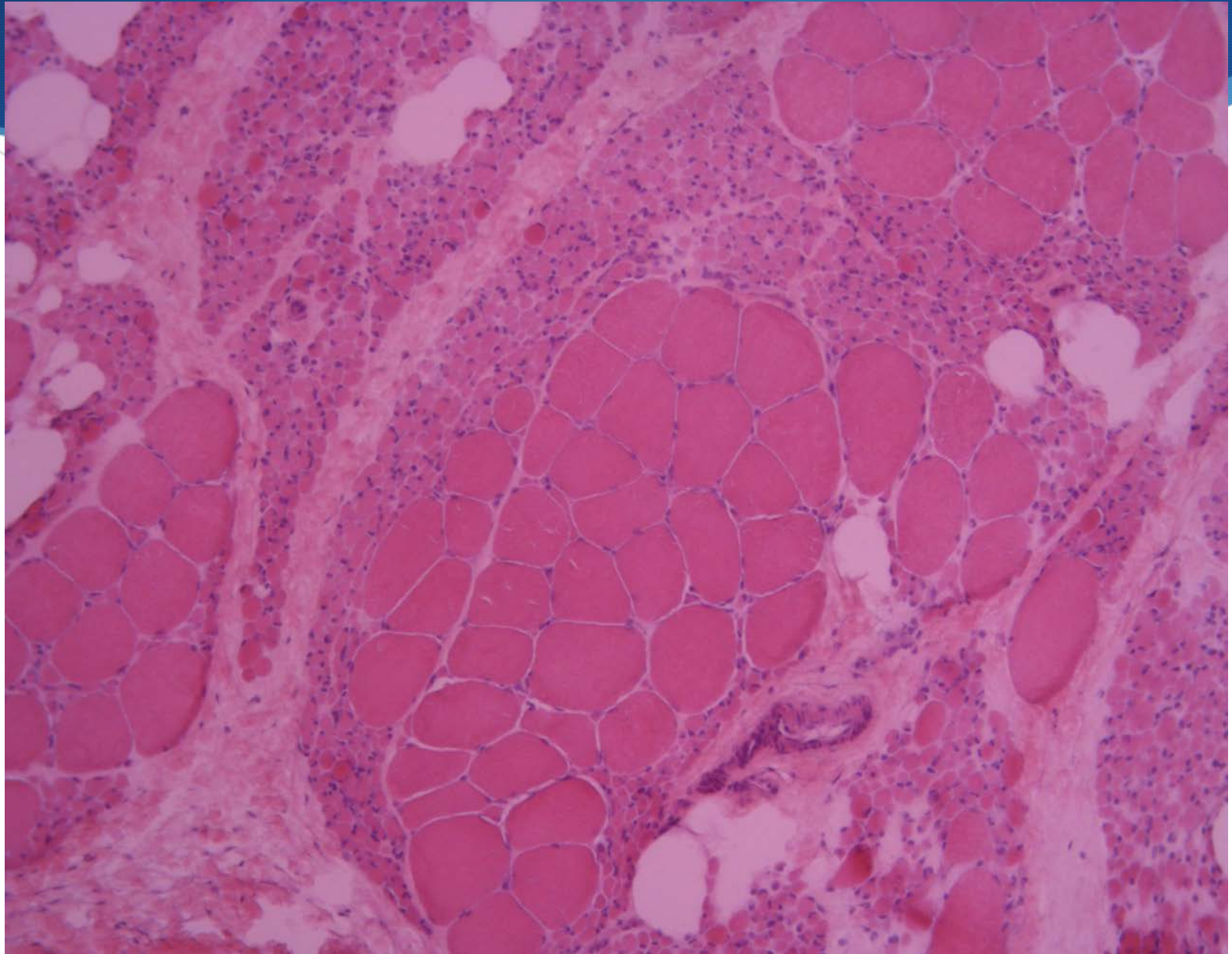
MIOPATIAS

Atrofia neurógena

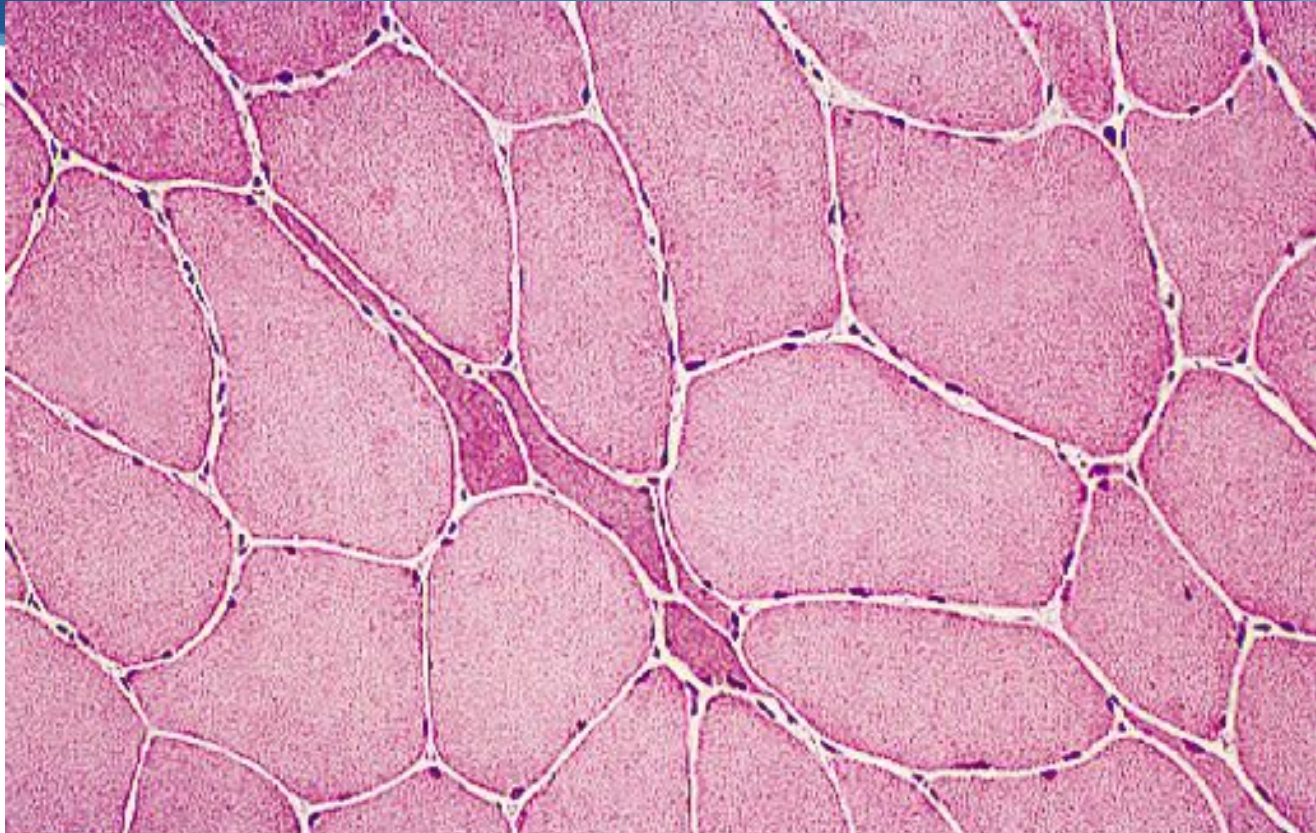


Reinervación

Atrofia neurógena. SMA

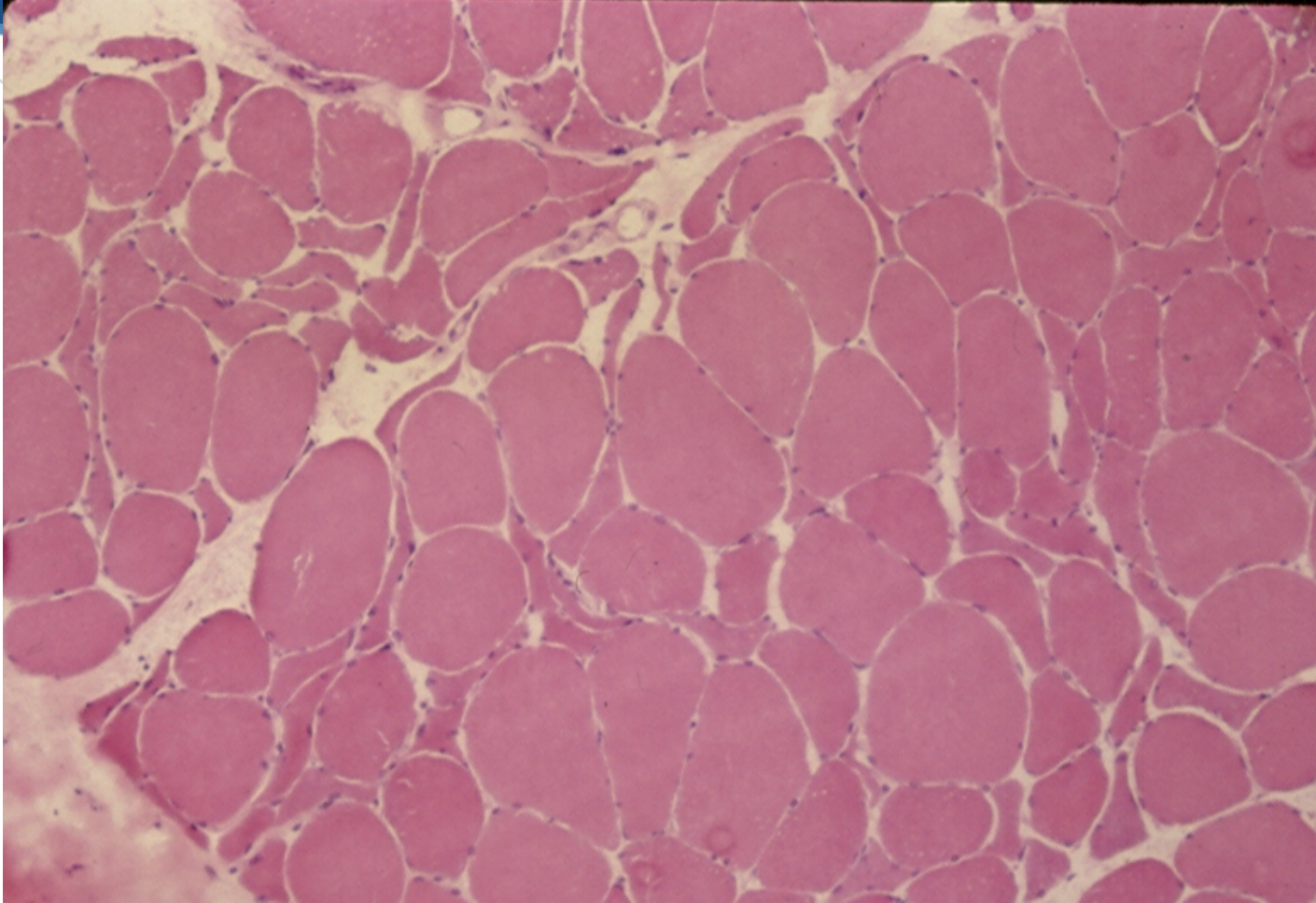


Atrofia neurógena

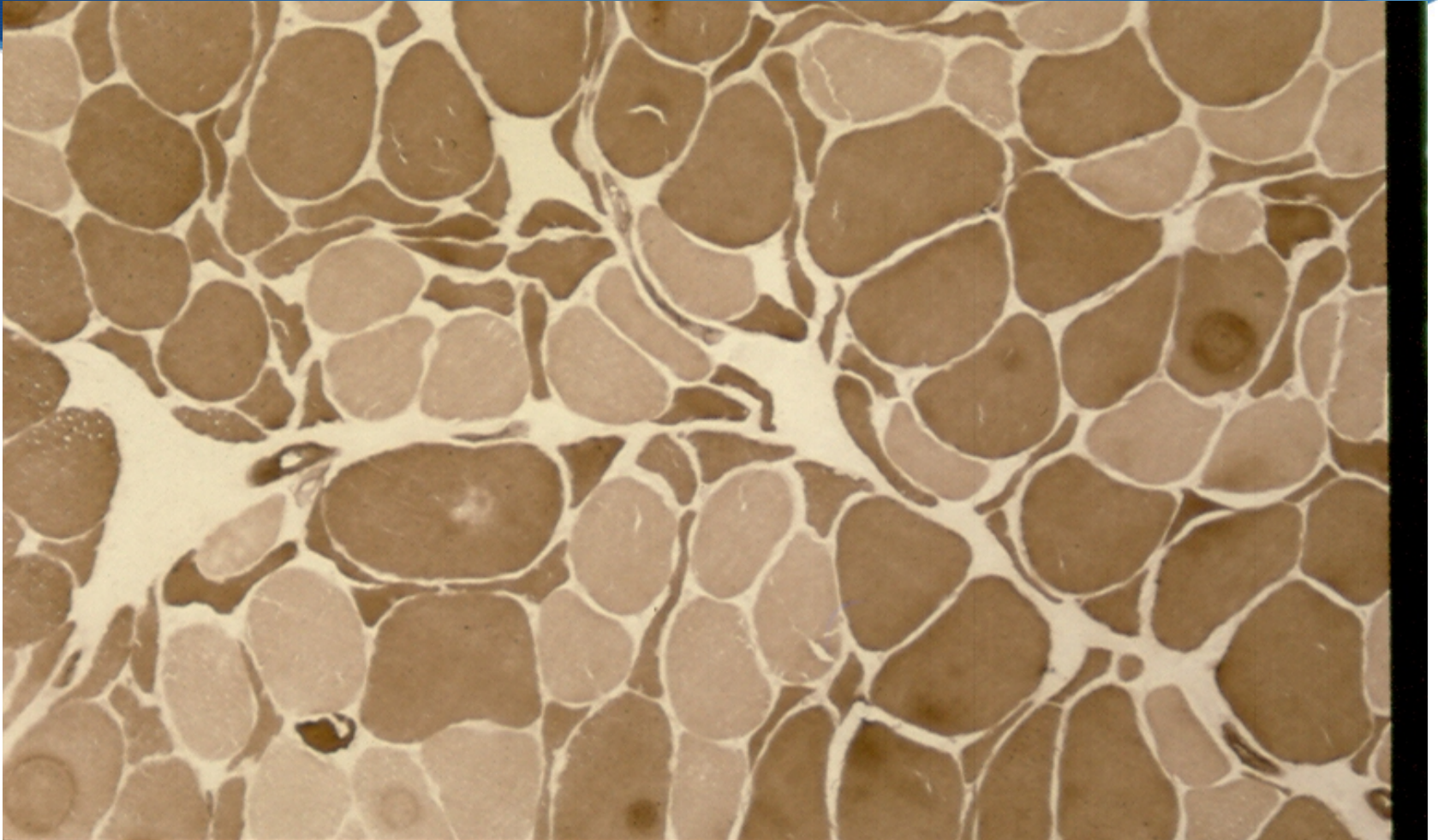


HEMATOXILINA-EOSINA

Atrofia neurógena

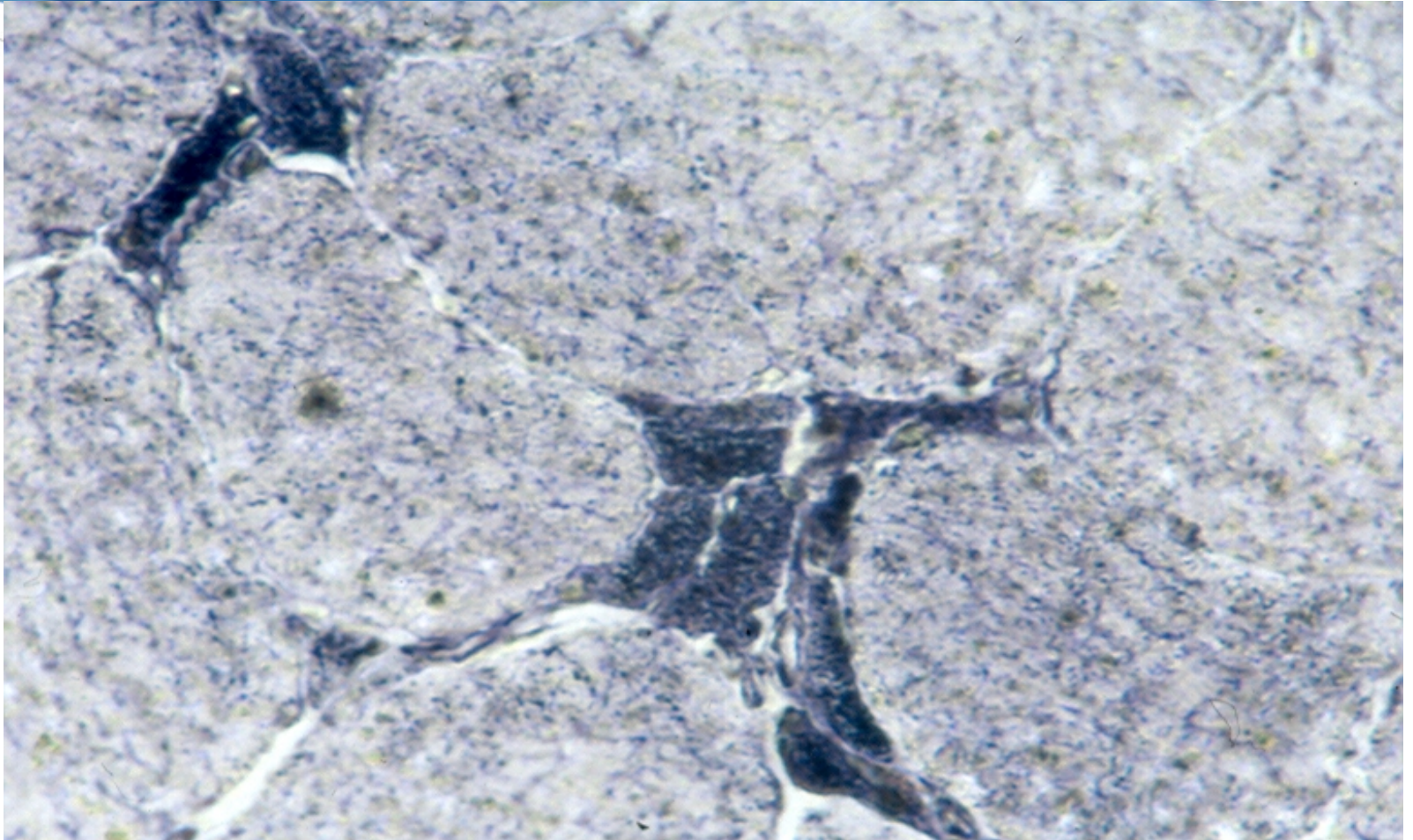


Atrofia neurógena



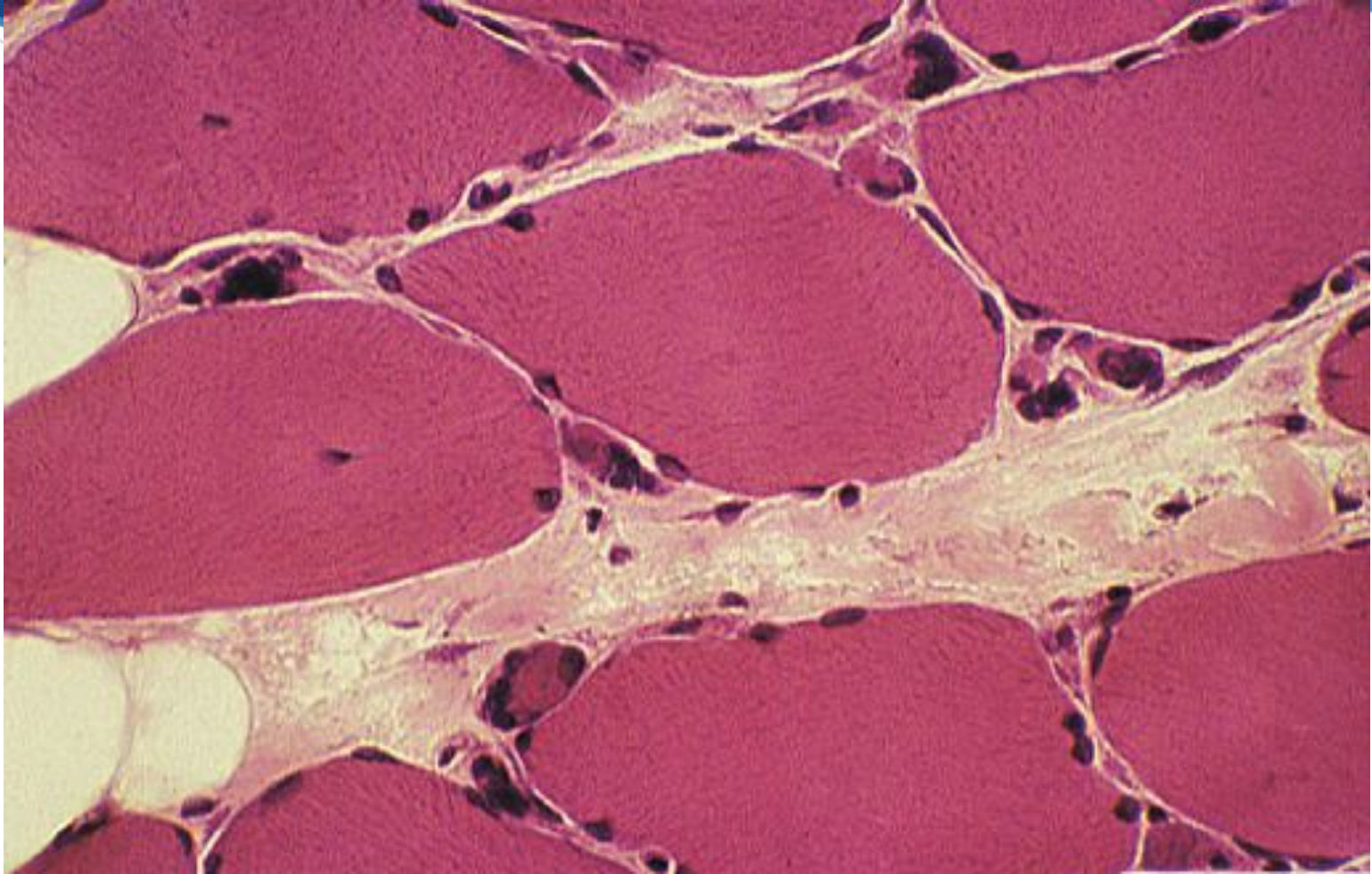
ATPasa 9.4

Atrofia neurógena

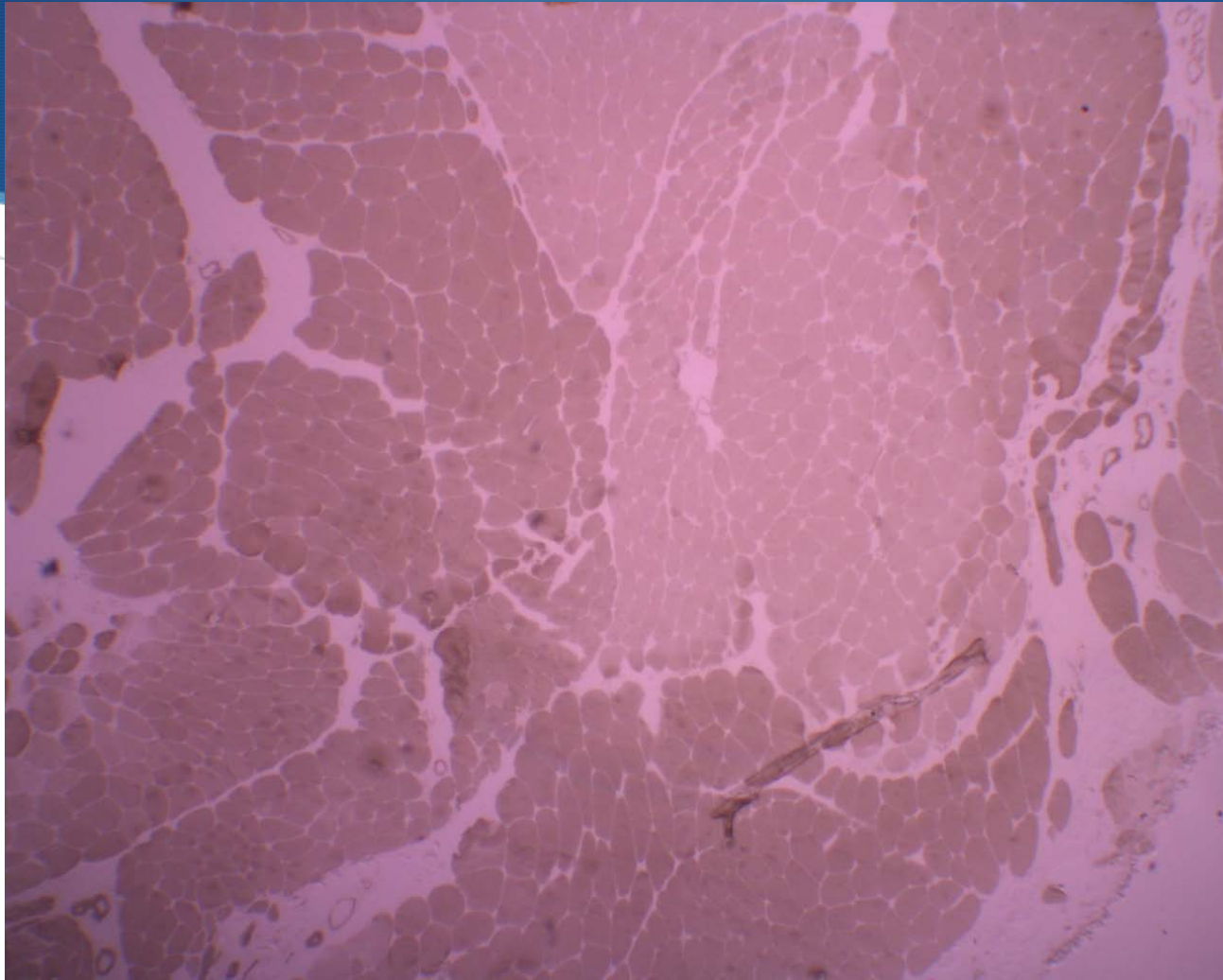


DPNH

Atrofia neurógena



Atrofia neurógena



Reinervación ATPasa 4.3

Unidad Motora

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Segmental demyelination

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related proteins

(c) Myopathies associated with systemic disorders

Endocrine and metabolic
diseases

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**ATROFIA
NEURÓGENA**

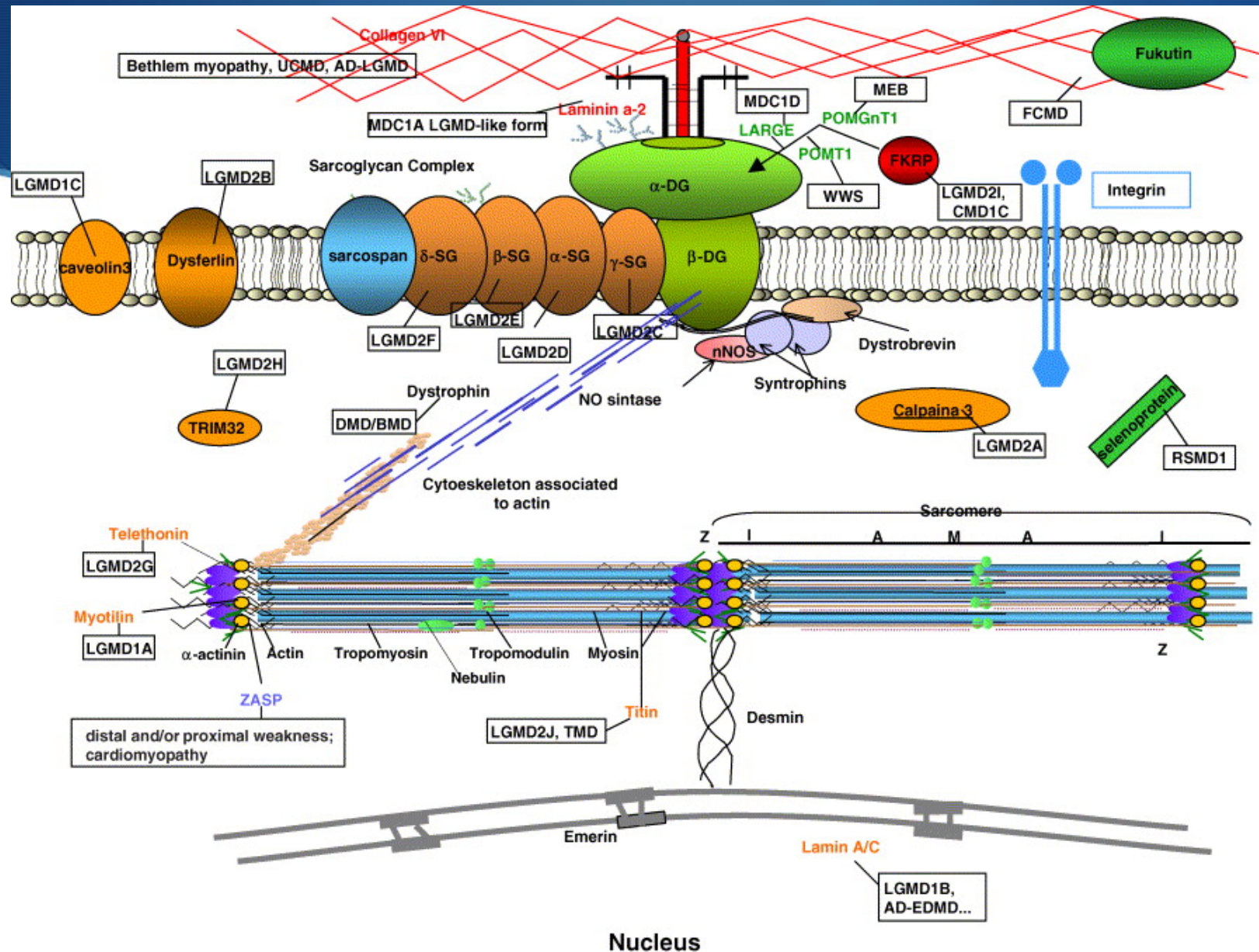
Alteración en la
Transmisión neuromuscular
MIASTENIA

