

# 神経・筋疾患

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医学系研究科神経内科学

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高齢者ブレインバンク

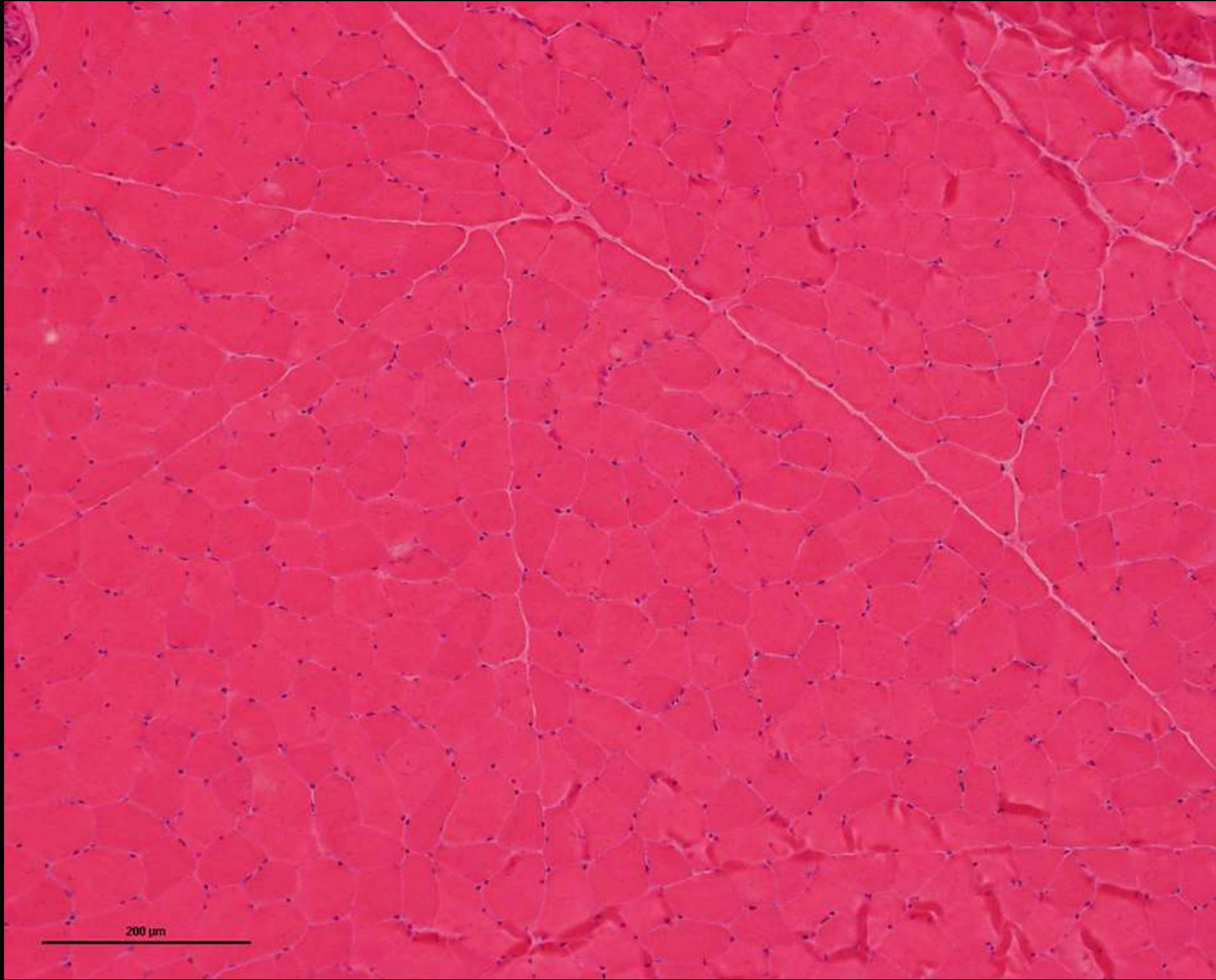
村山繁雄

# 神経・筋疾患病理の意味