MIOPATIAS

Miopatías

- ◆ **Distrofias musculares**
- ◆ Miopatías metabólicas
- ◆ Miopatías congénitas estructurales
- ◆ Miopatías inflamatorias (no infecciosas)
- ◆ Miopatías inflamatorias infecciosas
- ◆ Enfermedades endocrinas
- ◆ Tóxicos, tto corticoides y otros
- ◆ Neoplasias malignas
- ◆ Desuso

Distrofias musculares



Distrofias musculares

- ◆ Distrofinopatías (Duchenne y Becker...)
- ◆ Distrofias de cinturas
- ◆ Distrofias musculares congénitas
- ◆ Distrofia miotónica (Steinert)
- ◆ Distrofia facio-escapulo-humeral
- ◆ Distrofia oculo-faríngea
- ◆ Distrofia de Emery-Dreifuss

Distrofias musculares: Distrofias de Cinturas

Dominant

1A: Myotilin; 5q31; Dysarthria
1B: Lamin A/C; 1q21; + Cardiac
1C: Caveolin-3; 3p25; Child onset
1D: DNAJB6; 7q36
1E: Desmin; 2q35
1F: TNPO3; 7q32
1G: 4q21
1H: 3p23

Recessive

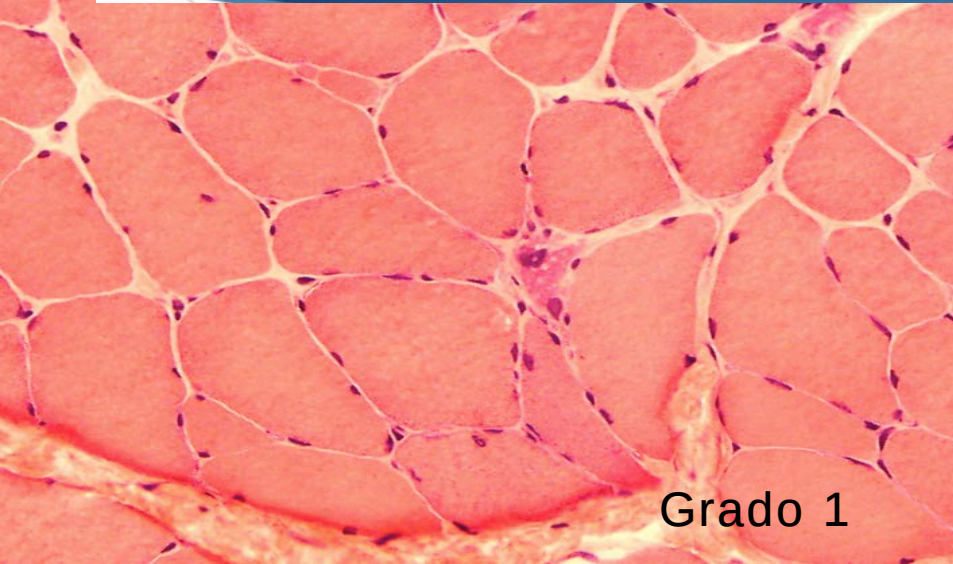
2A: Calpain-3 ;15q15
2B: Dysferlin; 2p13.1
2C: **γ**-Sarcoglycan; 13q12
2D: **α**-Sarcoglycan; 17q21
2E: **β**-Sarcoglycan; 4q12
2F: **δ**-Sarcoglycan; 5q33
2G: Telethonin; 17q12
2H: TRIM32; 9q33
2I (MDDGC5): FKRP; 19q13.3
2J: Titin; 2q24
2K (MDDGC1): POMT1; 9q34
2L: ANO5; 11p14
2M (MDDGC4): Fukutin; 9q31
2N (MDDGC2): POMT2; 14q24
2O (MDDGC3): POMGnT1; 1p32
2P (MDDGC7): DAG1; 3p21
2Q: Plectin 1f; 8q24

Distrofias musculares congénitas

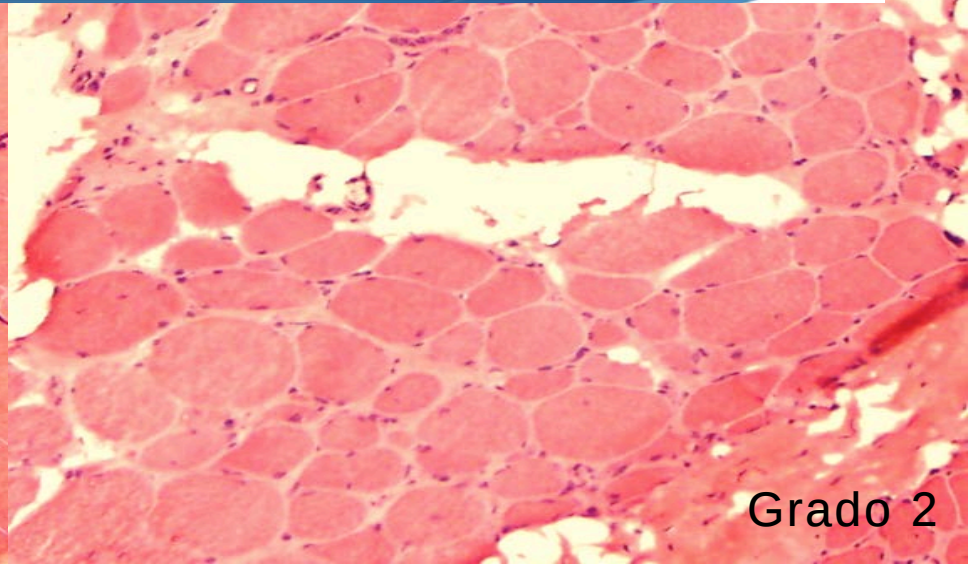
TABLE 12.4 Genetically Identified Forms of Congenital Muscular Dystrophy (CMD)

Common Disease Name	Abbreviation	Gene Symbol	Gene Locus	Protein	Protein Type
'Merosin deficient' CMD	MDC1A	<i>LAMA2</i>	6q	Laminin α 2	Extracellular matrix
Ullrich CMD	UCMD	<i>COL6A1</i>	21q22	Collagen VI	Extracellular matrix
	UCMD	<i>COL6A2</i>	21q22	Collagen VI	Extracellular matrix
	UCMD	<i>COL6A3</i>	2q37	Collagen VI	Extracellular matrix
Integrin α 7 deficiency		<i>ITGA7</i>	12q13	Integrin α 7	Transmembrane (plasma membrane)
Fukuyama CMD	FCMD (MDDGA4)*	<i>FKTN**</i>	9q31-q33	Fukutin	Possible substrate for glycosyltransferase
Muscle-eye-brain disease	MEB (MDDGA3)	<i>POMGNT1</i>	1p3	O-mannose β -1,2-N-acetyl-glucosaminyl transferase	Glycosyltransferase
Walker-Warburg syndrome	WWS				
	(MDDGA1)	<i>POMT1</i>	9q34	Protein-O-mannose transferases 1 & 2	Glycosyltransferase
	(MDDGA2)	<i>POMT2</i>	14q24.3	Isoprenoid synthase containing domain	?
	(MDDGA7)	<i>ISPD</i>	7p21		
–	MDC1B	?	1q42	?	?
–	MDC1C (MDDGA5)	<i>FKRP</i>	19q1	Fukutin-related protein	Possible phosphosugar transferase
–	MDC1D (MDDGA6)	<i>LARGE</i>	22q12	LARGE	Possible glycosyltransferase
Rigid spine syndrome	RSMD1	<i>SEPN1</i>	1q36	Selenoprotein N1	Glycoprotein of endoplasmic reticulum

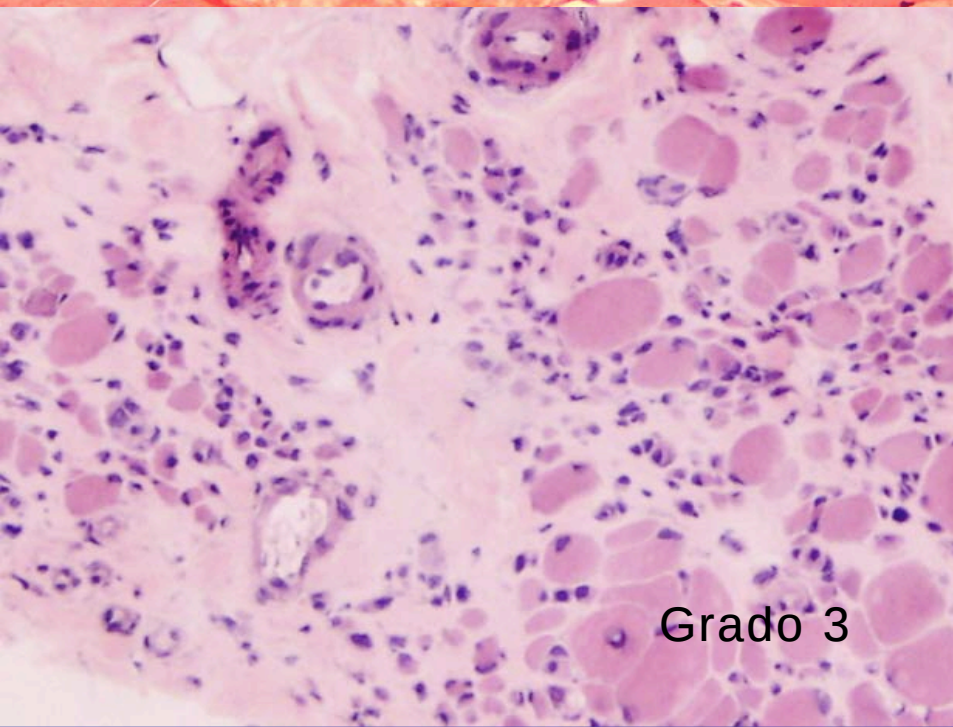
Alteración arquitectura



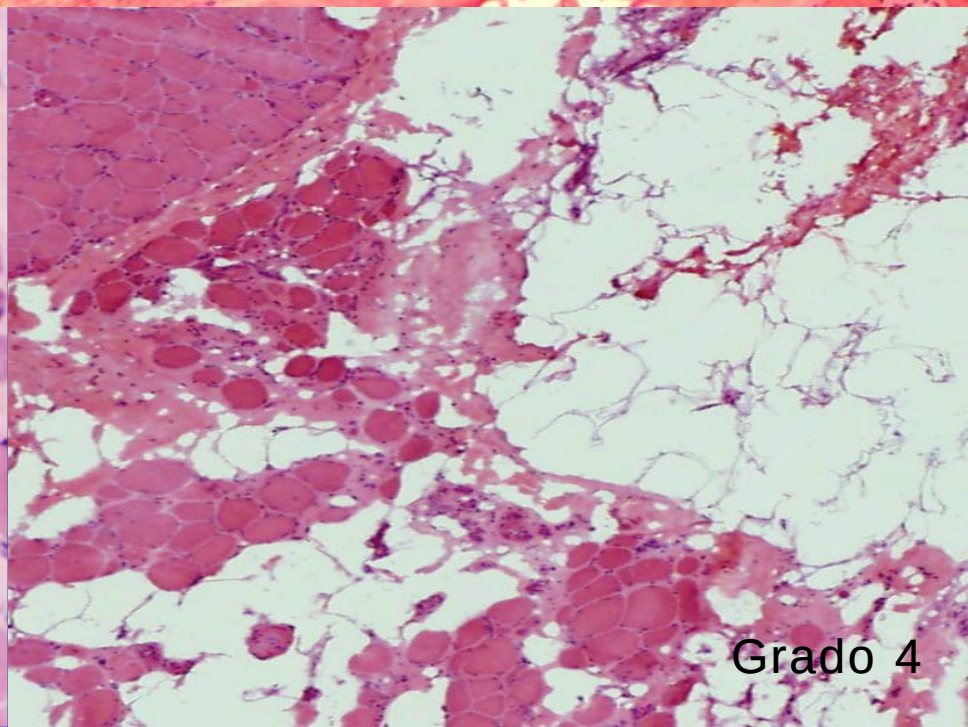
Grado 1



Grado 2

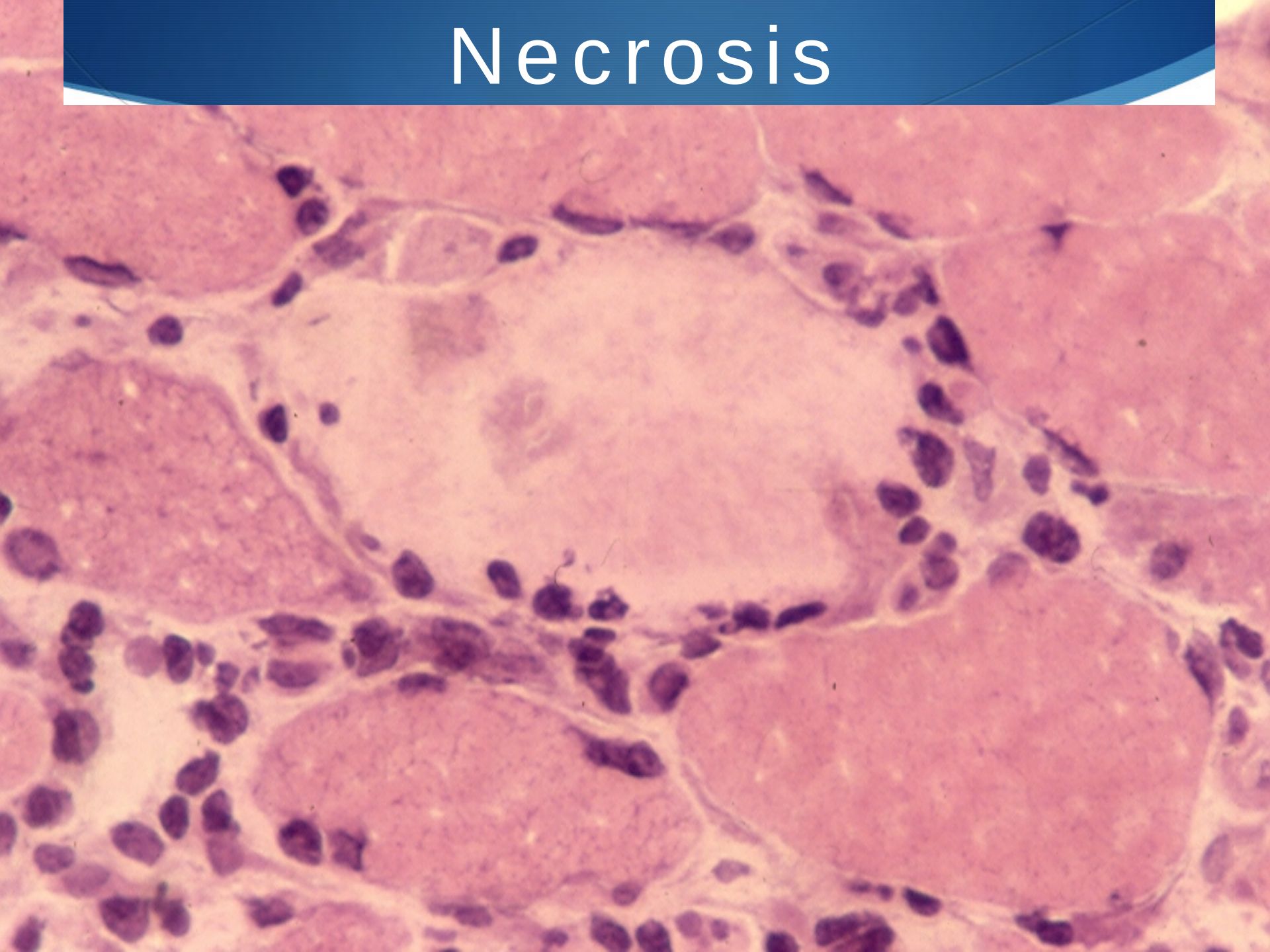


Grado 3

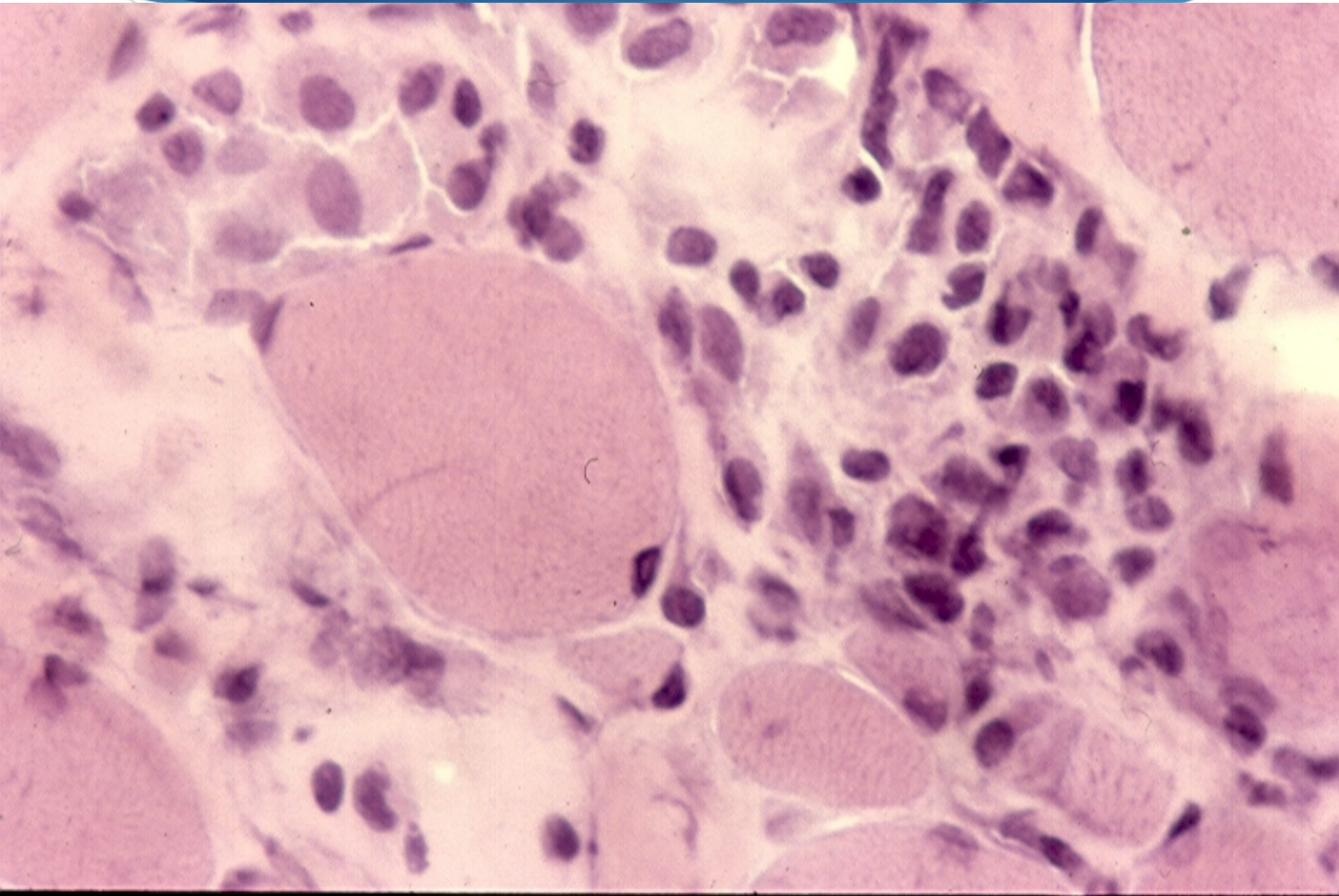


Grado 4

Necrosis



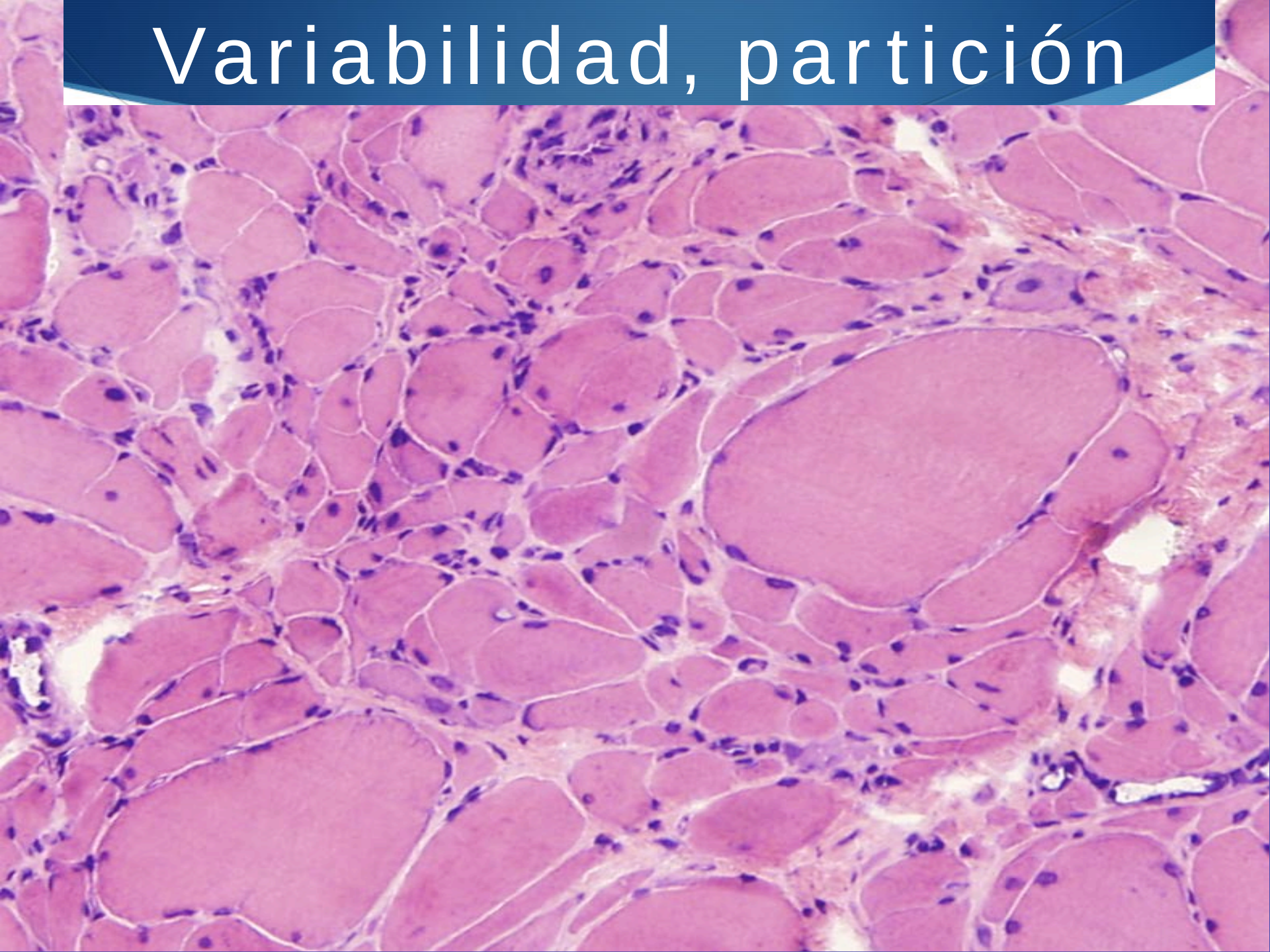
Inflamación, miofagocitosis



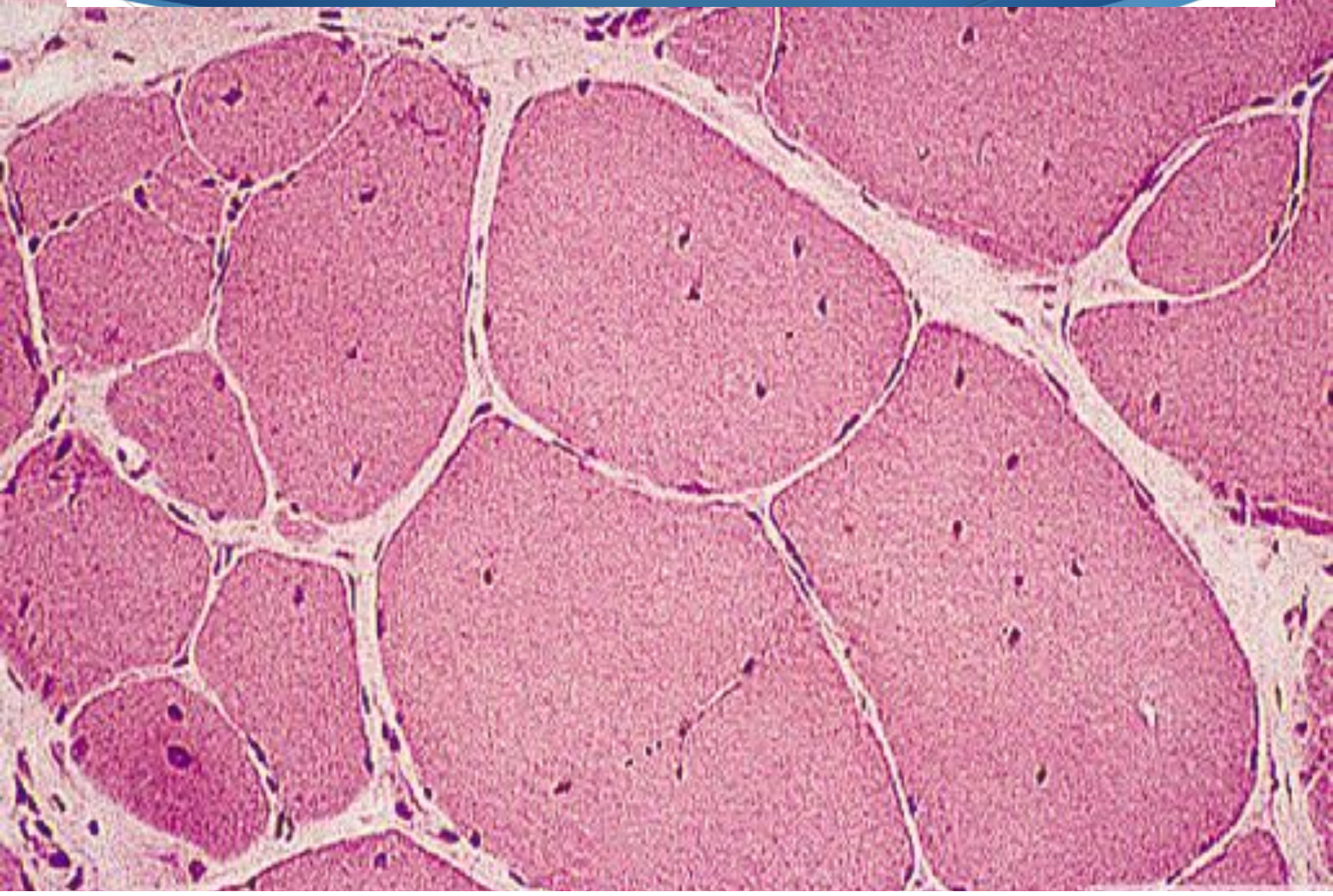
Regeneración



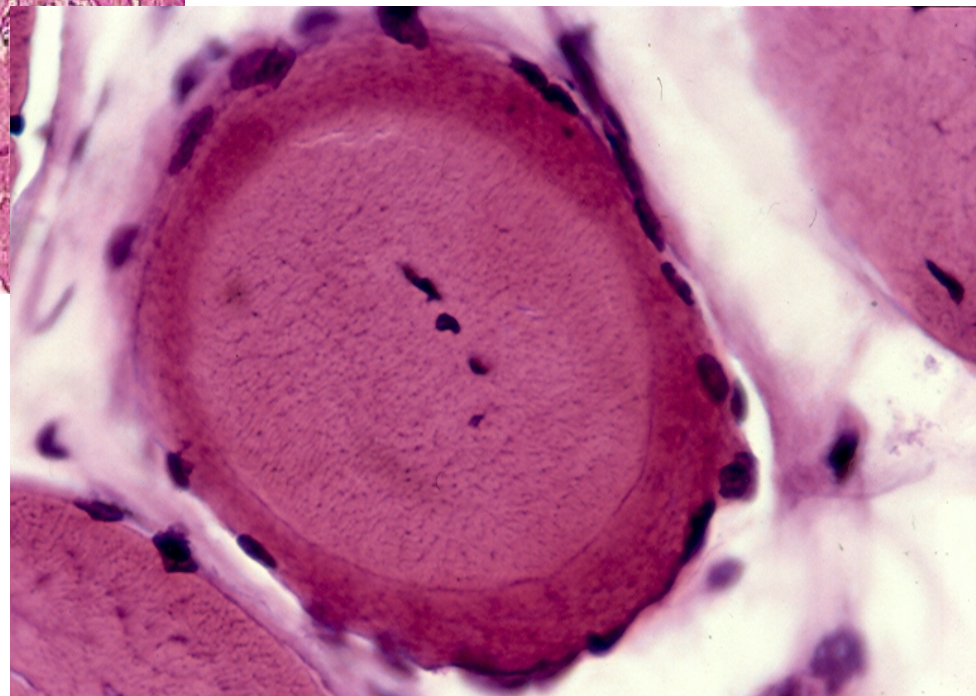
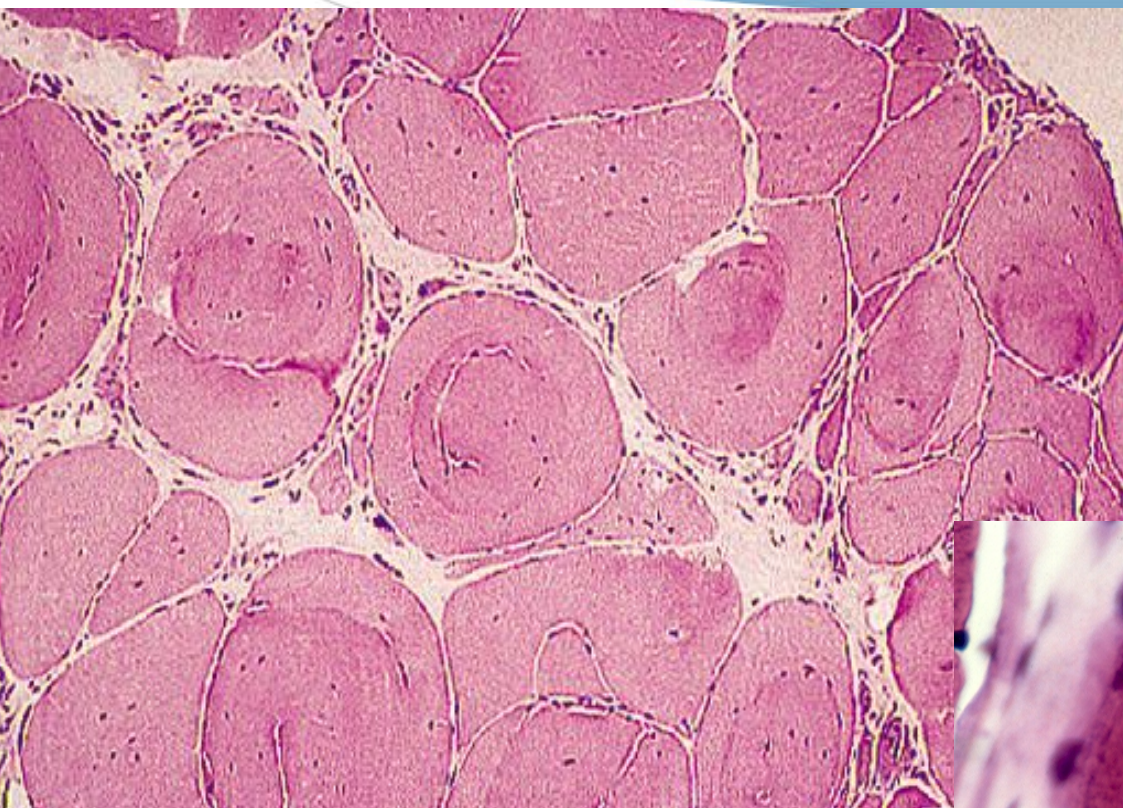
Variabilidad, partición

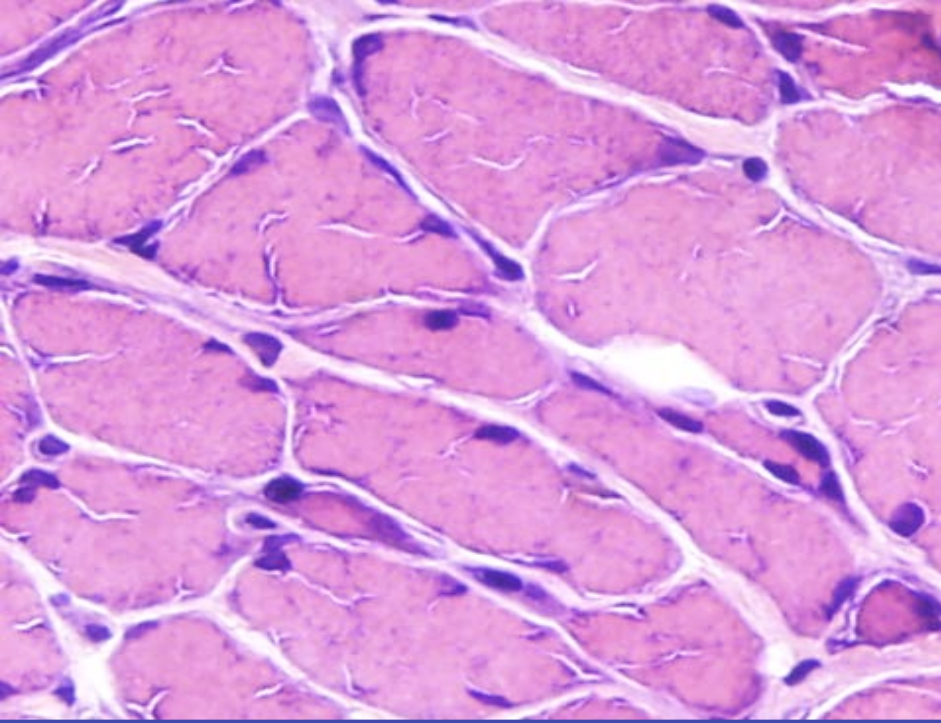


Internalización nuclear



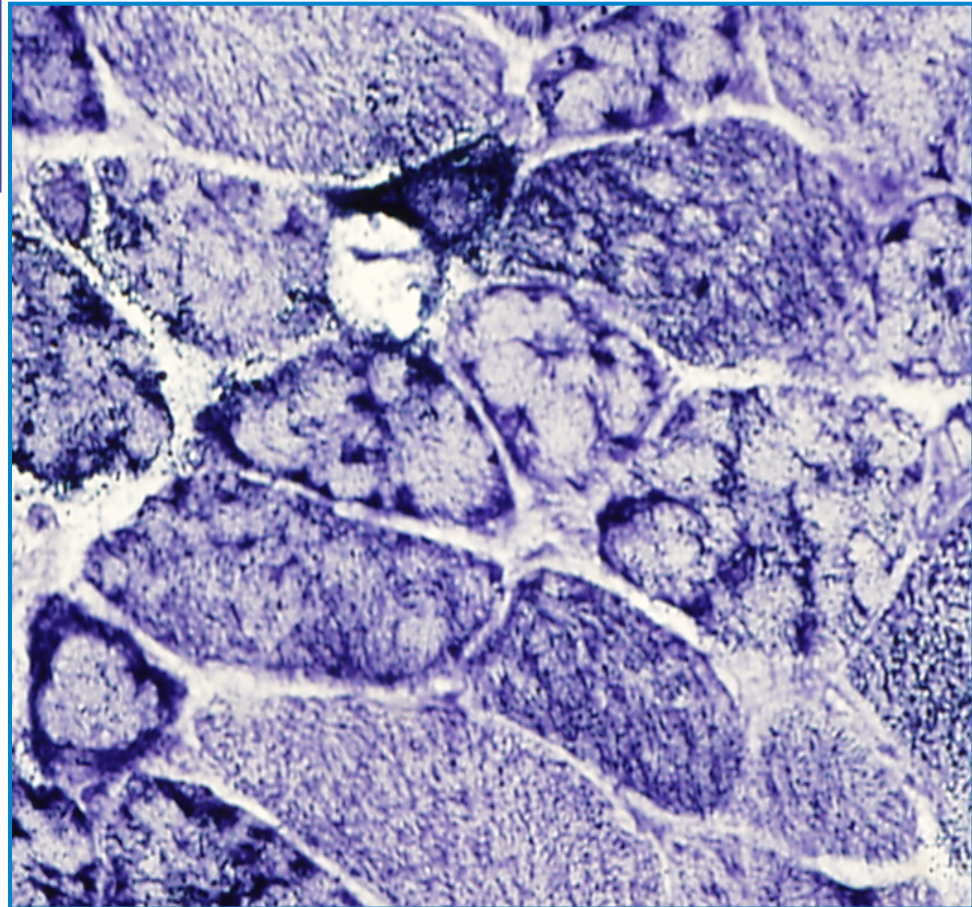
Alteraciones estructurales

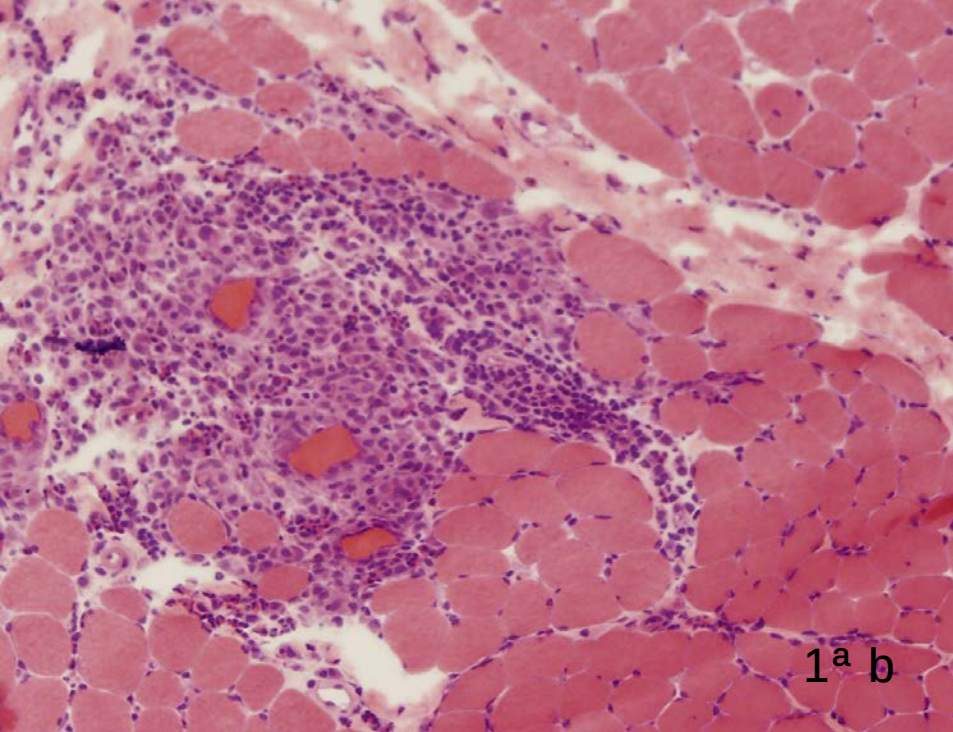




Fibras lobuladas

Calpainopatías-DC 2A



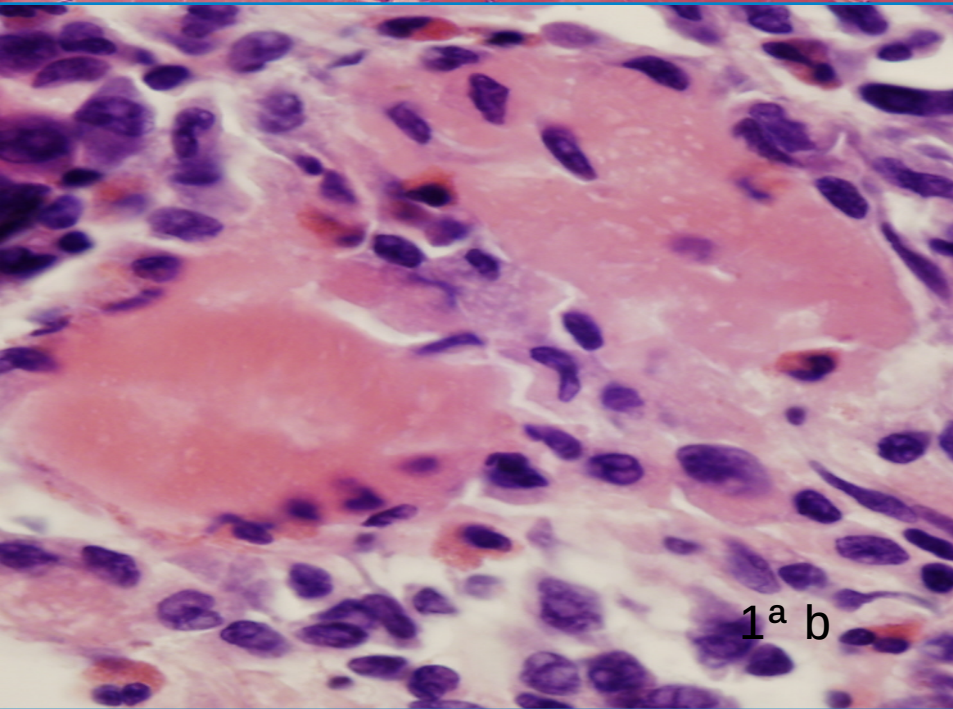


1ª b

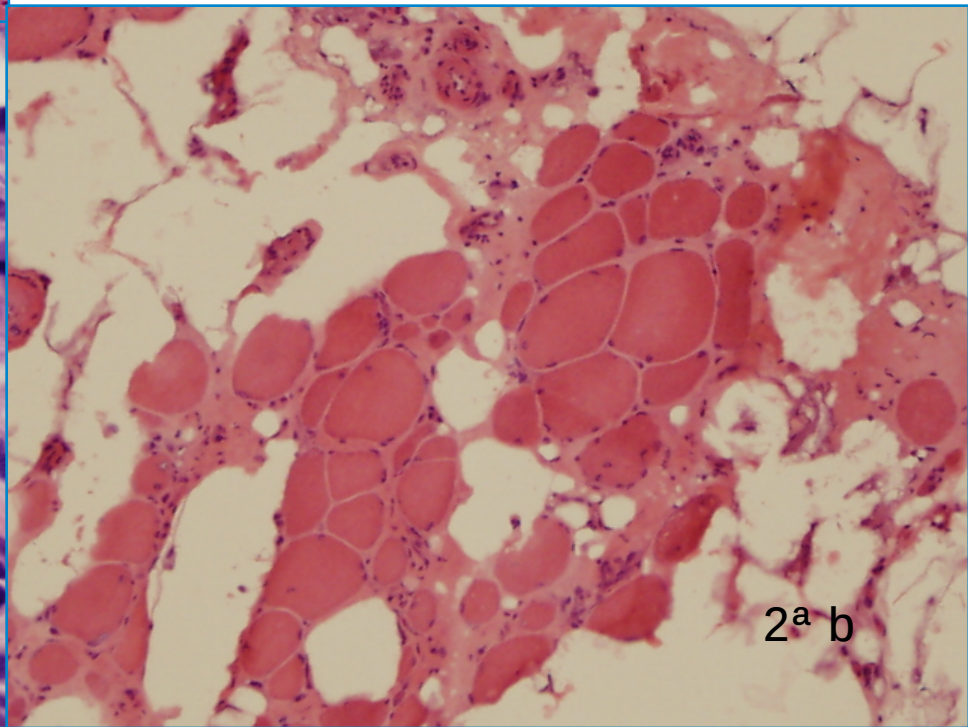
Inflamación + Eosinófilos

DC 2A – Calpainopatía

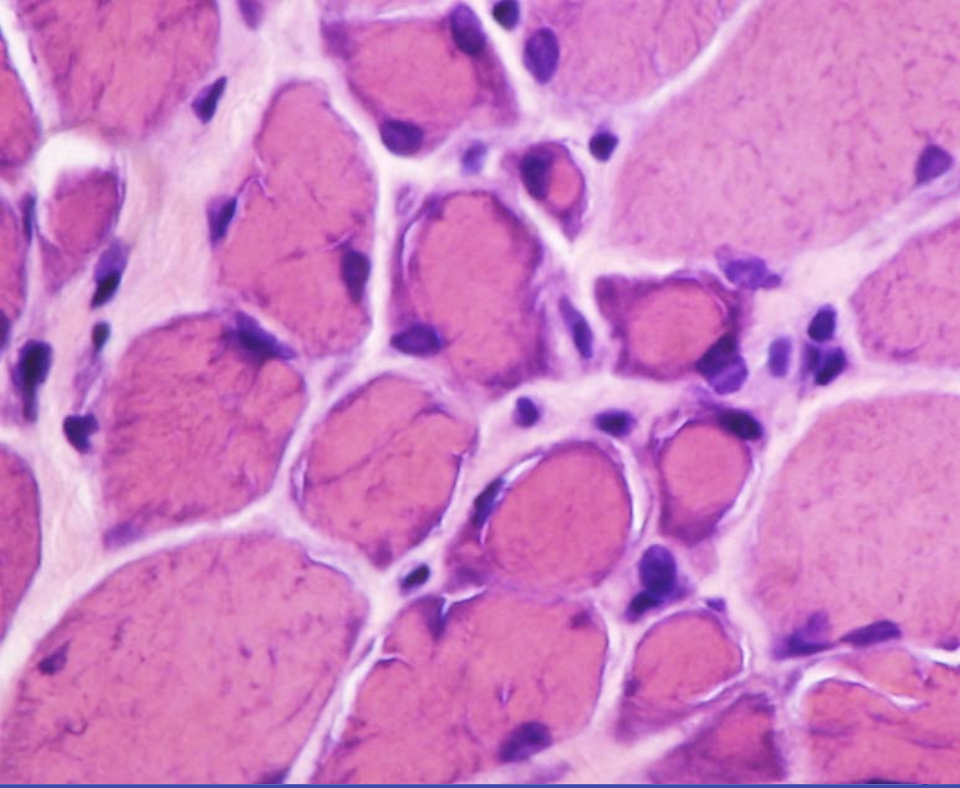
Fase precoz



1ª b

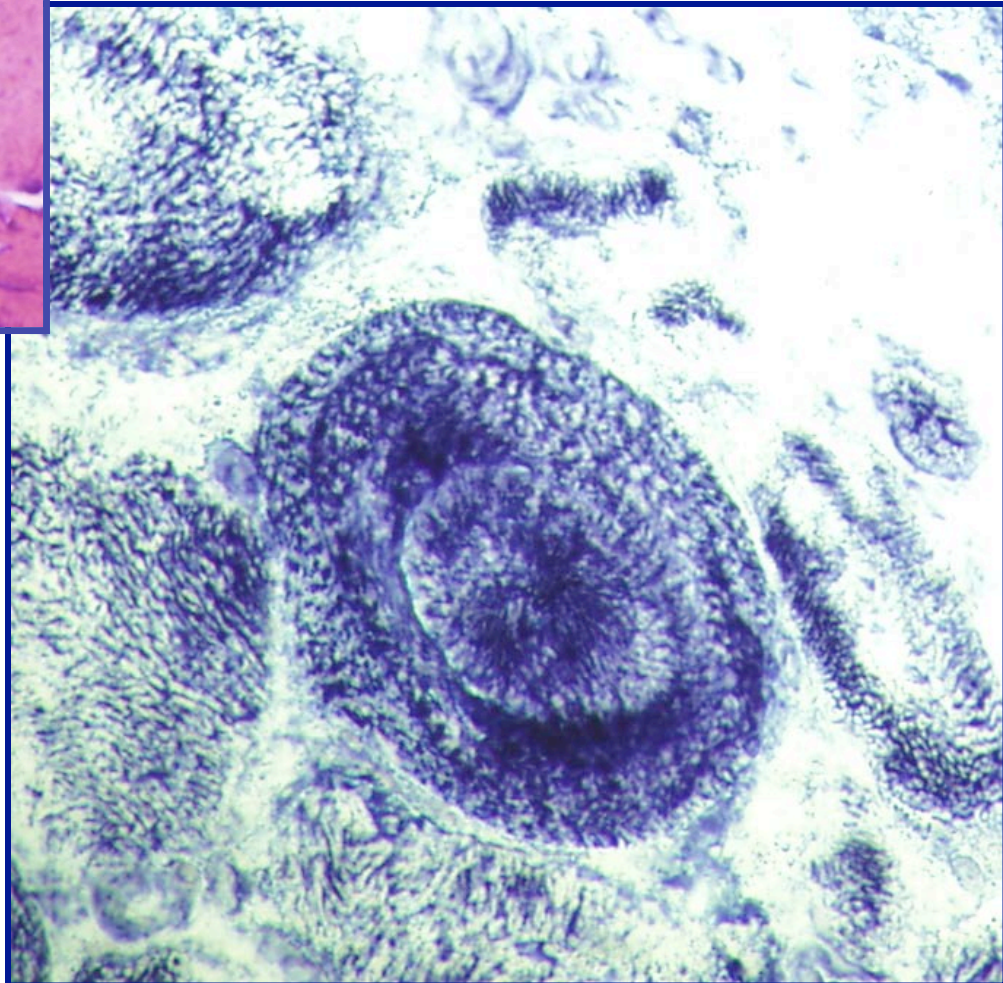


2ª b



Anillos y masas sarcoplásmicas

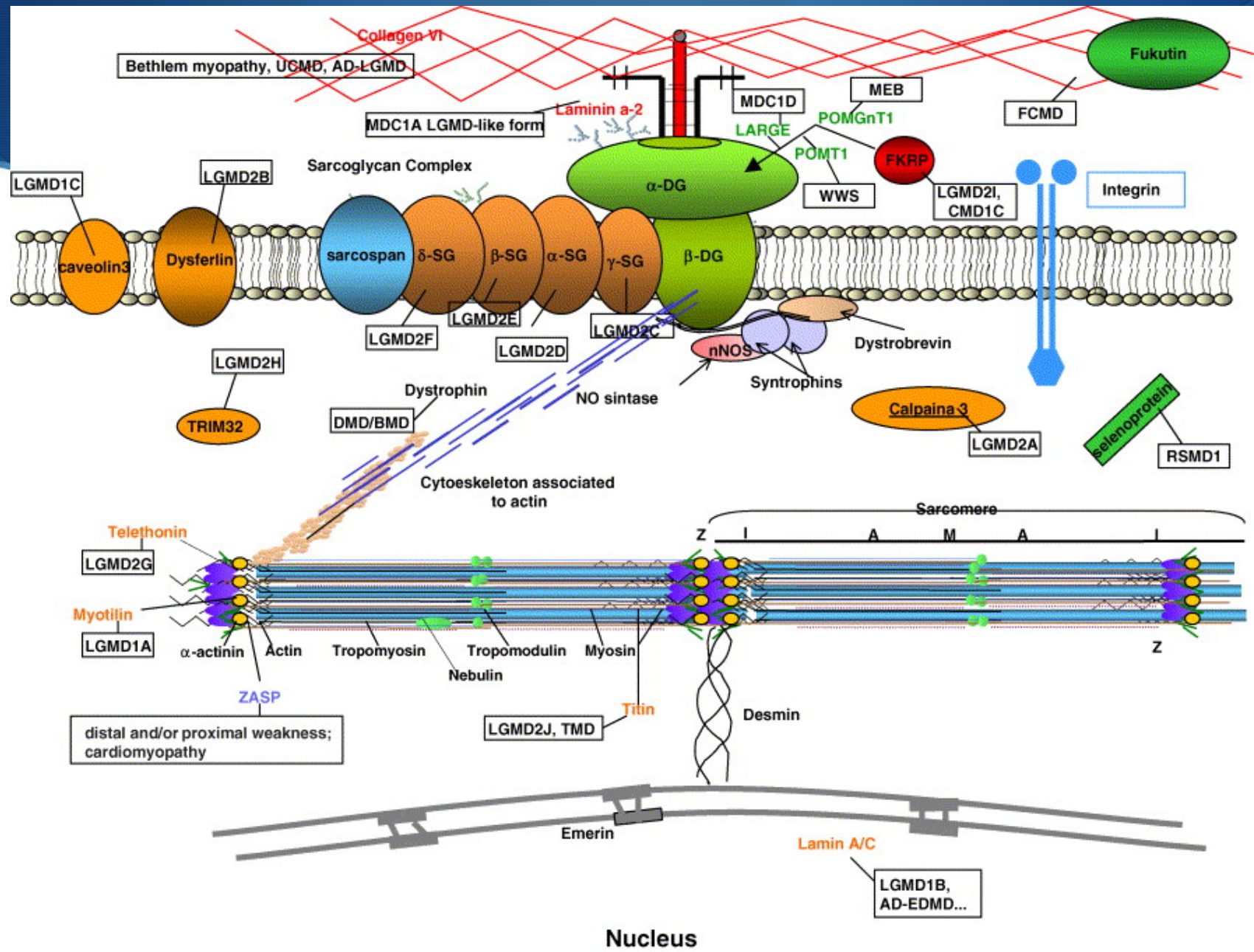
Disferlinopatías- DC2B



Distrofias musculares

- ◆ Distrofinopatías (Duchenne y Becker...)
- ◆ Distrofias de cinturas
- ◆ Distrofias musculares congénitas
- ◆ Distrofia de Emery-Dreifuss
- ◆ Distrofia miotónica (Steinert)
- ◆ Distrofia facio-escapulo-humeral
- ◆ Distrofia oculo-faríngea

Distrofias musculares



Proteínas de membrana

Inmunohistoquímica

Distrofinopatías:

- ♦-Distrofina

Distrofias de Cinturas

- ♦-Caveolina

- ♦-Sarcoglicanos α , β , γ , δ ,

- ♦-Disferlina

- ♦Calpaína (WB)

Distrofia muscular congénita

- ♦Merosina

- ♦Colágeno VI

- ♦Alfa-distroglicano

Enf Emery-Dreifuss:

- ♦Emerina

M. Miofibrilares: Desmina, Miotilina

Immunohistoquímica

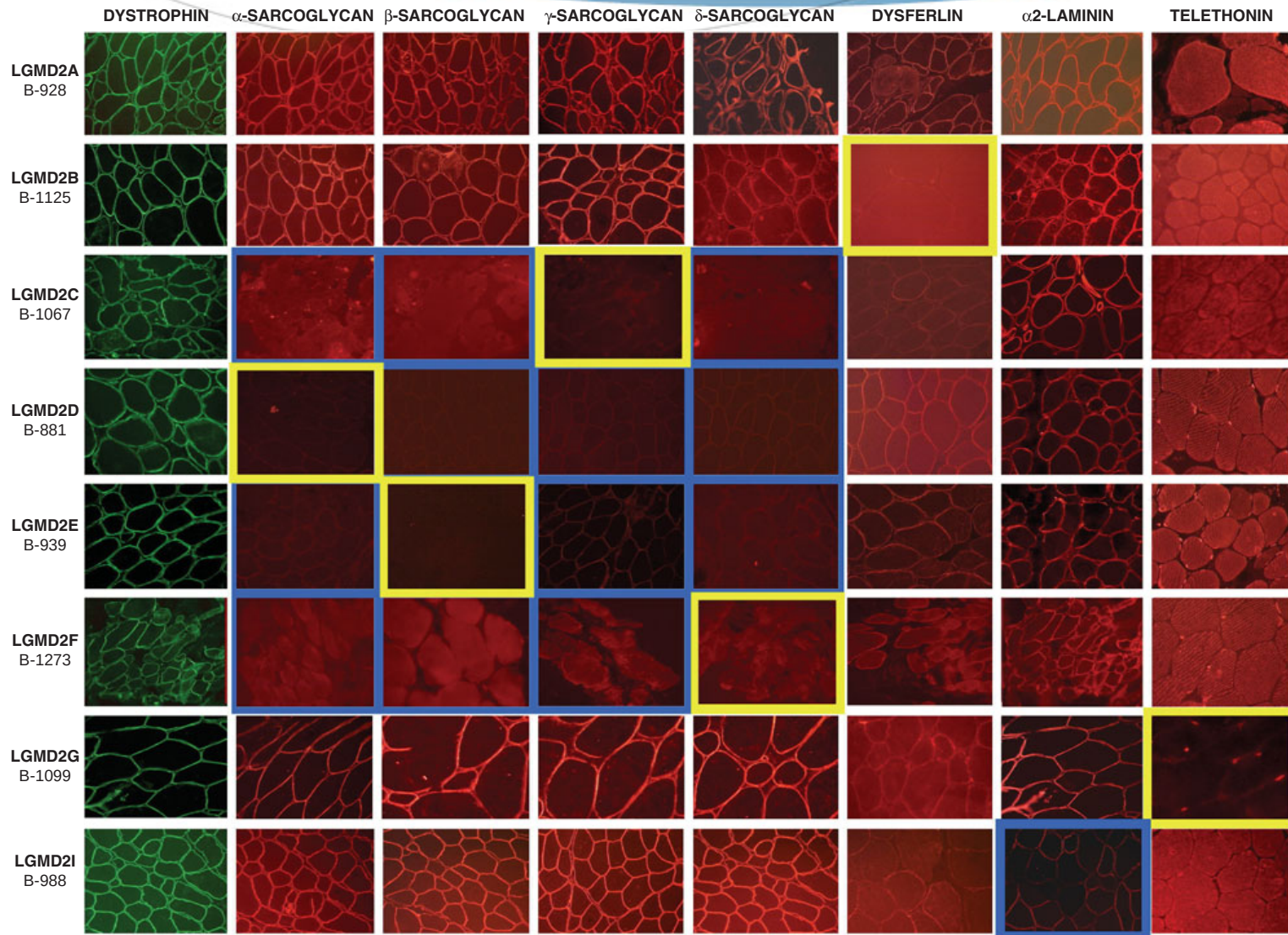


Figure 11.2. Immunohistochemical analysis for muscle proteins in patients with AR forms of LGMDs. Yellow square, primary deficient protein; blue square, secondary deficient proteins.

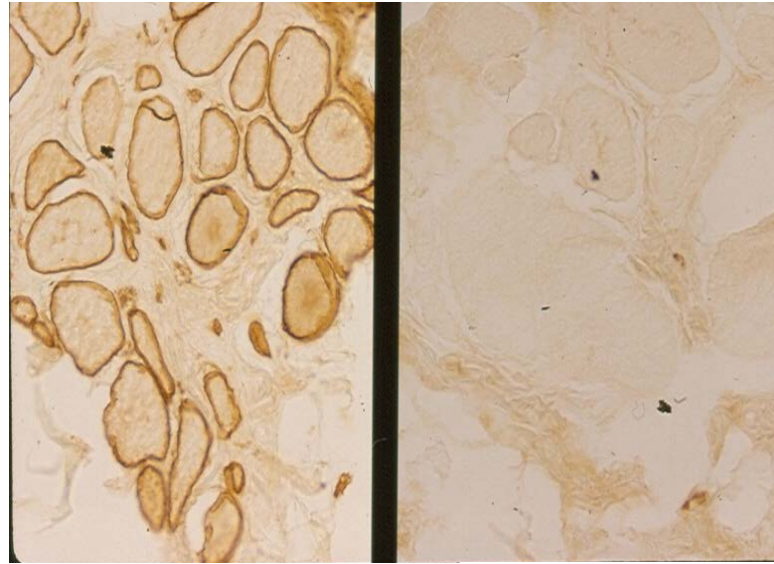
Proteínas de membrana

Inmunohistoquímica



Normal

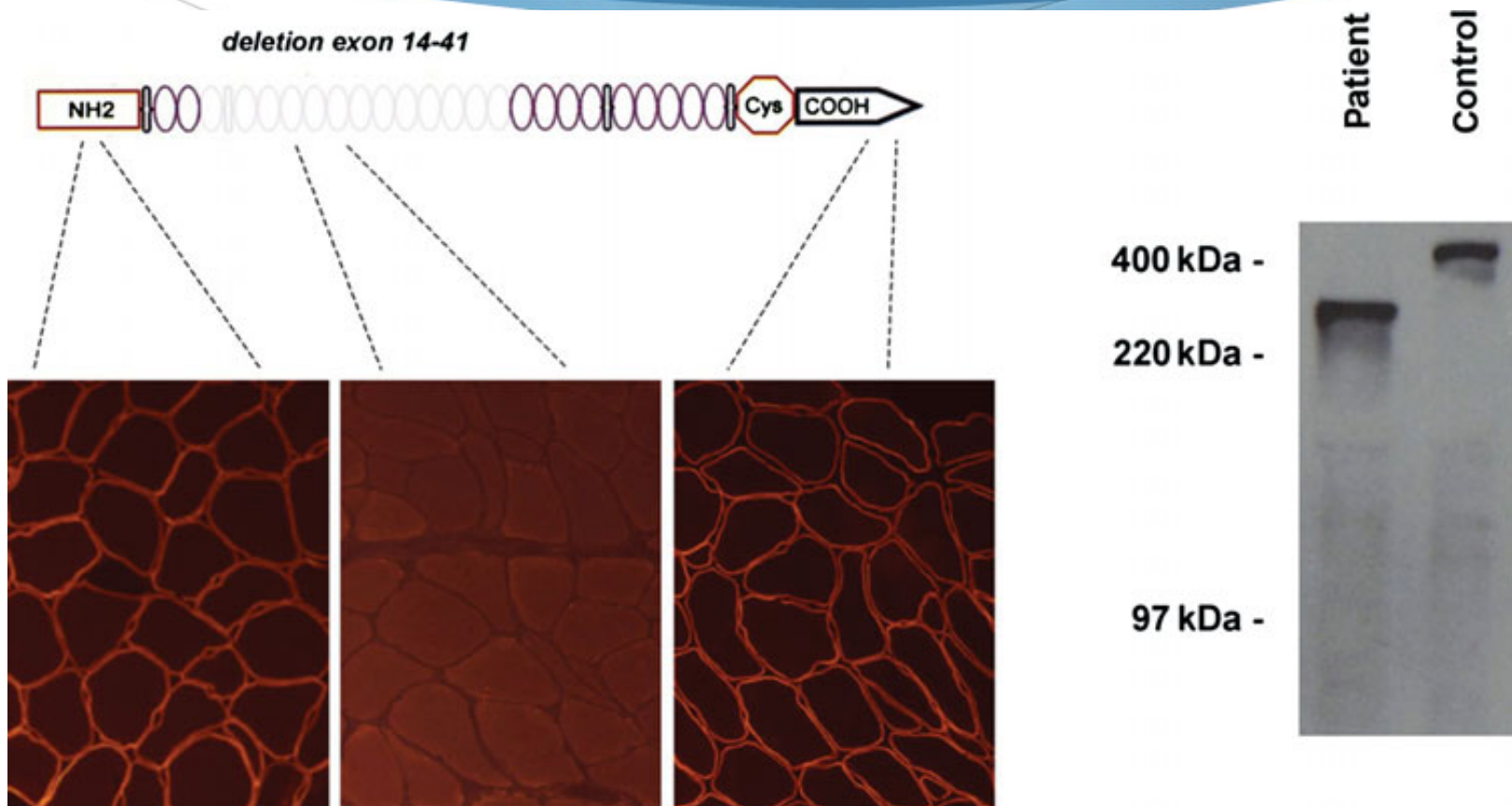
Distrofinopatía grave, enf. Duchenne



Espectrina-
Control

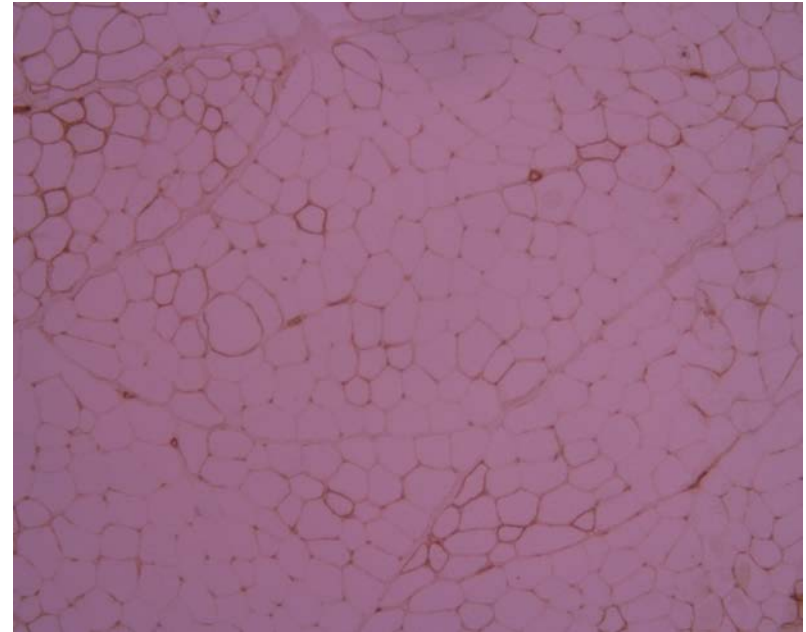
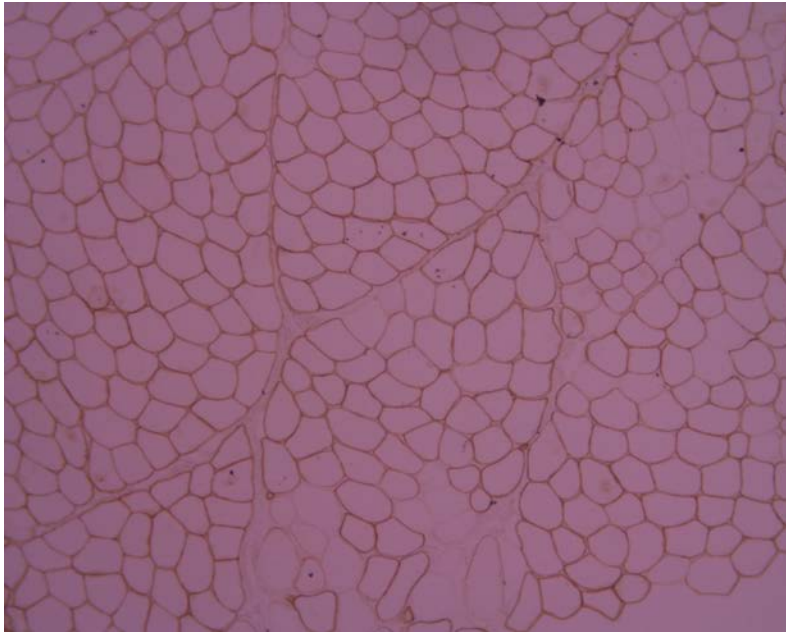
Distrofina

Distrofinopatía leve, enf. Becker



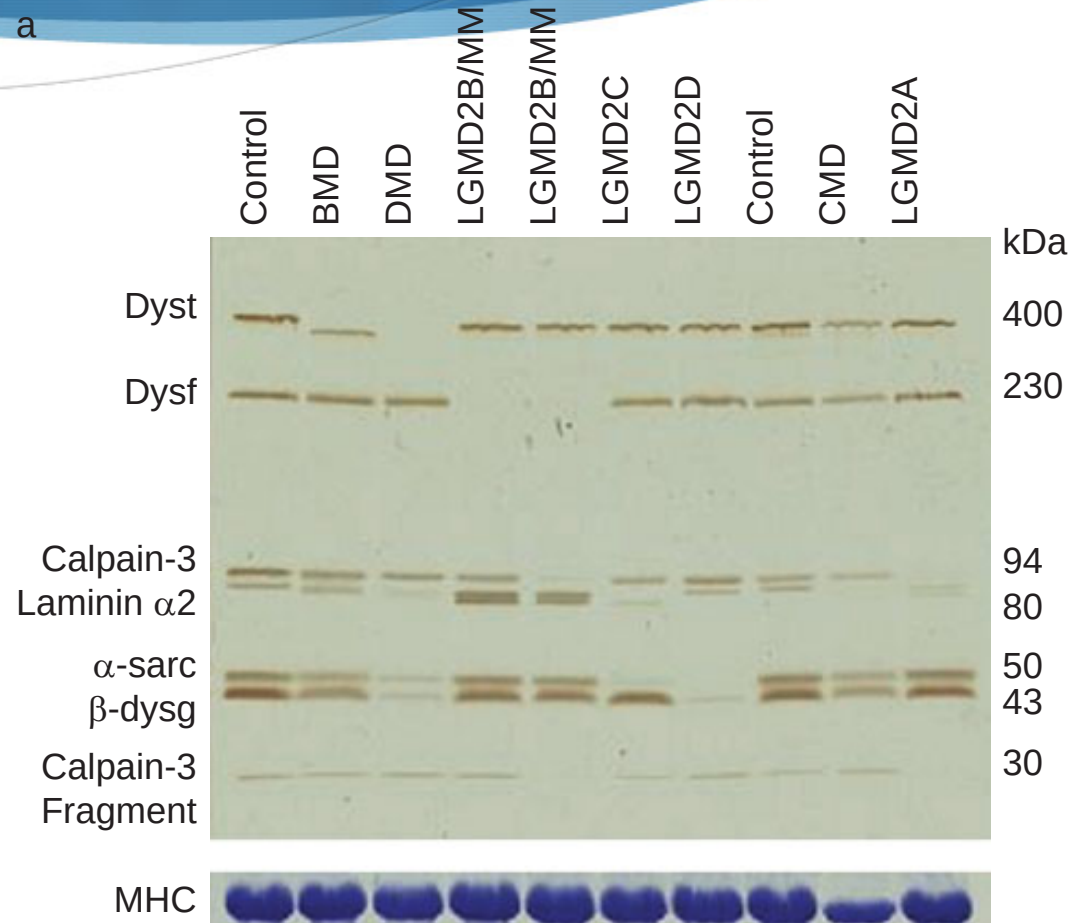
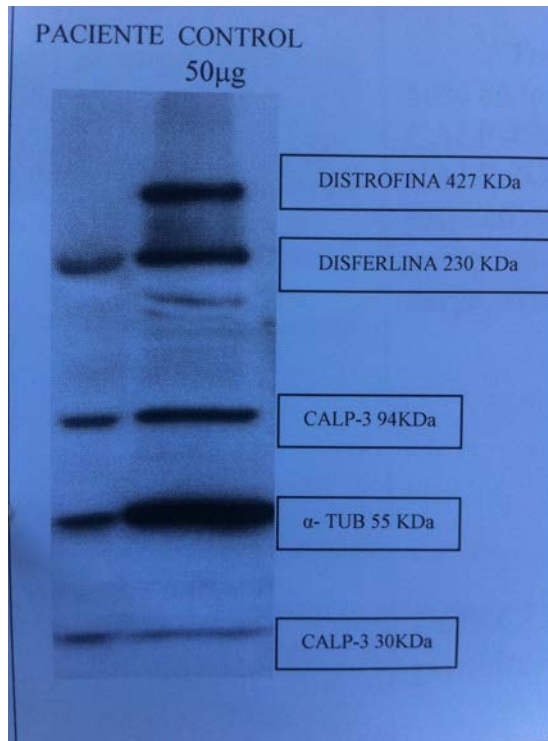
Distrofinopatía

Portadora sintomática



Estudio de proteínas por Western Blot

Variaciones en el tamaño y cuantificación



Miopatías Miofibrilares

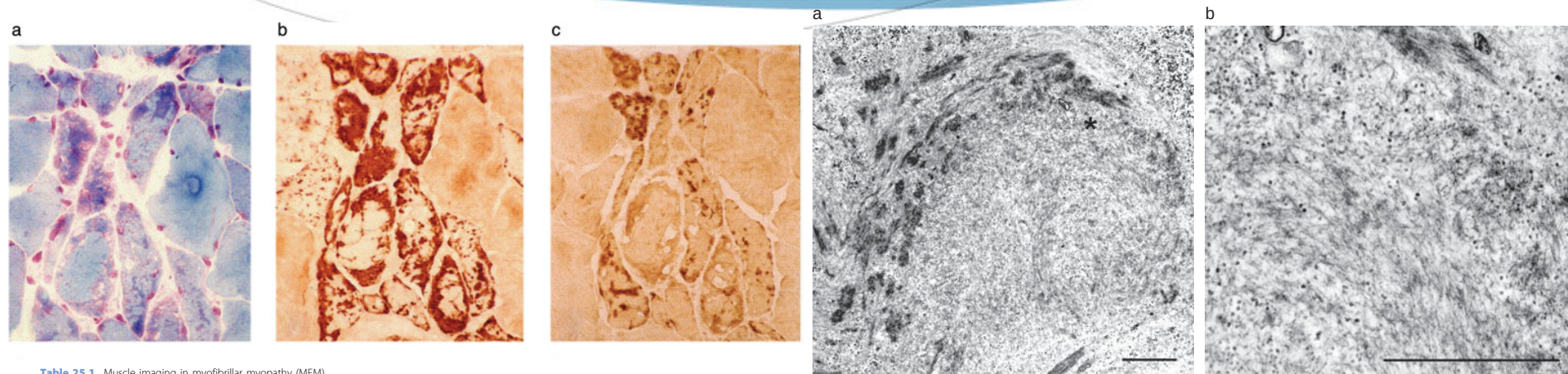


Table 25.1. Muscle imaging in myofibrillar myopathy (MFM)

Muscles	Desminopathy [8, 30, 32]	α B-Crystallinopathy [32]	Myotilinopathy [13, 14, 16, 31, 32]	Zaspopathy [19, 32]	Filaminopathy [32]
Gluteus maximus	+	+	+	+	
Sartorius	+	+	+		
Gracilis	+	+			
Iliopsoas	+				
Rectus femoris					
Vastus intermedius			+	+	+
Vastus medialis			+	+	+
Vastus lateralis			+	+	
Adductor magnus	+		+	+	+
Semimembranosus	+		+	+	+
Semitendinosus	+	+	+		
Biceps femoris	+		+	+	+
Soleus	+		+	+	+
Peroneal	+	+		+	
Medial gastrocnemius	+		+	+	+
Tibialis anterior	+		+	+	

Miopatías

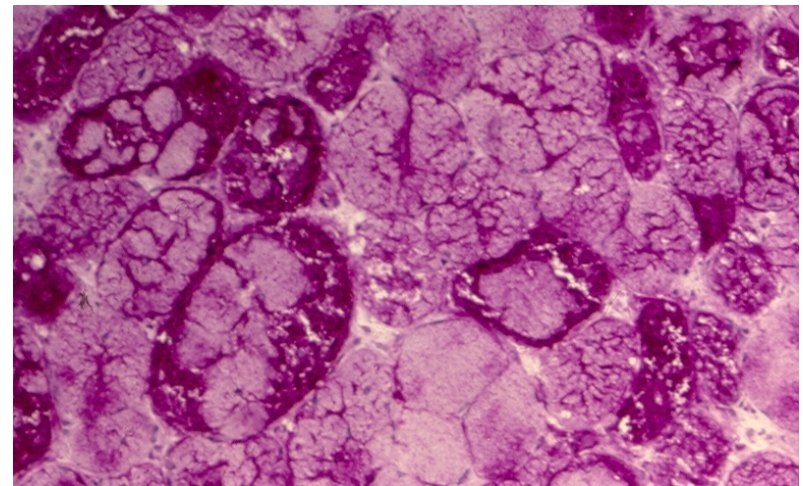
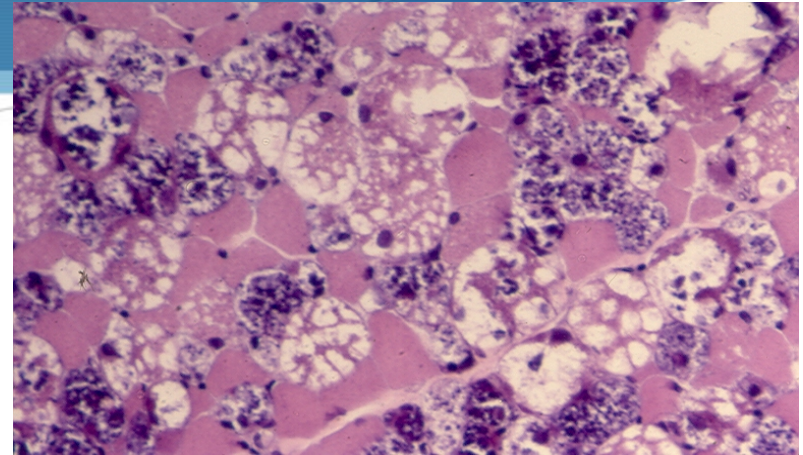
- ◆ Distrofias musculares
- ◆ **Miopatías metabólicas**
- ◆ Miopatías congénitas
- ◆ Miopatías inflamatorias (no infecciosas)
- ◆ Miopatías inflamatorias infecciosas
- ◆ Enfermedades endocrinas
- ◆ Tóxicos, tto corticoides y otros
- ◆ Neoplasias malignas
- ◆ Desuso

Miopatías metabólicas

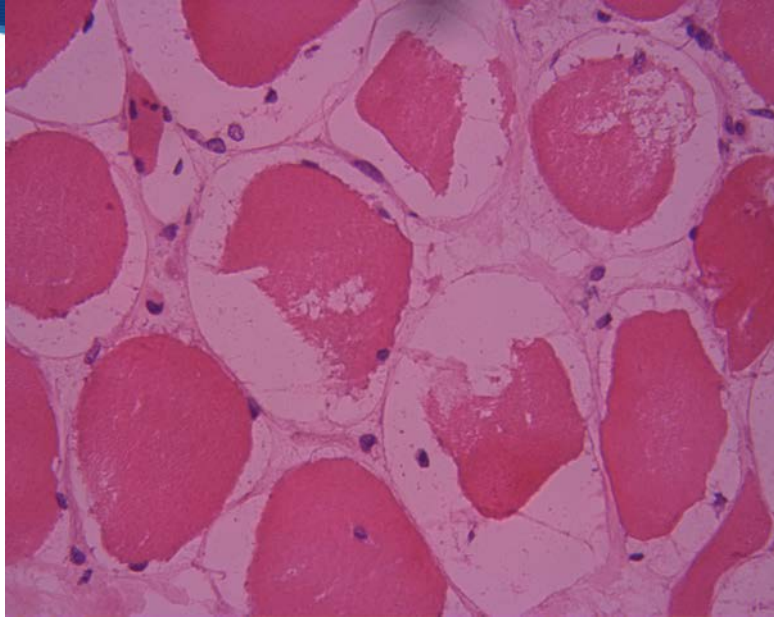
- 💧 Glucogenosis
- 💧 Miopatías mitocondriales
- 💧 Miopatías lipídicas

M. Metabólicas- Glucogenosis

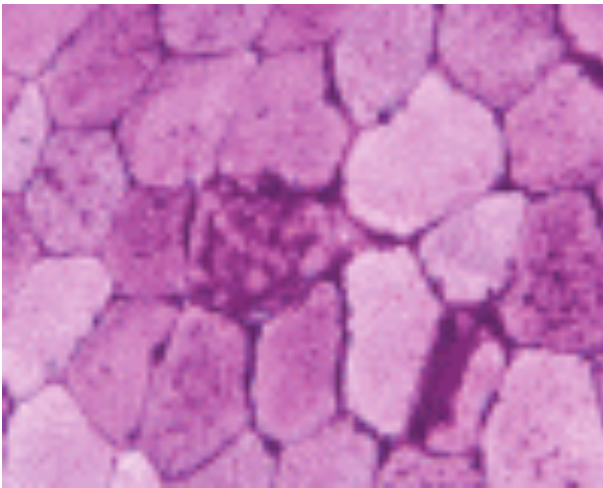
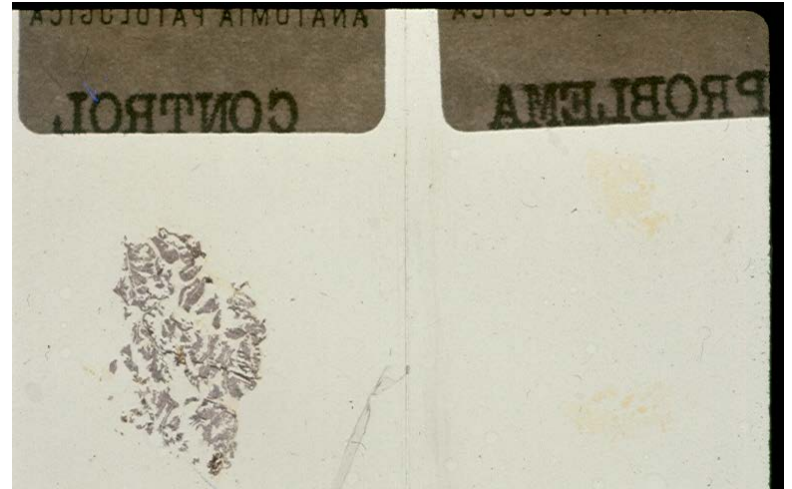
- 💧 Tipo II (Pompe)
- 💧 Tipo III
- 💧 Tipo IV
(Amilopectinosis)
- 💧 Tipo V (McArdle)
- 💧 Tipo VII (Tarui)



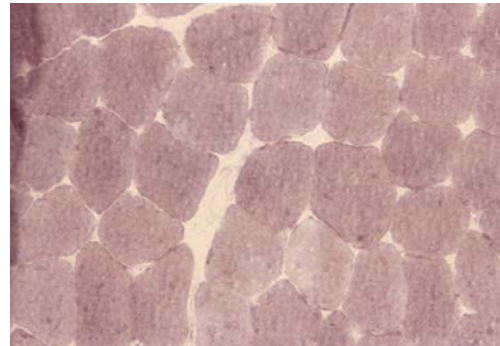
Glucogenosis tipo V, enf McArdle



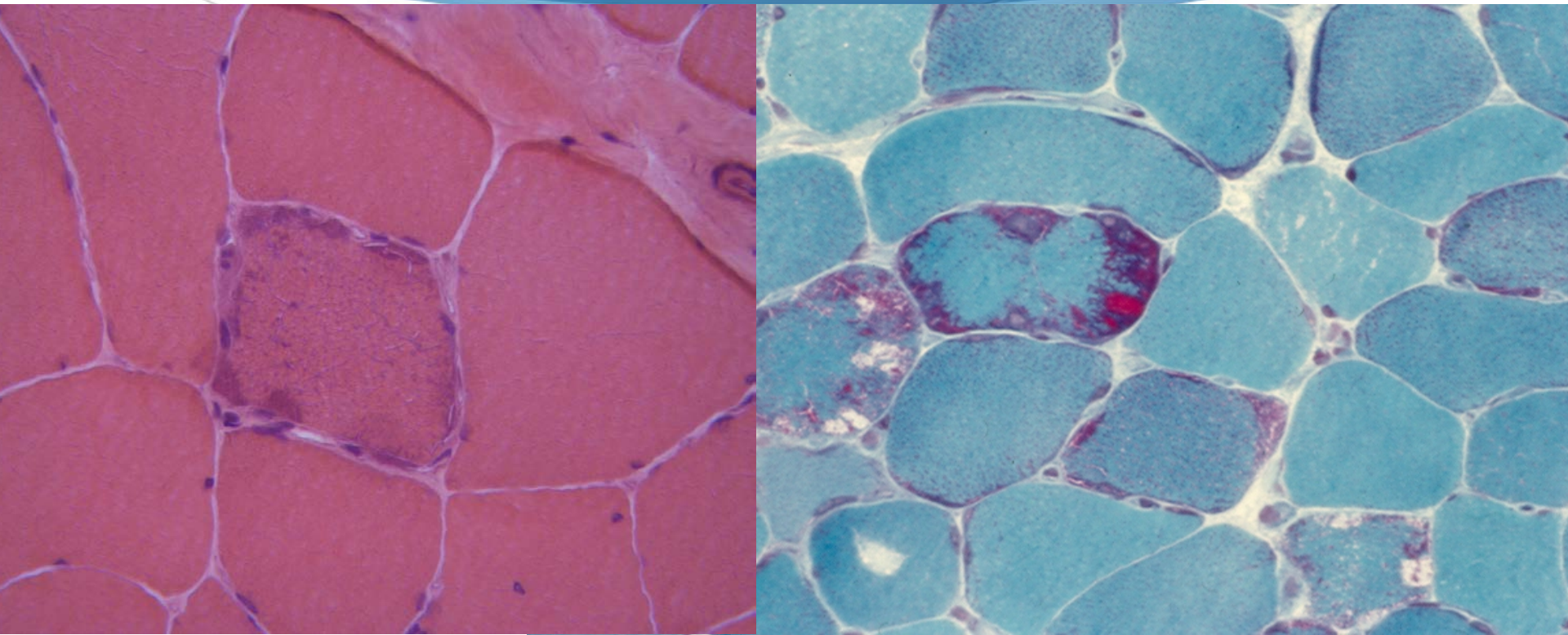
Miofosforilasa



PAS

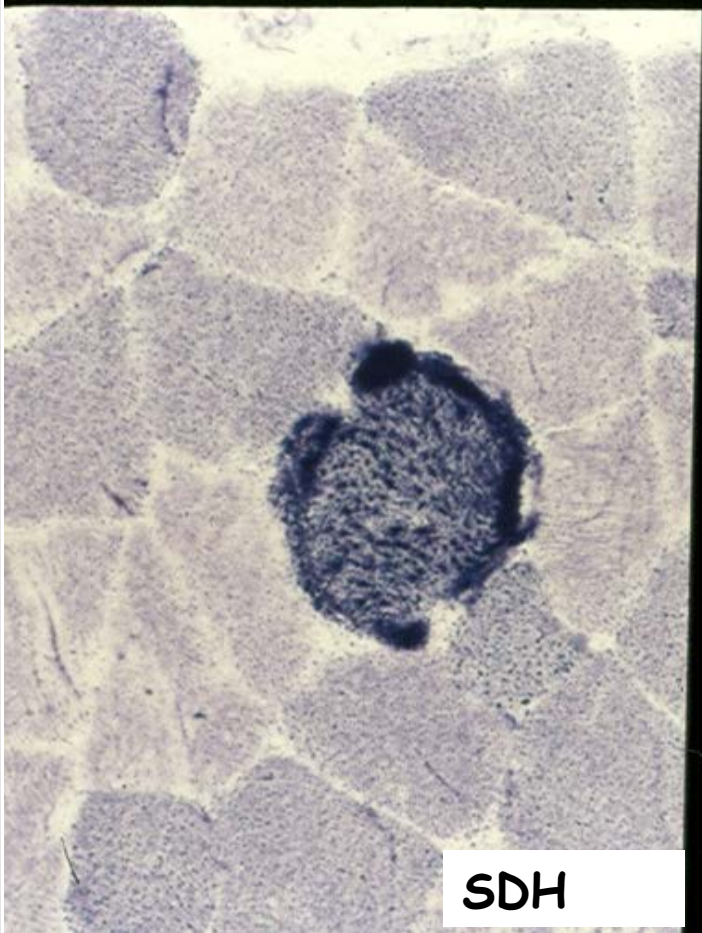


M. Metabólicas- Mitocondriales

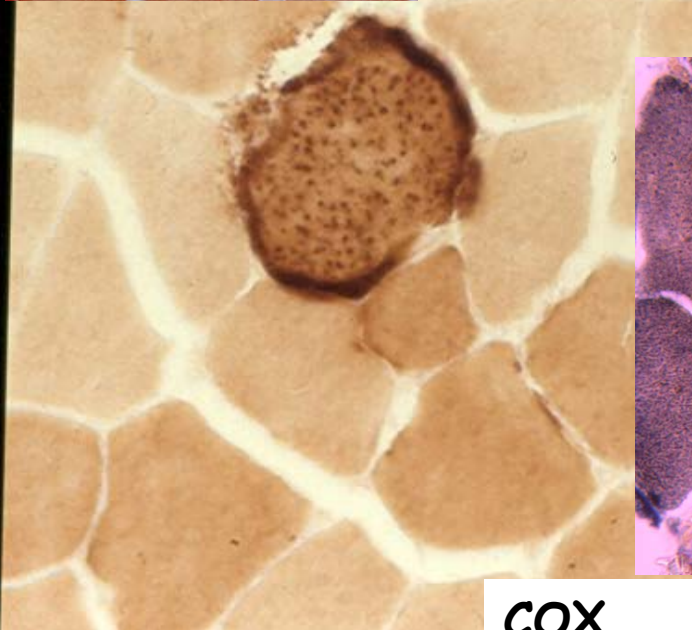
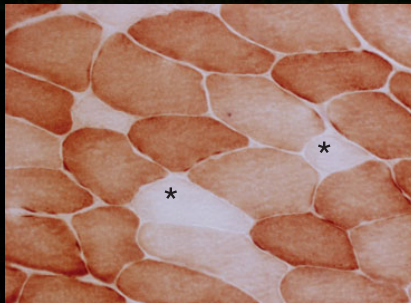


Fibras rojo-rasgadas

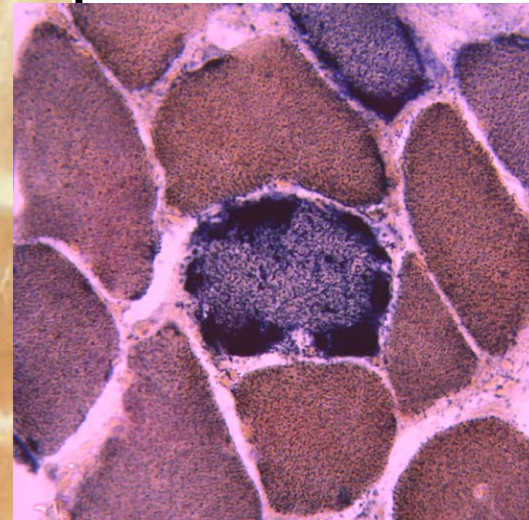
M.Mitochondrial Fibras Rojo-Rotas



SDH

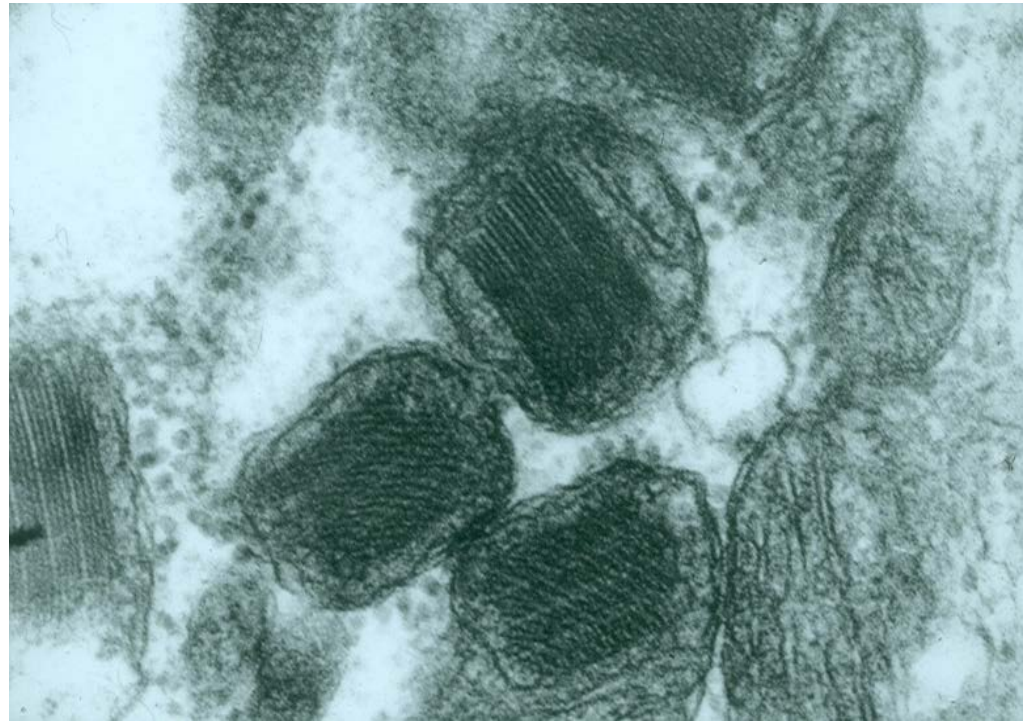
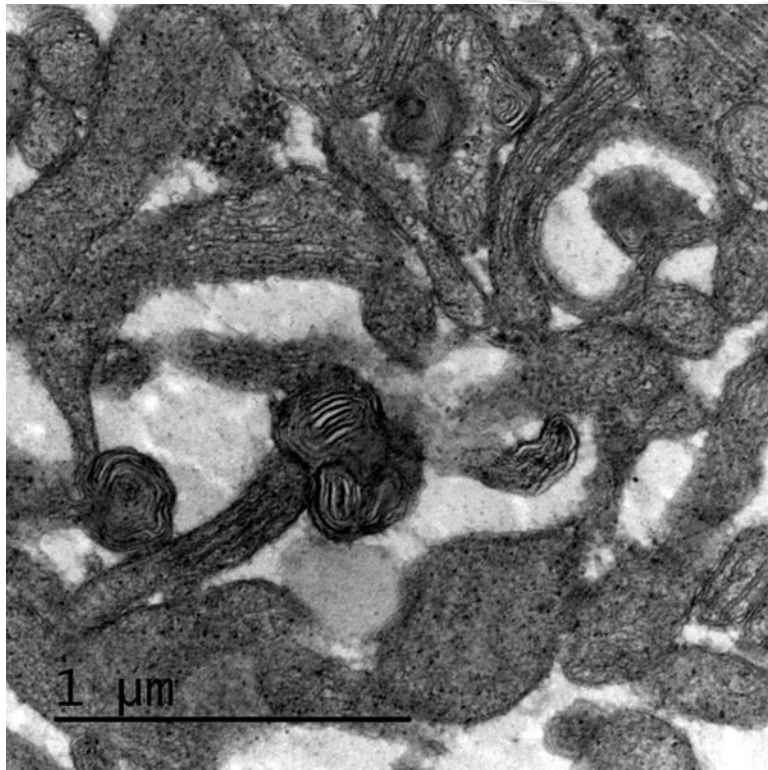


COX



COX-SDH

Miopatía mitocondrial



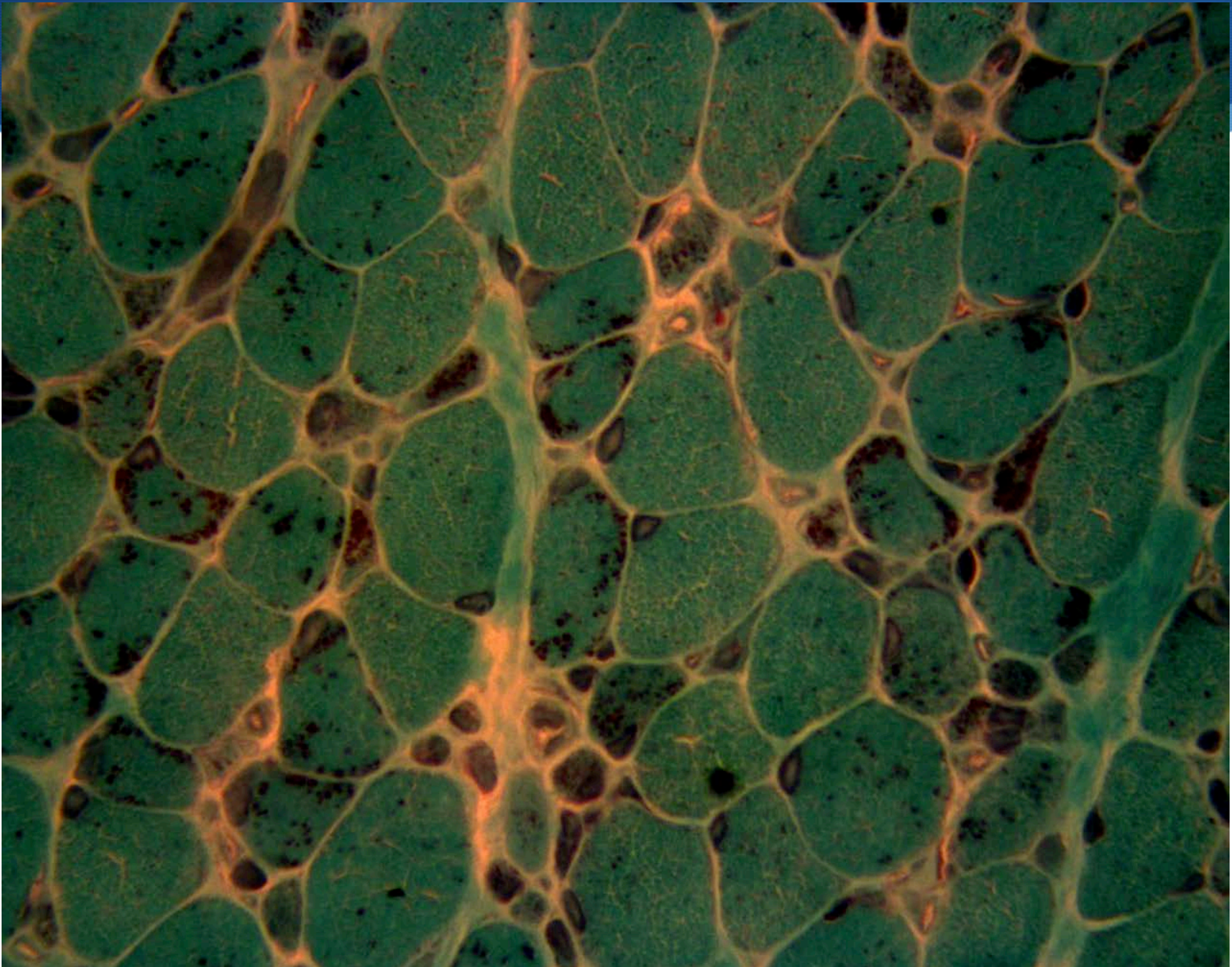
Miopatías

- 💧 Distrofias musculares
- 💧 Miopatías metabólicas
- 💧 **Miopatías congénitas**
- 💧 Miopatías inflamatorias (no infecciosas)
- 💧 Miopatías inflamatorias infecciosas
- 💧 Enfermedades endocrinas
- 💧 Tóxicos, tto corticoides y otros
- 💧 Neoplasias malignas
- 💧 Desuso

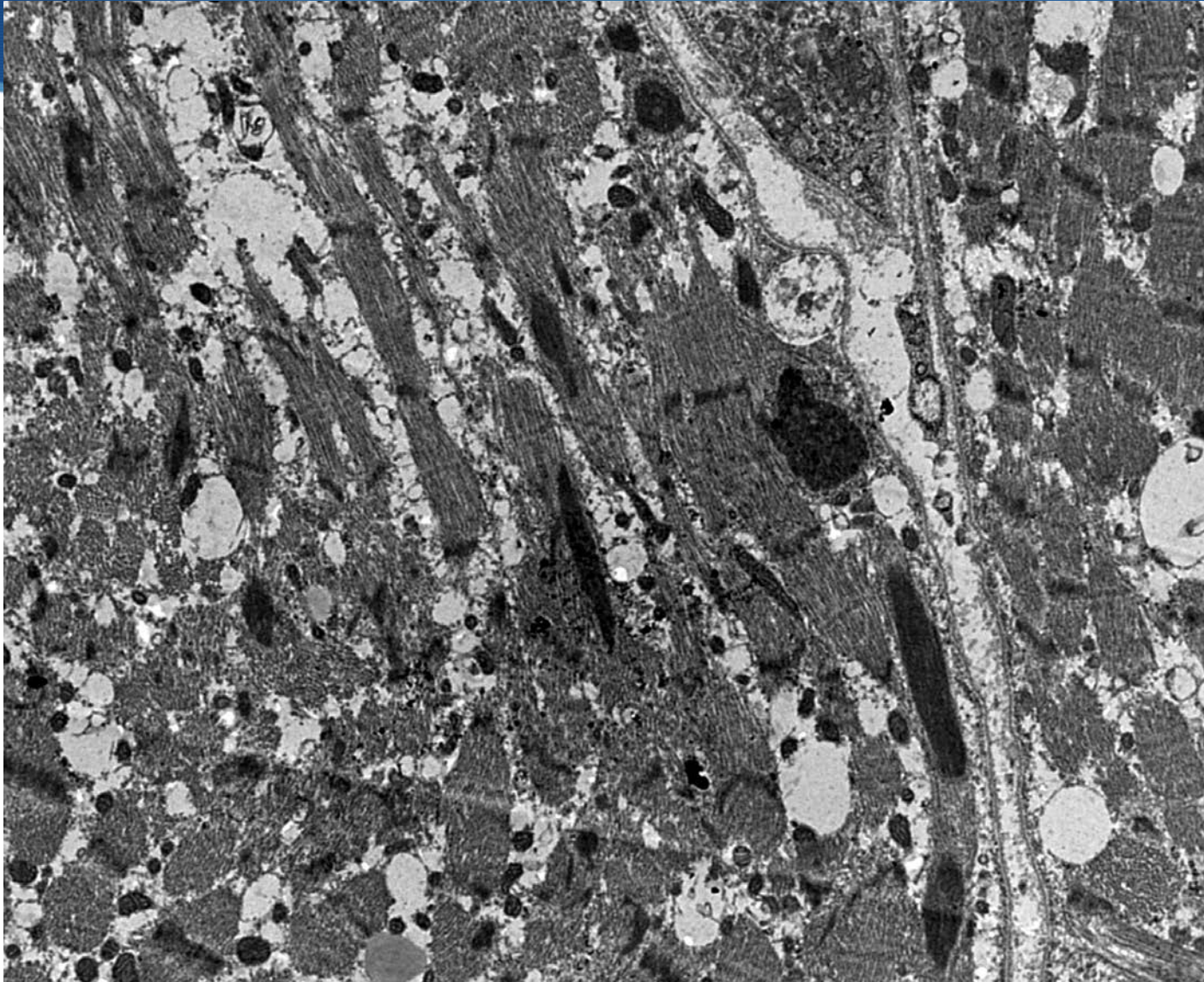
Miopatías Congénitas

- 1. M. nemalínica
- 2. M. con cores
- 3. M. Miotubular/centronuclear
- 4. Desproporción congénita de tipos

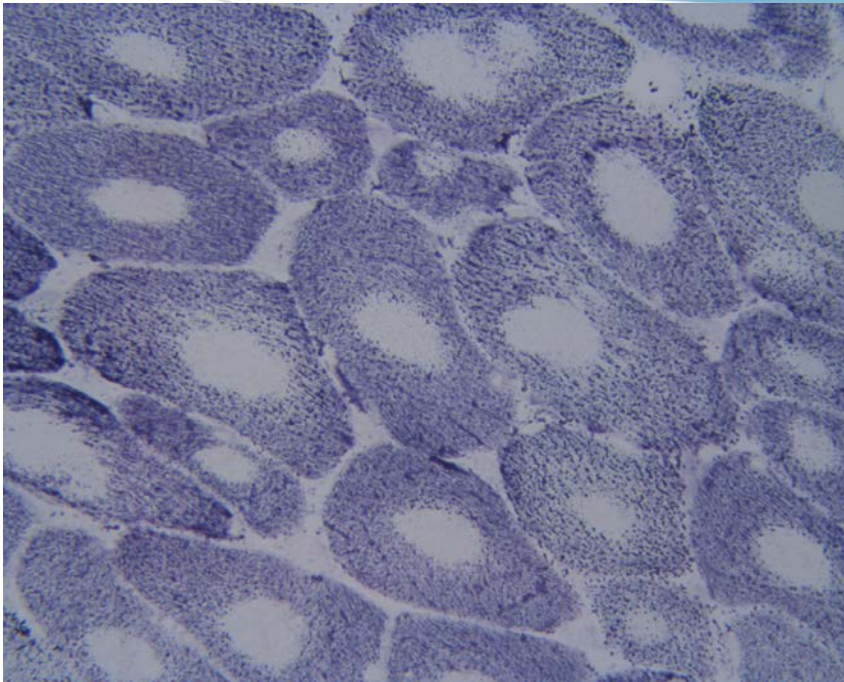
Nemalínica



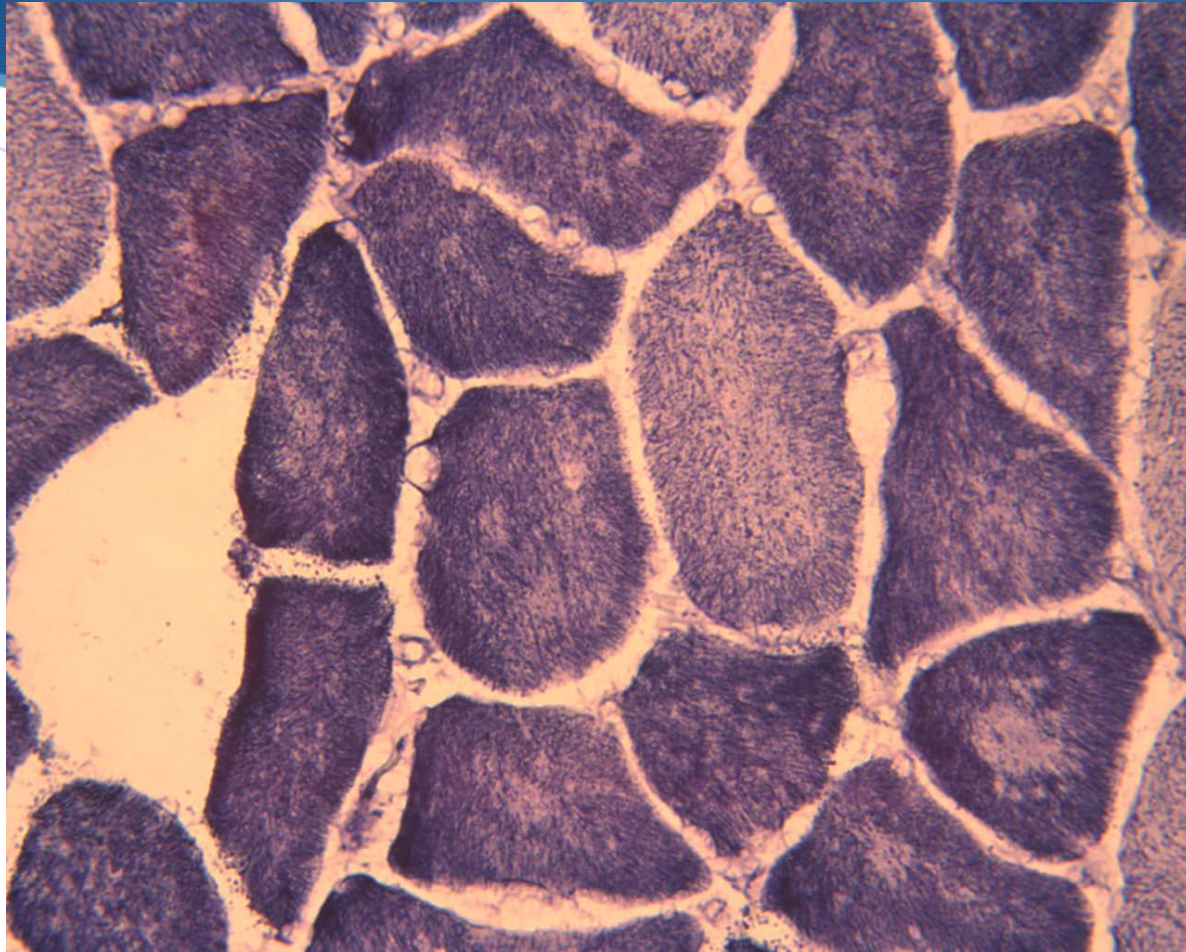
Nemalínica

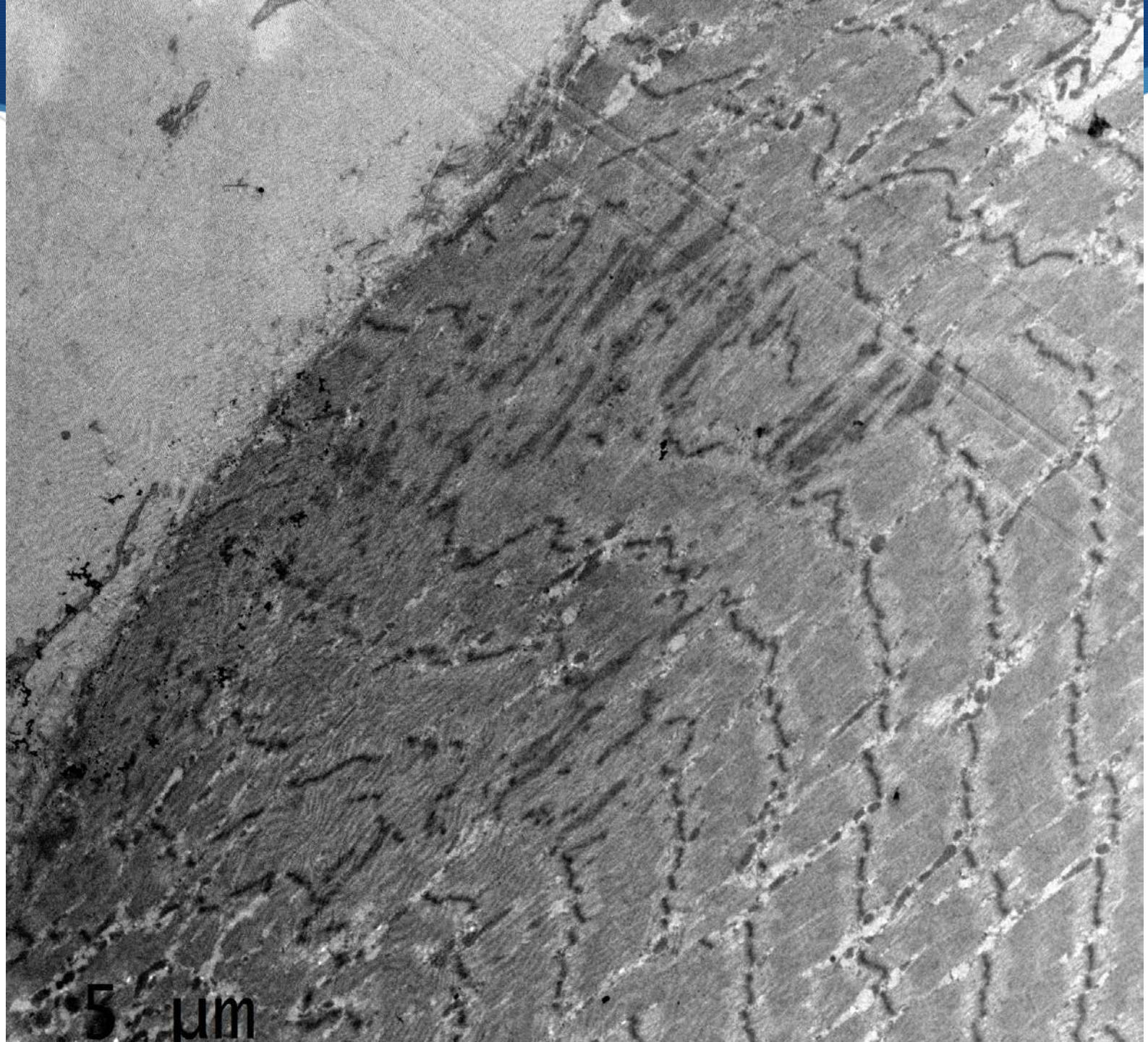


Cores centrales SDH y COX

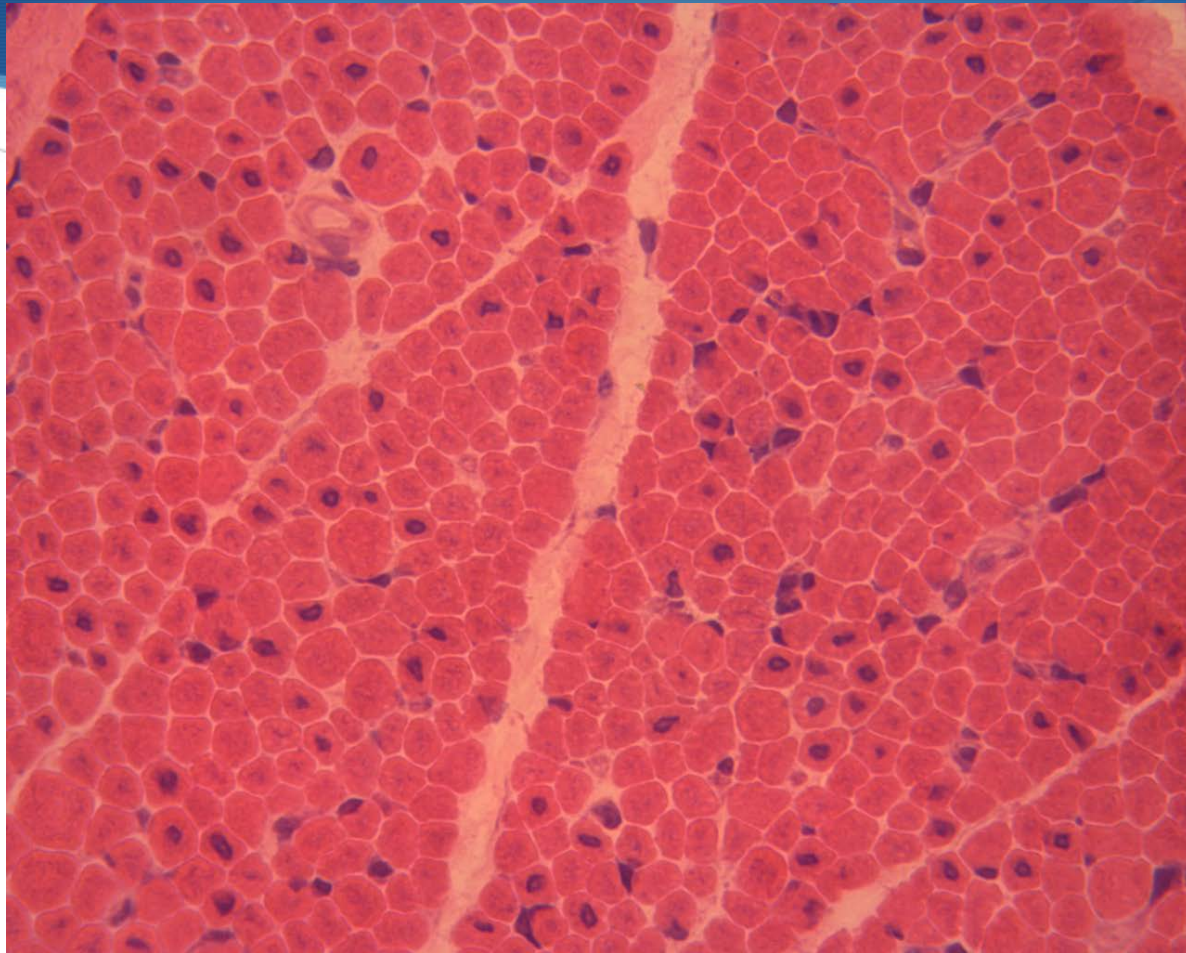


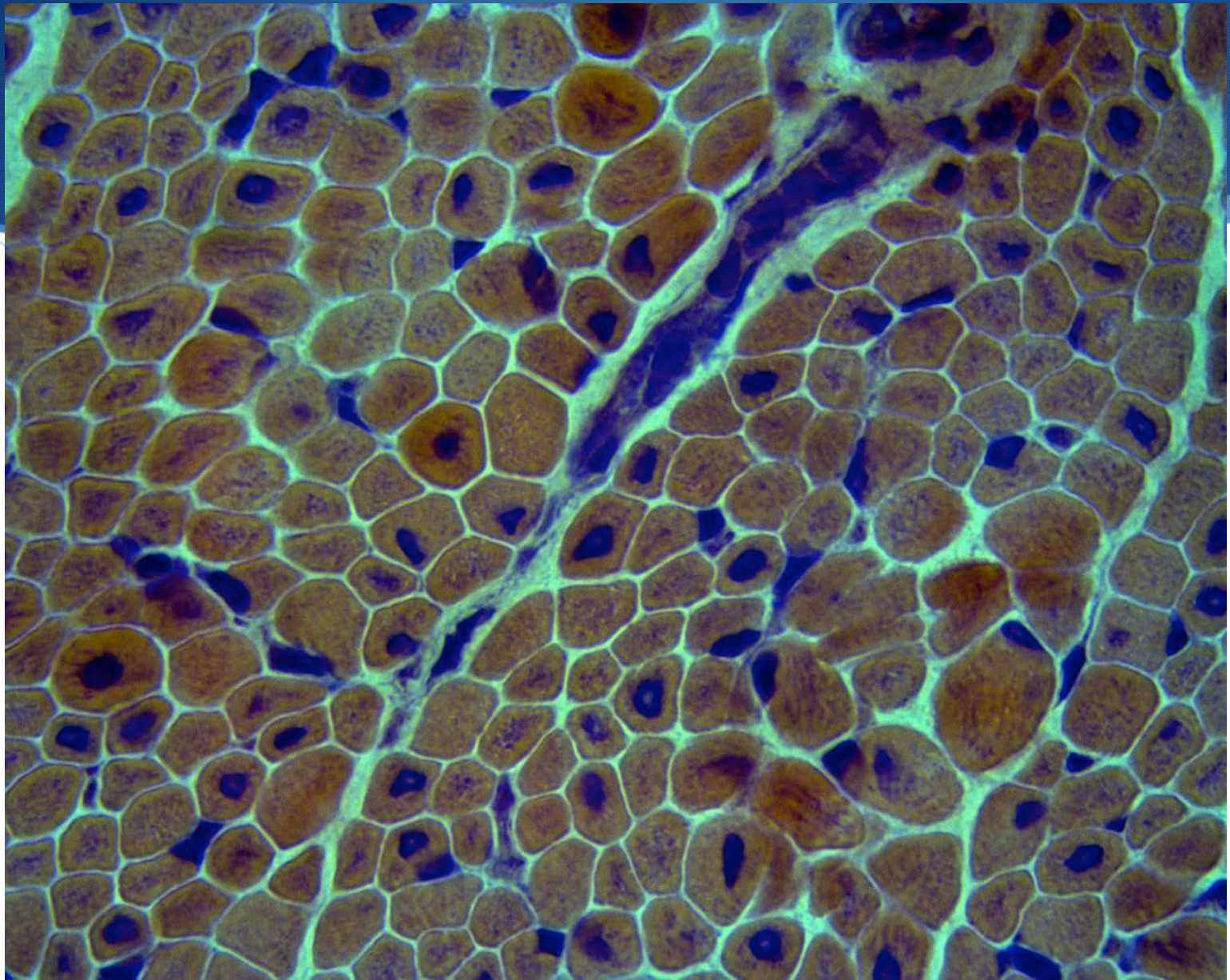
Minicores



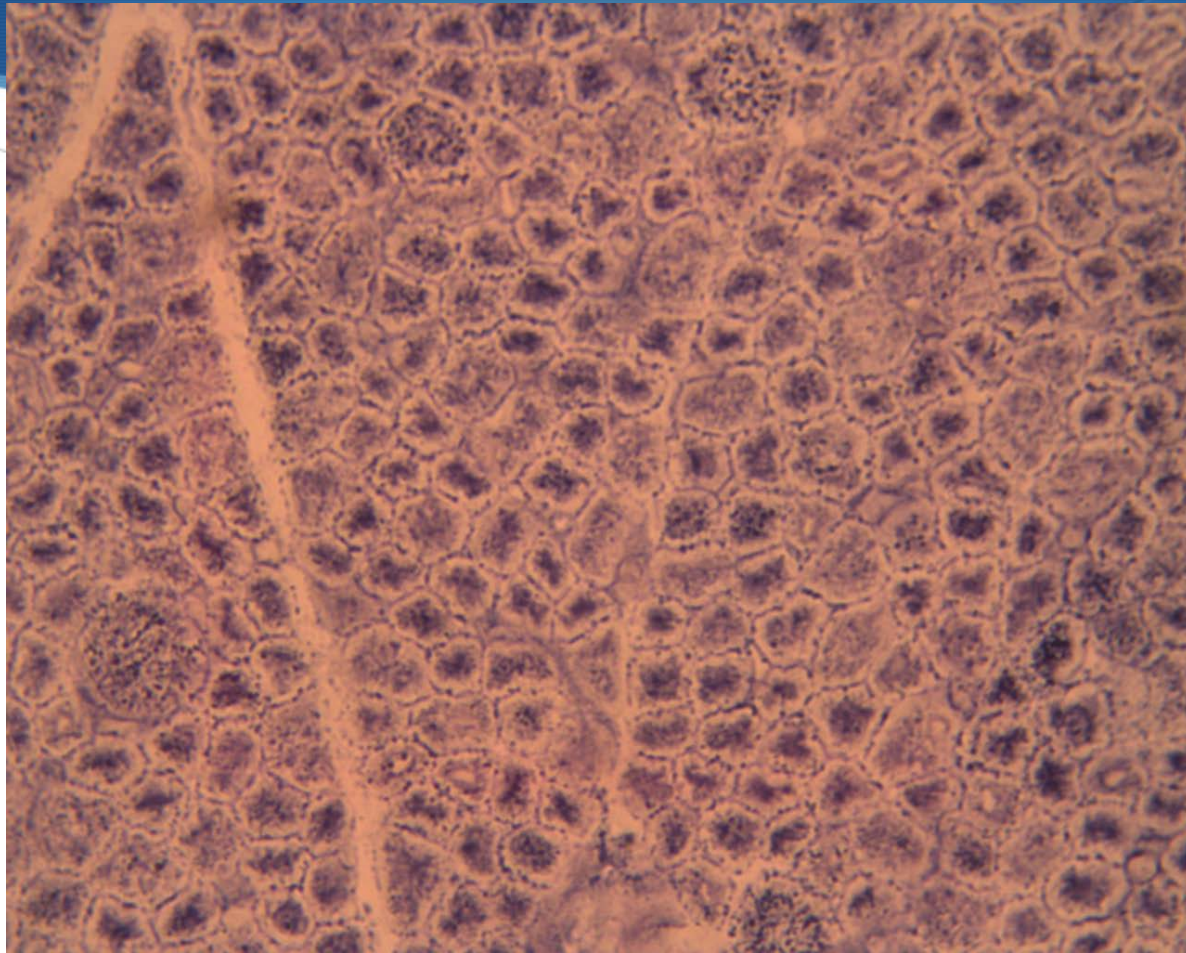


Centronuclear/Miotubular

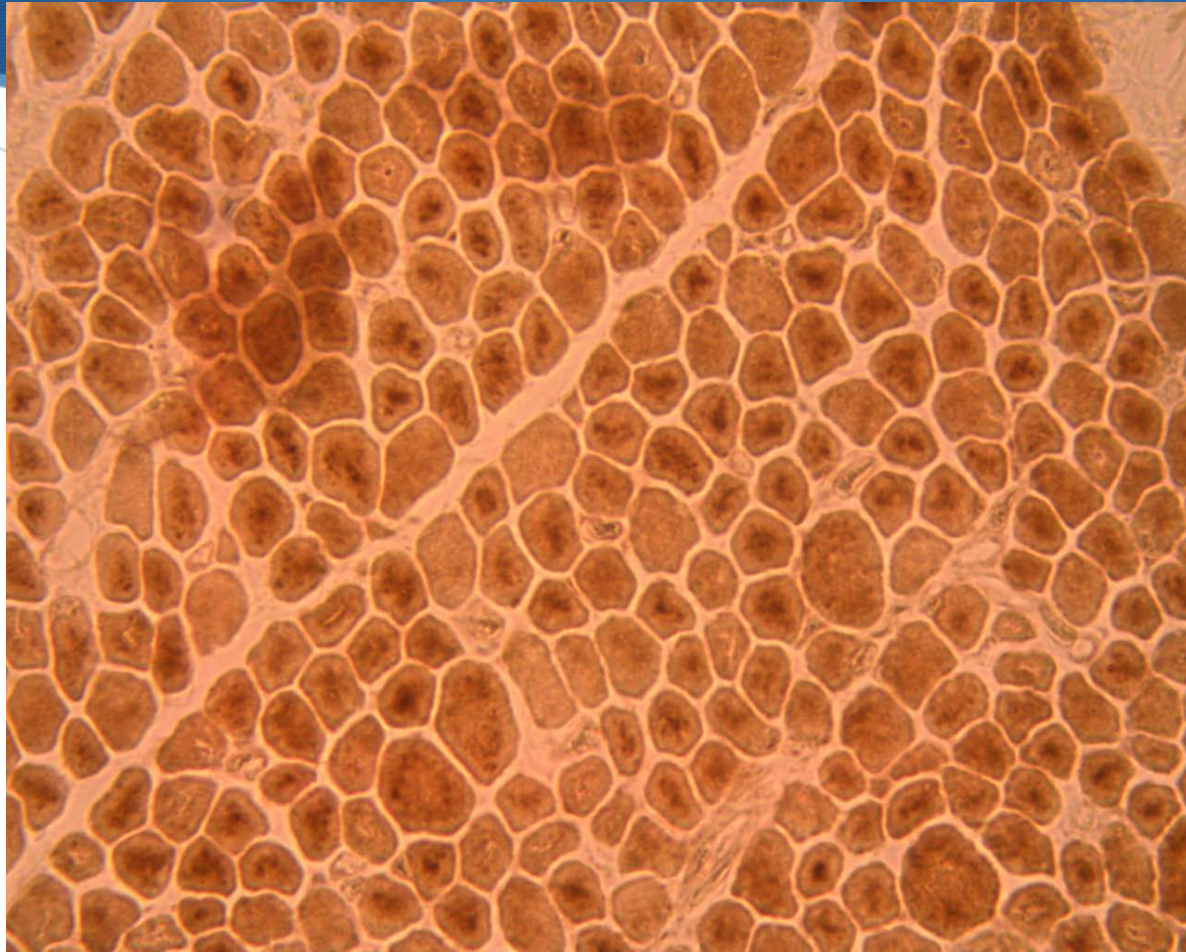




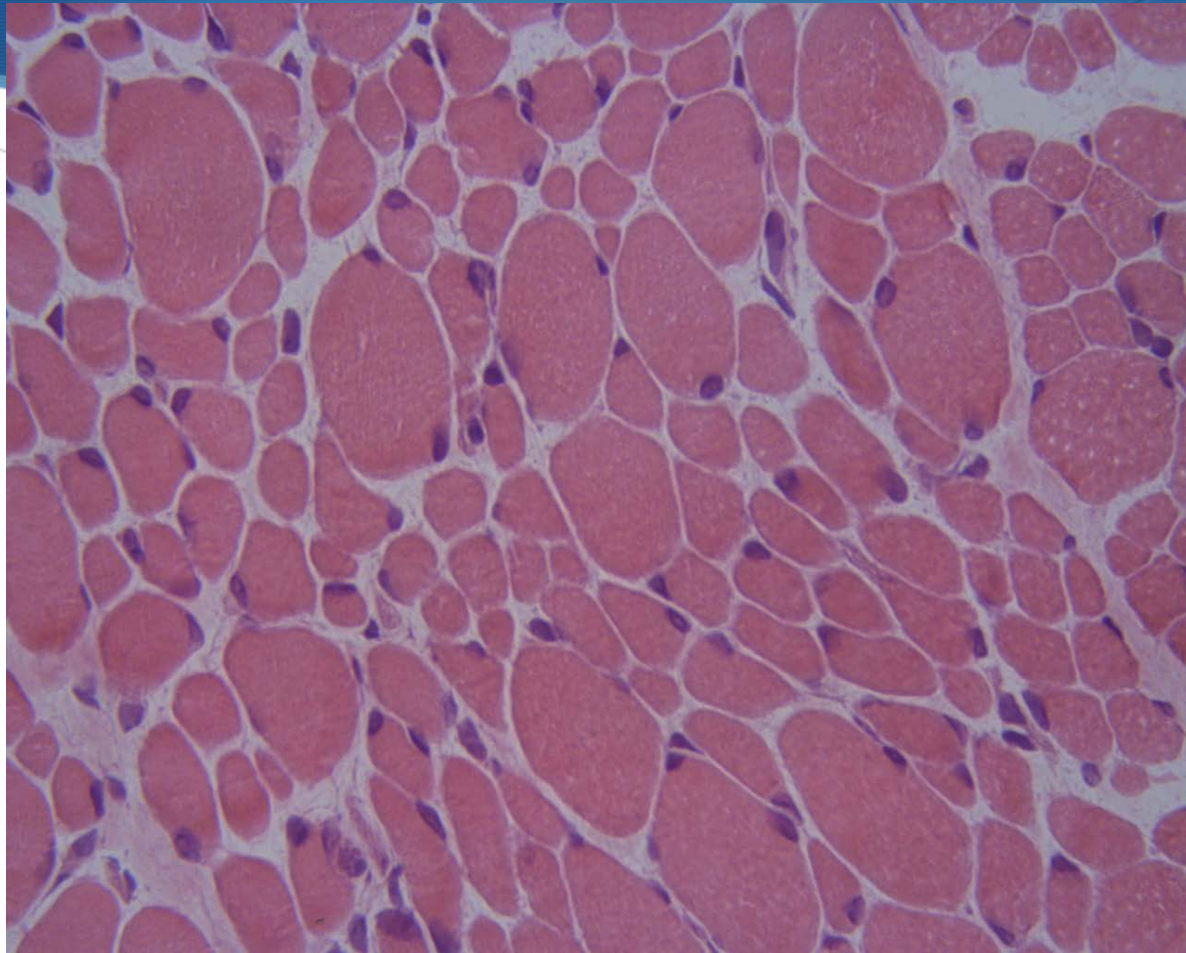
NADH



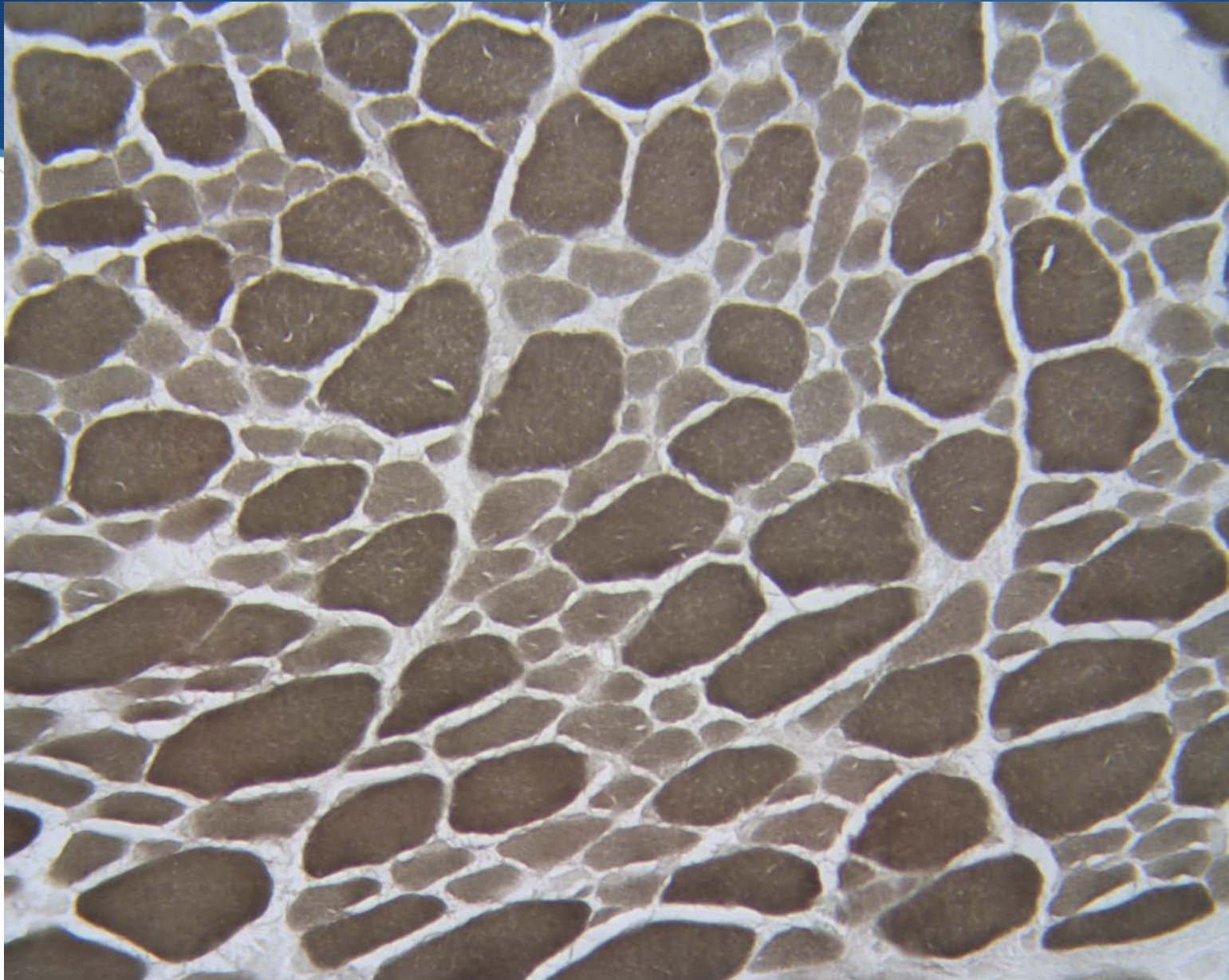
COX



Desproporción por tipos



ATPasa 9,4



Miopatías

- ◆ Distrofias musculares
- ◆ Miopatías metabólicas
- ◆ Miopatías congénitas estructurales
- ◆ **Miopatías inflamatorias (no infecciosas)**
- ◆ Miopatías inflamatorias infecciosas
- ◆ Enfermedades endocrinas
- ◆ Tóxicos, tto corticoides y otros
- ◆ Neoplasias malignas
- ◆ Desuso

Miopatías Inflammatorias Inmunes

- ◆ **1a. Dermatomiositis:** afectación cutánea, exantema heliotropo, lesiones Gottron, debilidad proximal, disfagia. 20% paraneoplásicas.
- ◆ **1b. Polimiositis:** Puede haber afectación sistémica/asociada a enf. tejido conectivo
- ◆ **1c. Miositis con cuerpos de inclusión:** mayores de 50, lentamente progresiva, distal manos y en cuádriceps.

Polimiositis

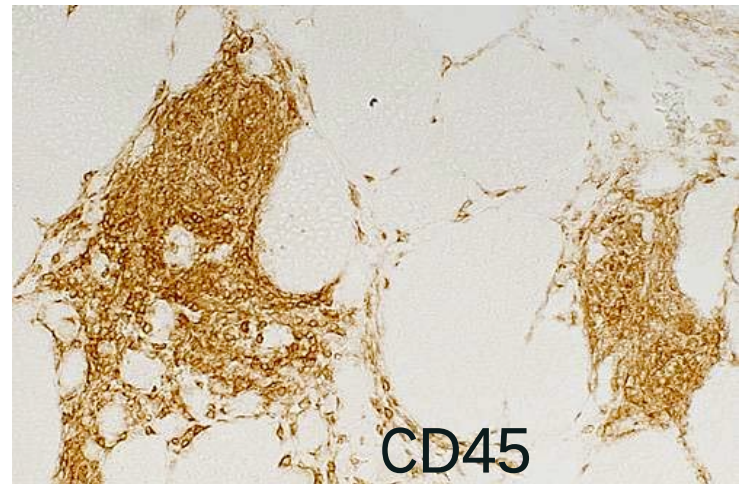
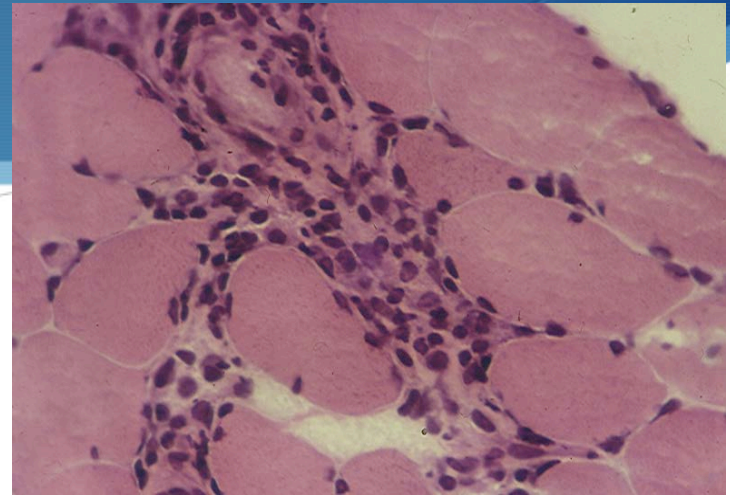
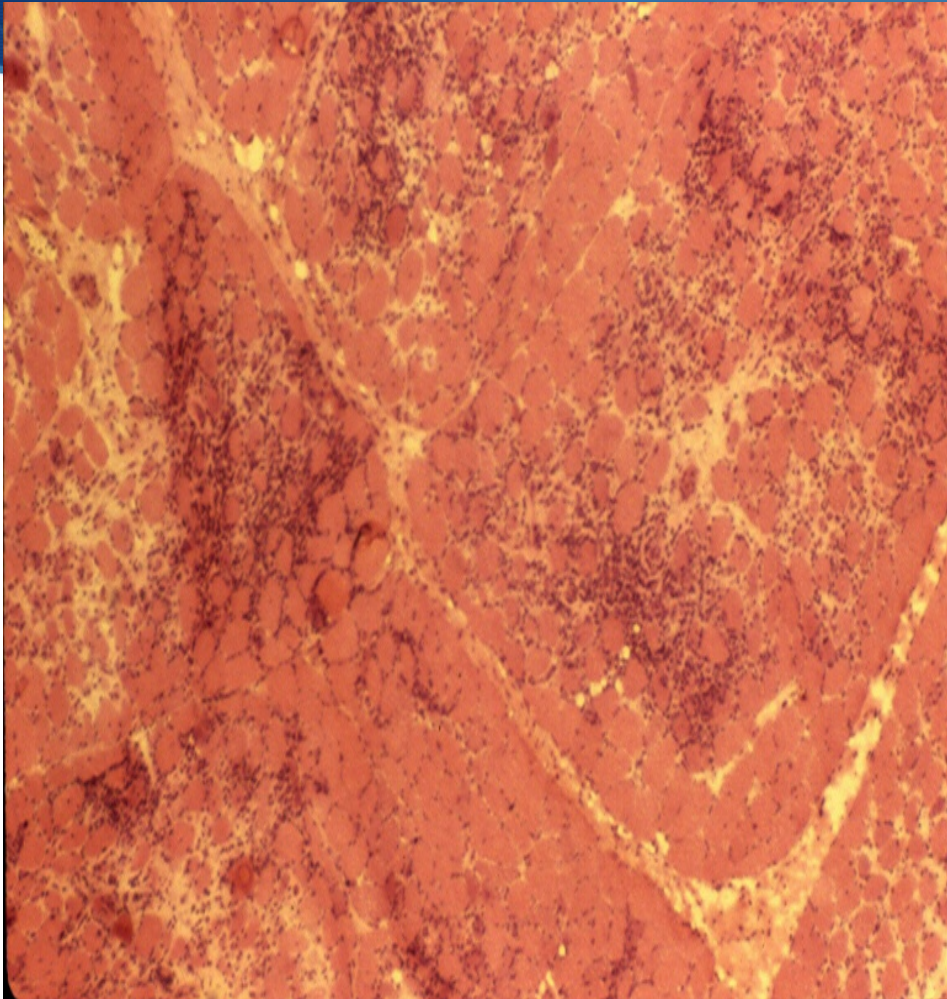
- Inflamación

predominante de linfocitos T y endomisial

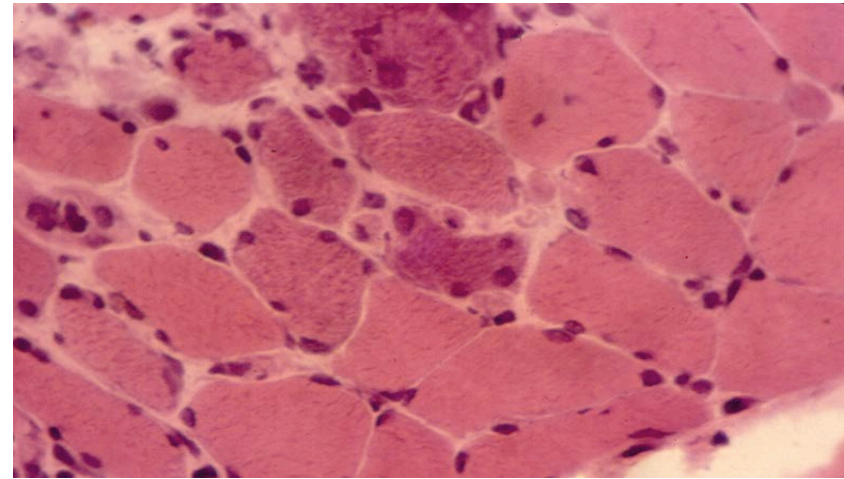
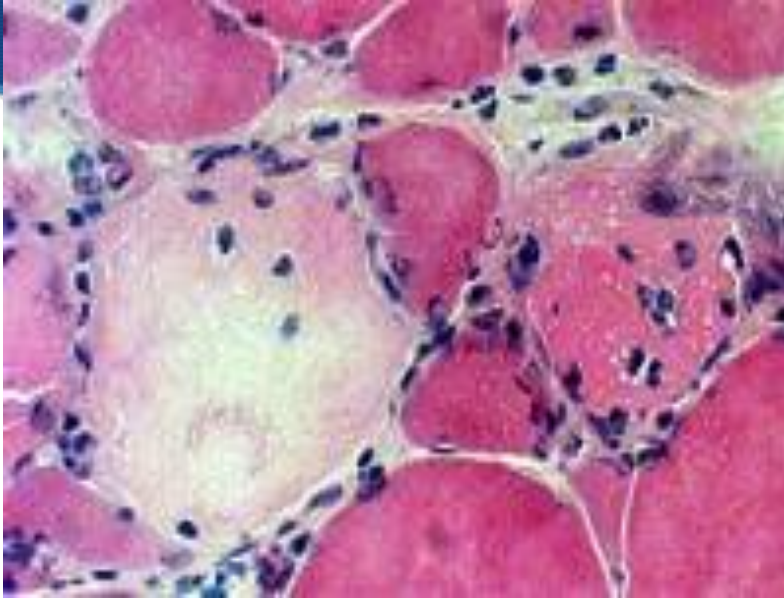
- Necrosis y regeneración de fibras musculares

- Expresión de MHC-1 (HLA-ABC) en la superficie de las fibras

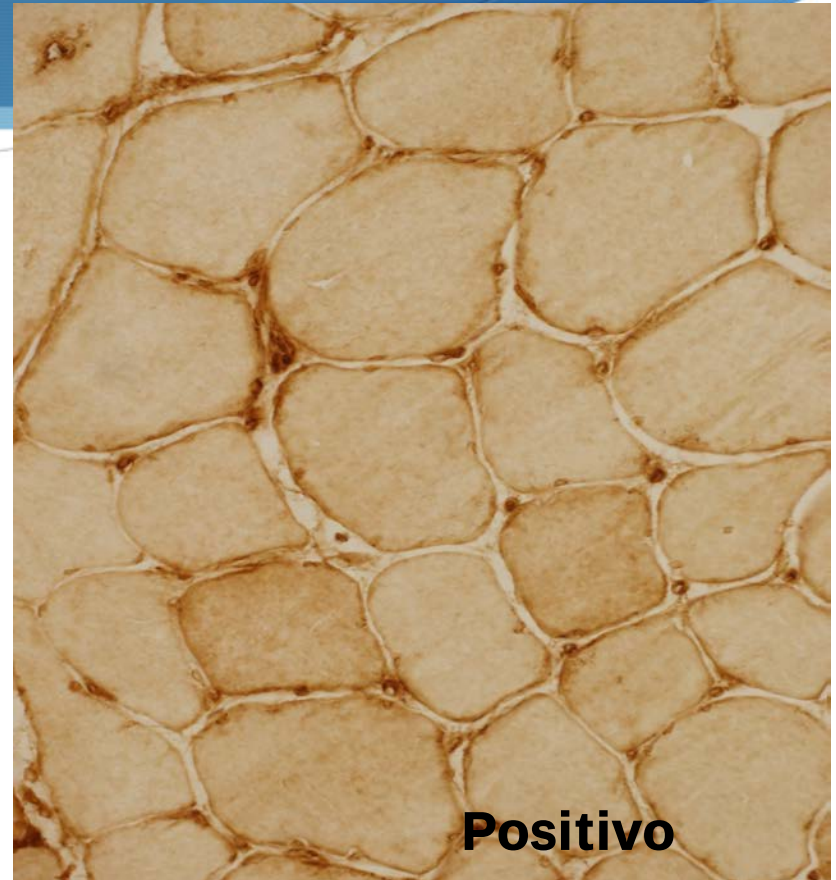
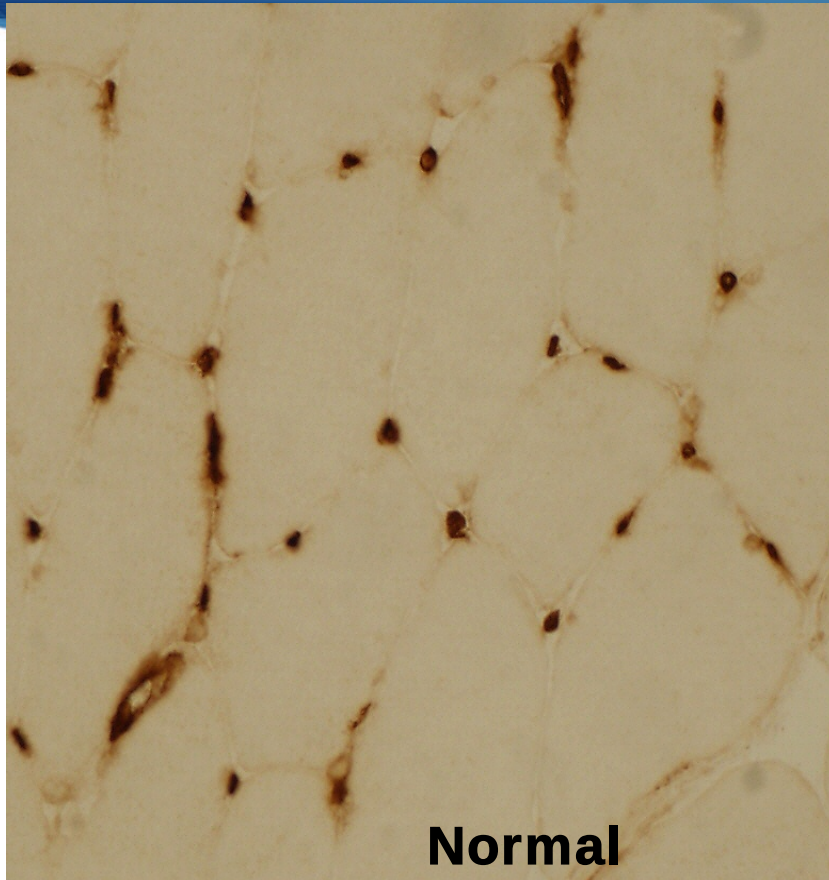
Inflamación



Necrosis/Regeneración



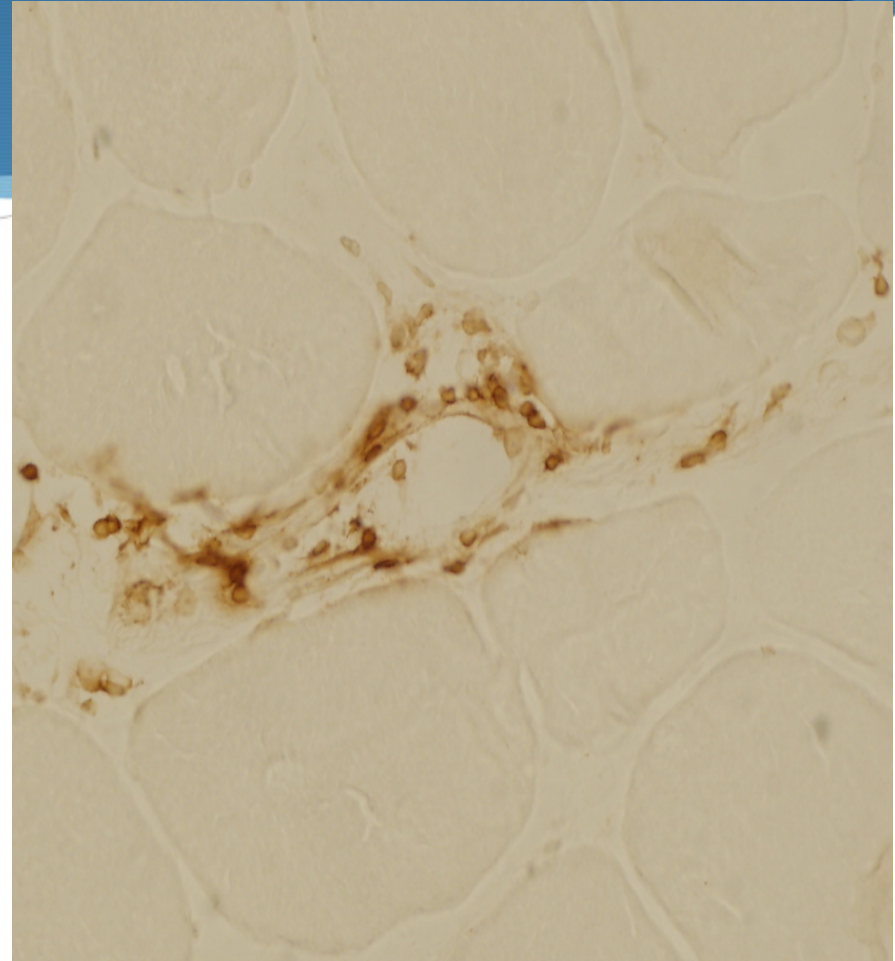
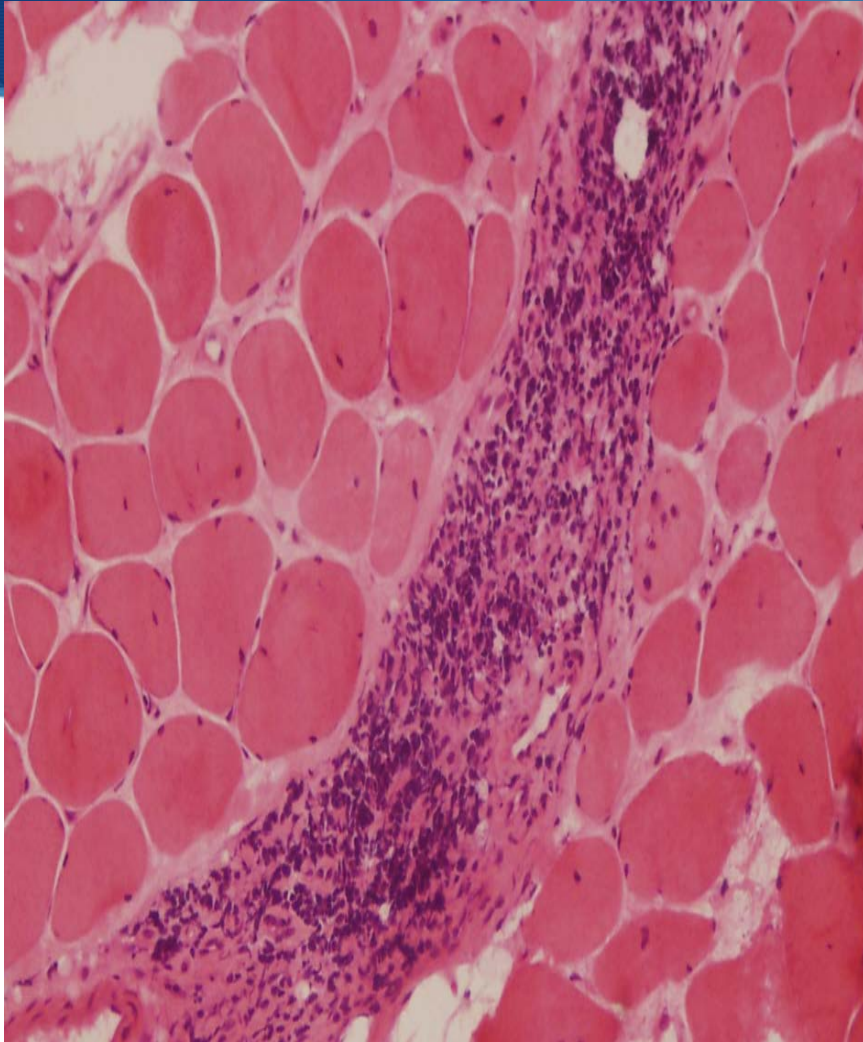
MHC-1 (HLA-ABC)



Dermatomiositis

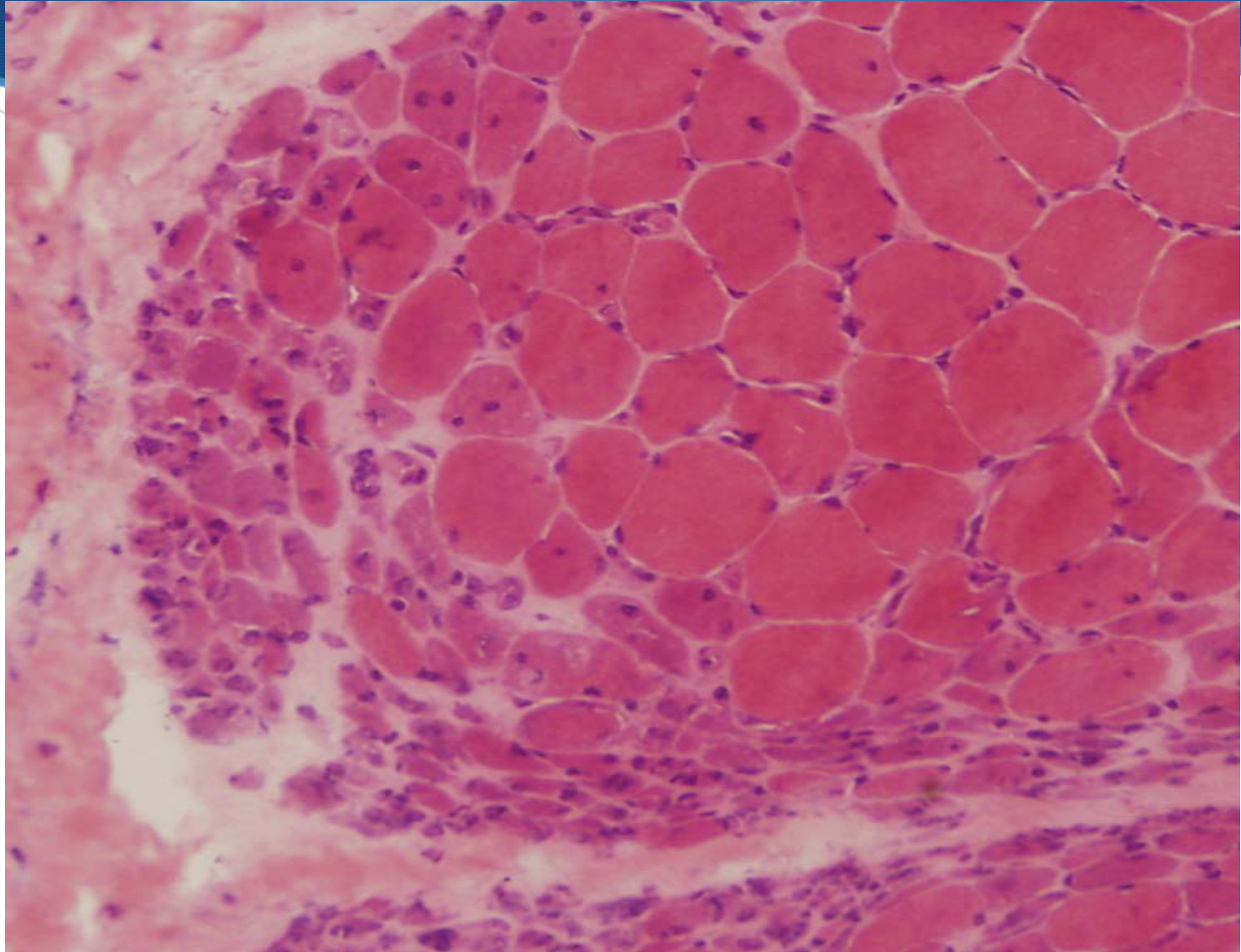
- Inflamación: Pred. de células B y T CD4 perivascular/perimisial
- Arteriolas perimisiales y capilares endomisiales: Depósito de inmunocomplejos y MAC.
- Necrosis y regeneración
- Expresión de MHC-1 (95%) Predominante perifascicular
- Atrofia perifascicular

DM- Inflamación

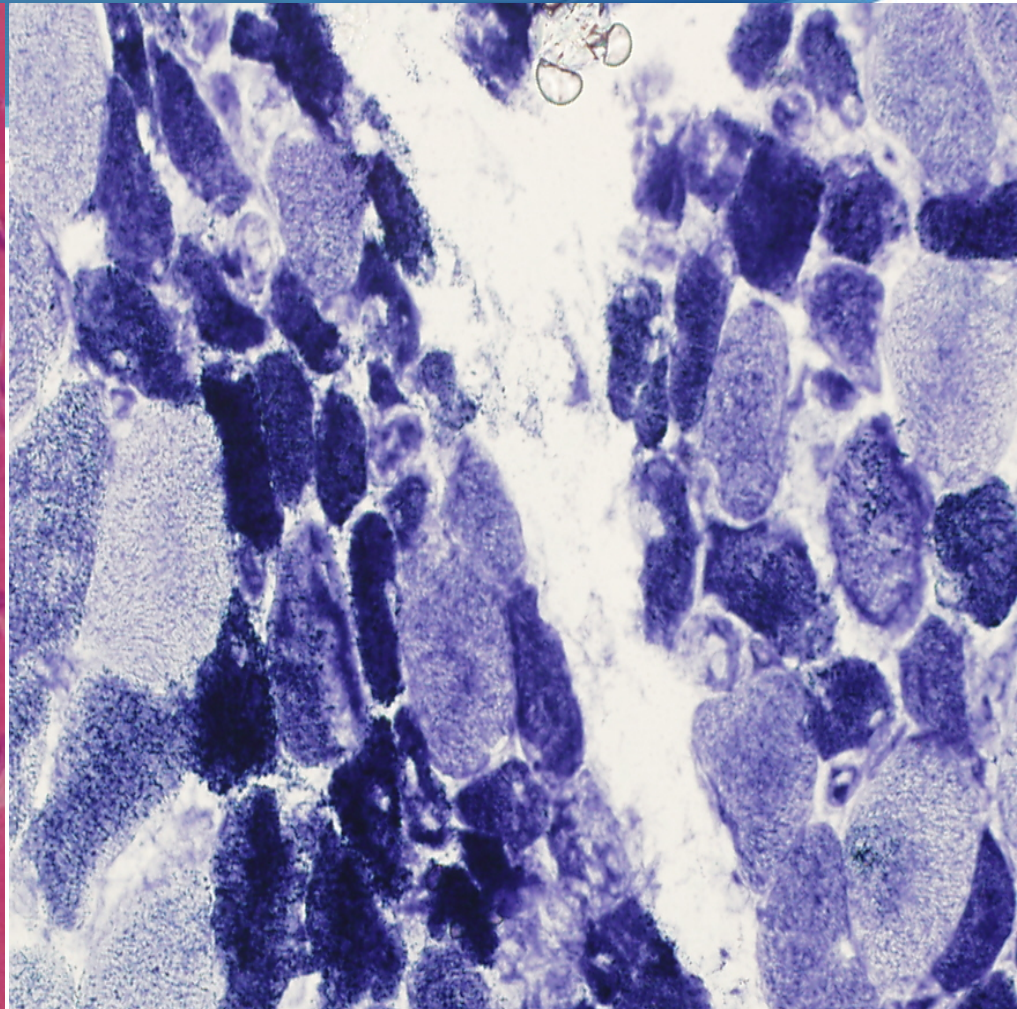
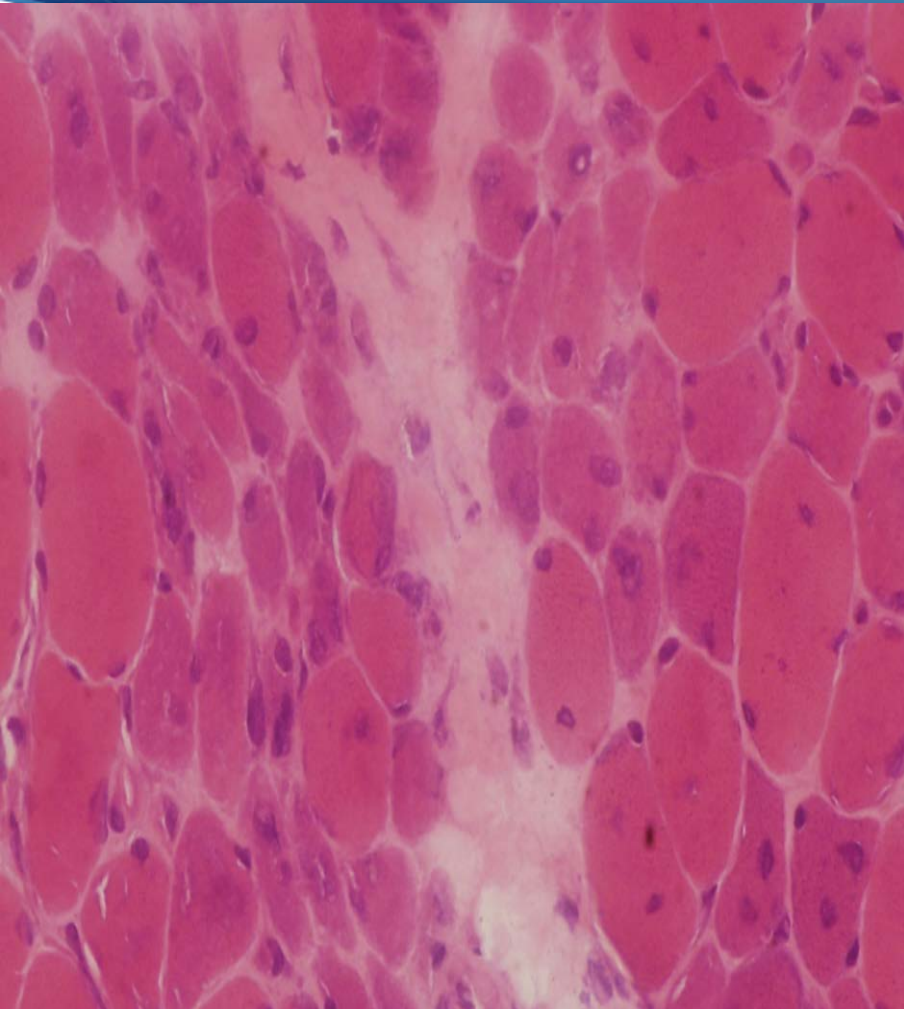


CD-20

DM-Atrofia perifascicular

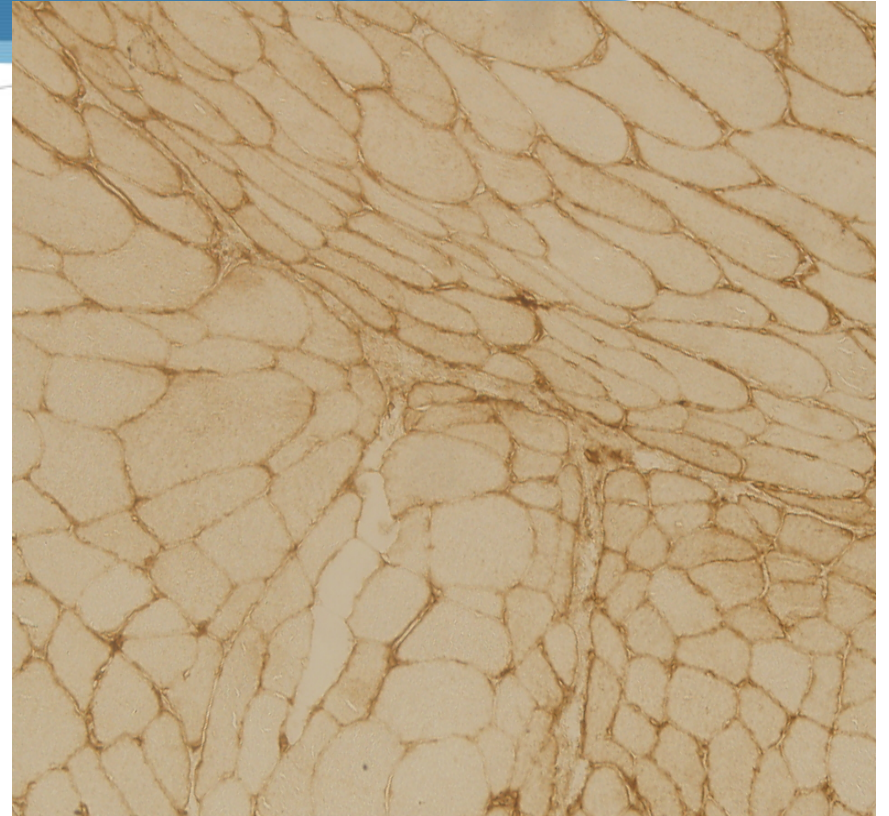
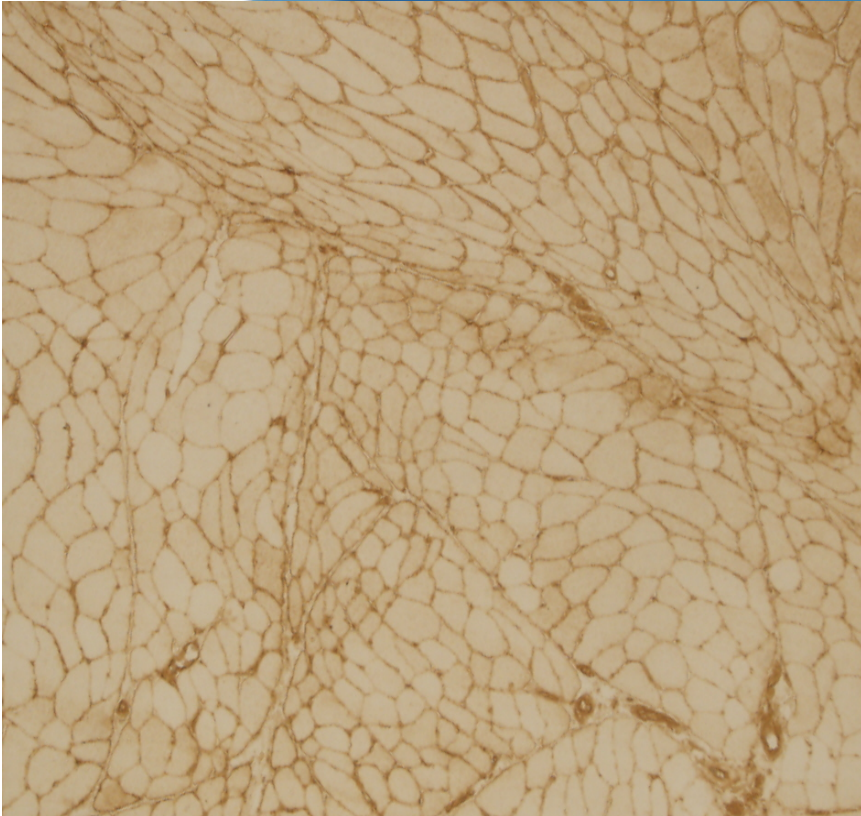


DM-Atrofia perifascicular



DM

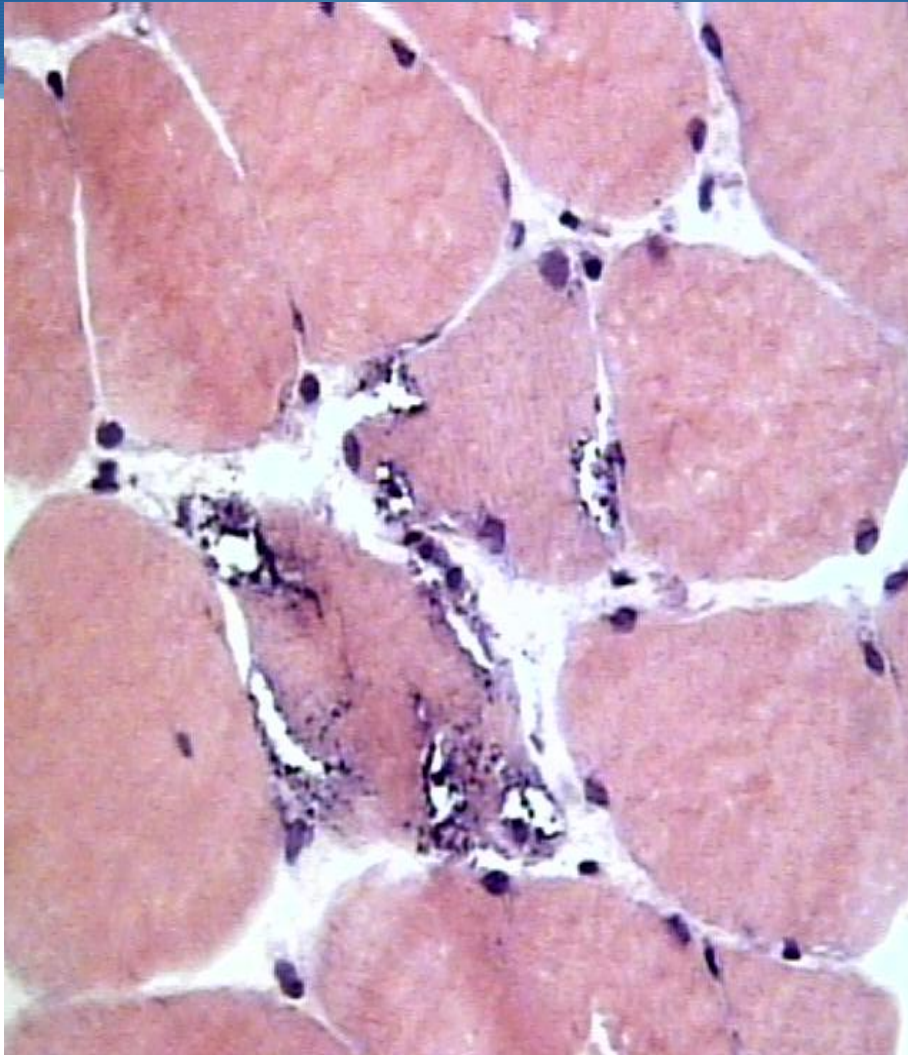
IHQ MHC-1



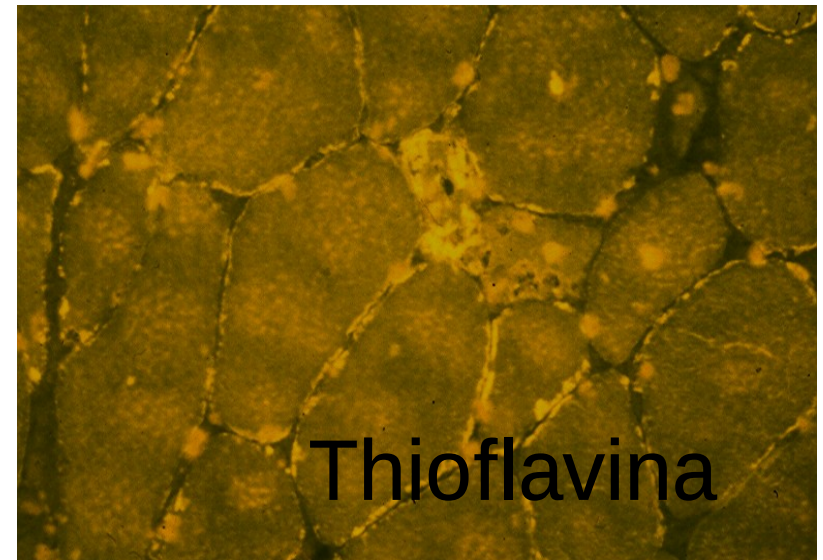
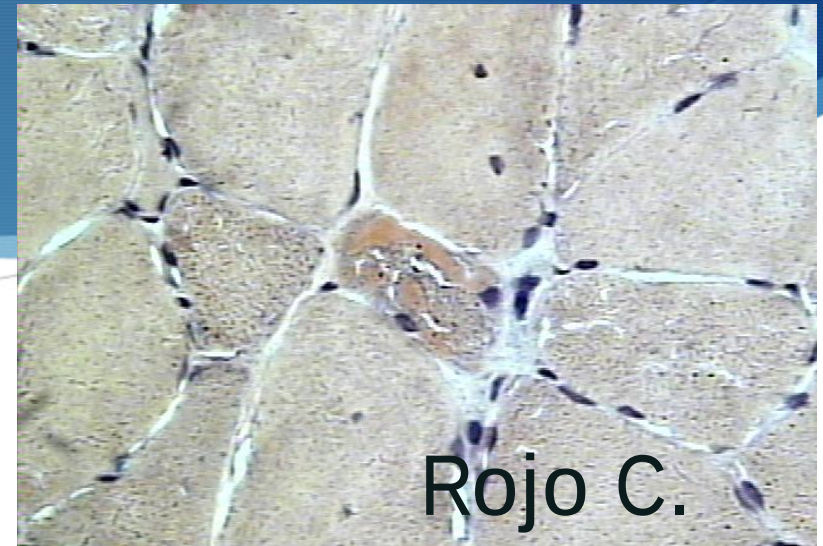
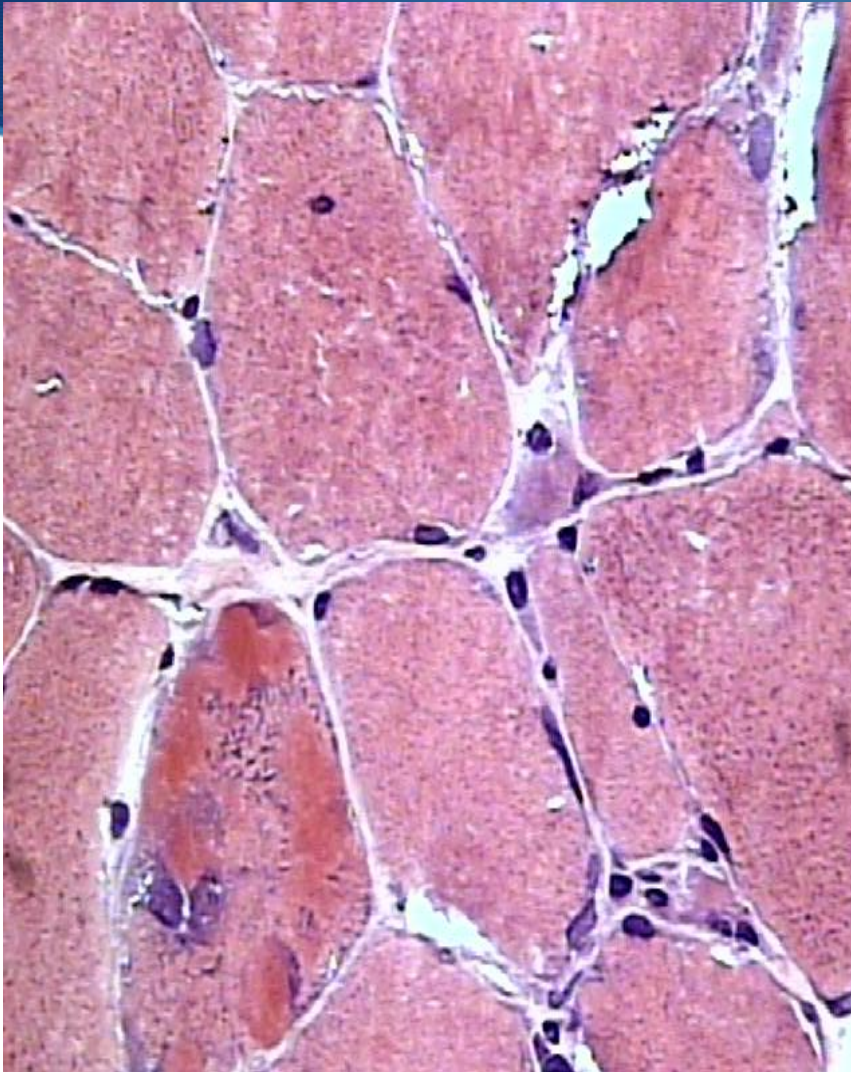
Miositis Cuerpos de Inclusión (IBM)

- ◆ Inflamación: predominante células T y endomisial
- . Necrosis y regeneración
- . Expresión de MHC-1
- . Vacuolas “tapizadas”. Inclusiones eosinófilas
- . Otras: Infiltración conectivo-adiposa, fibras rojo-rasgadas, COX -, fibras atróficas anguladas: pseudodenervación
- . ME: filamentos 15-18 nm

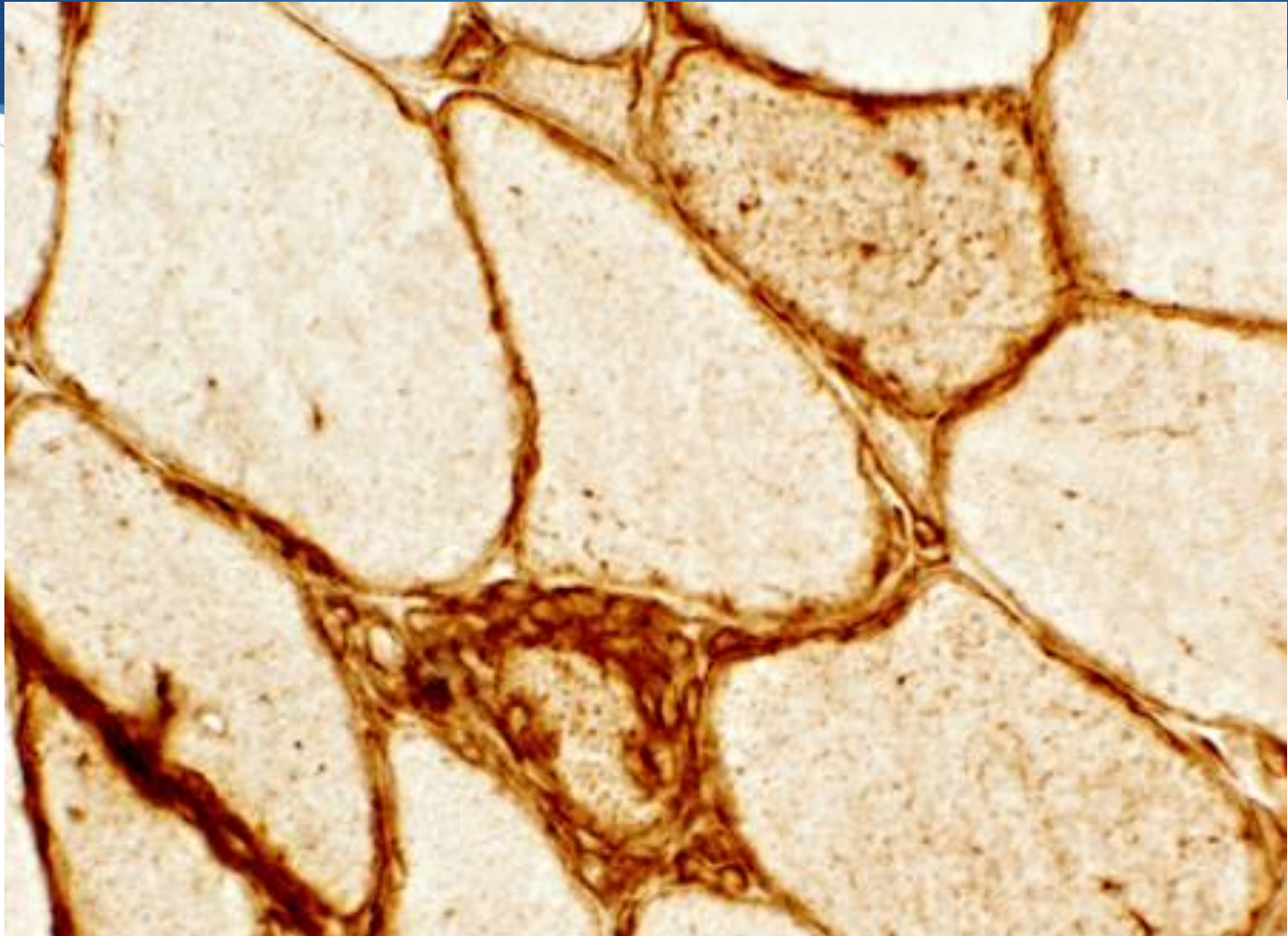
IBM- Vacuolas tapizadas



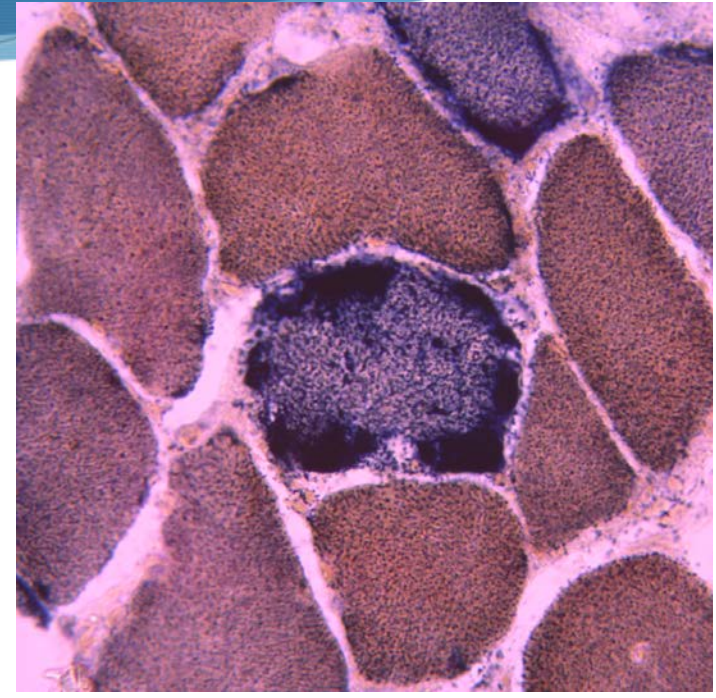
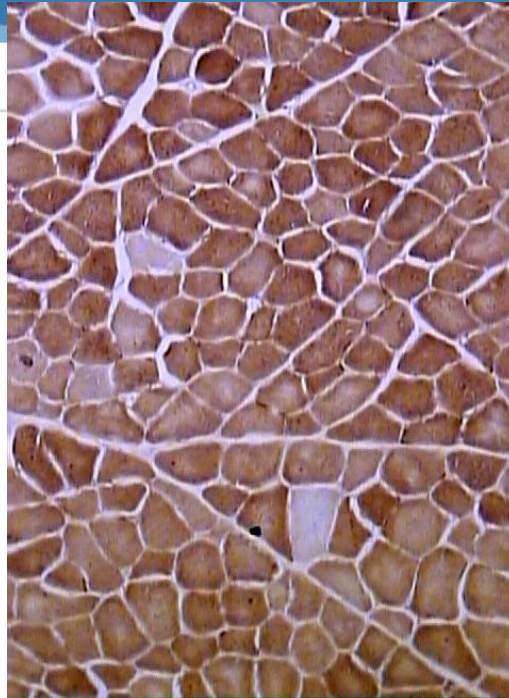
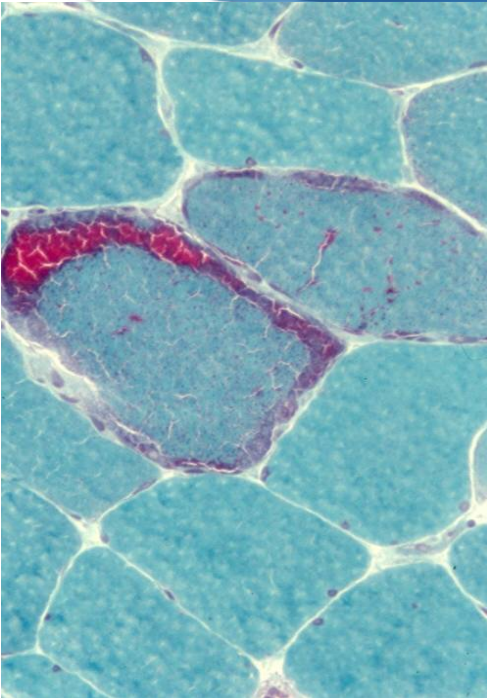
IBM- Inclusiones eosinófilas



IBM- MHC-1



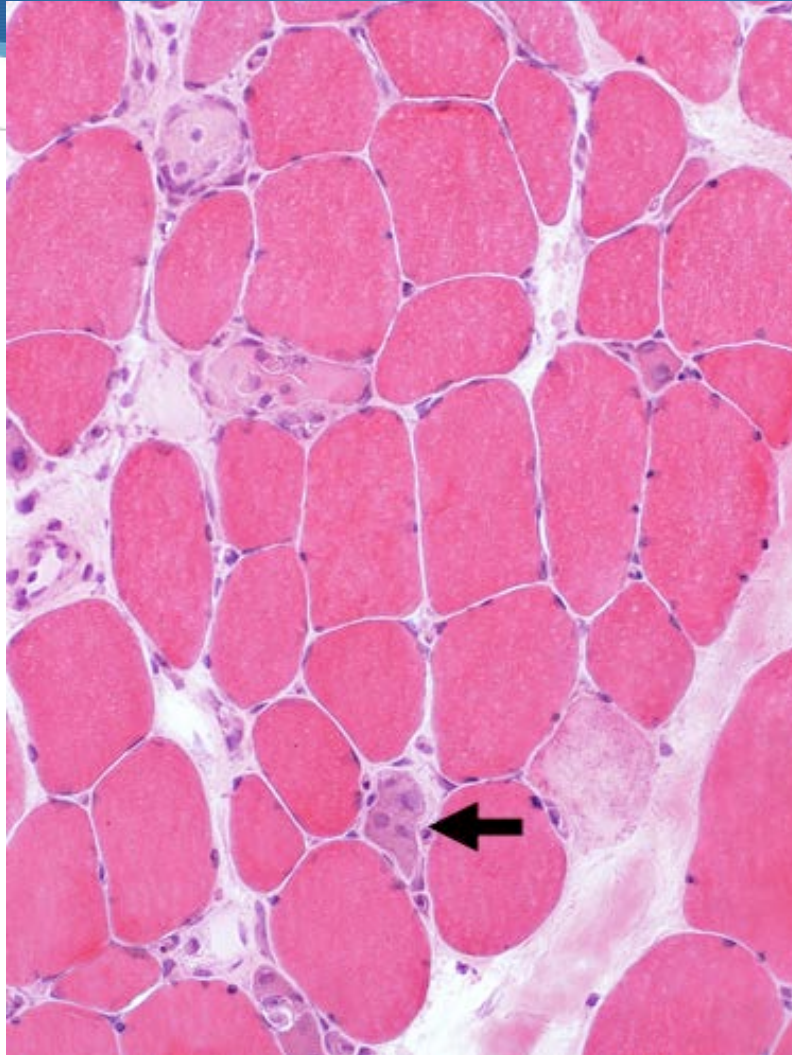
IBM-Alteraciones mitocondriales



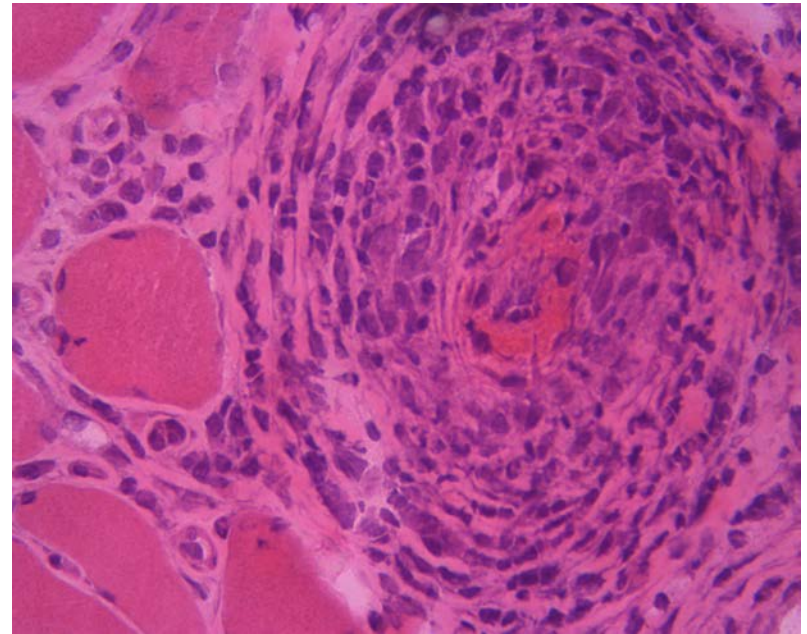
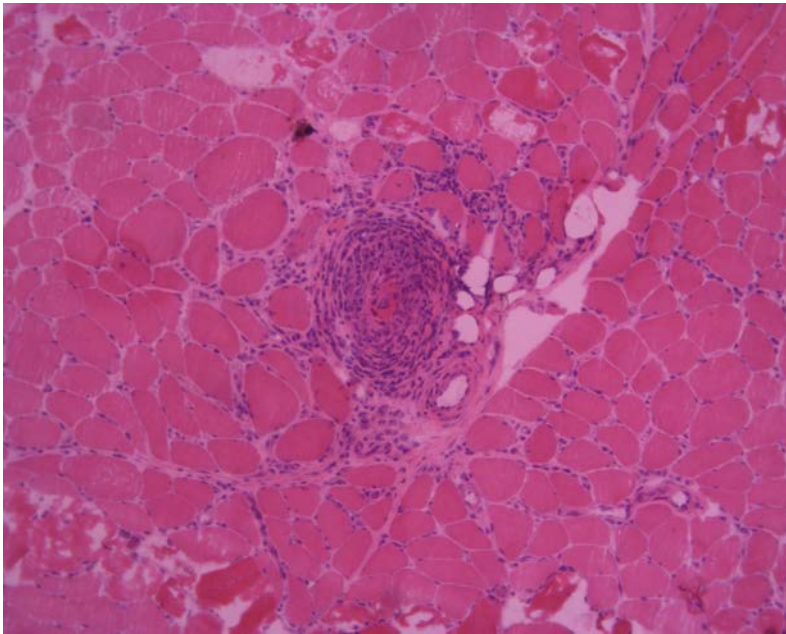
Miopatías

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- ◆ Tóxicos, tto corticoides y otros
- ◆ Neoplasias malignas
- ◆ Desuso

Miopatía tóxica por estatinas



Miopatía tóxica por estatinas



Miopatías secundarias



Atrofia selectiva de fibras tipo II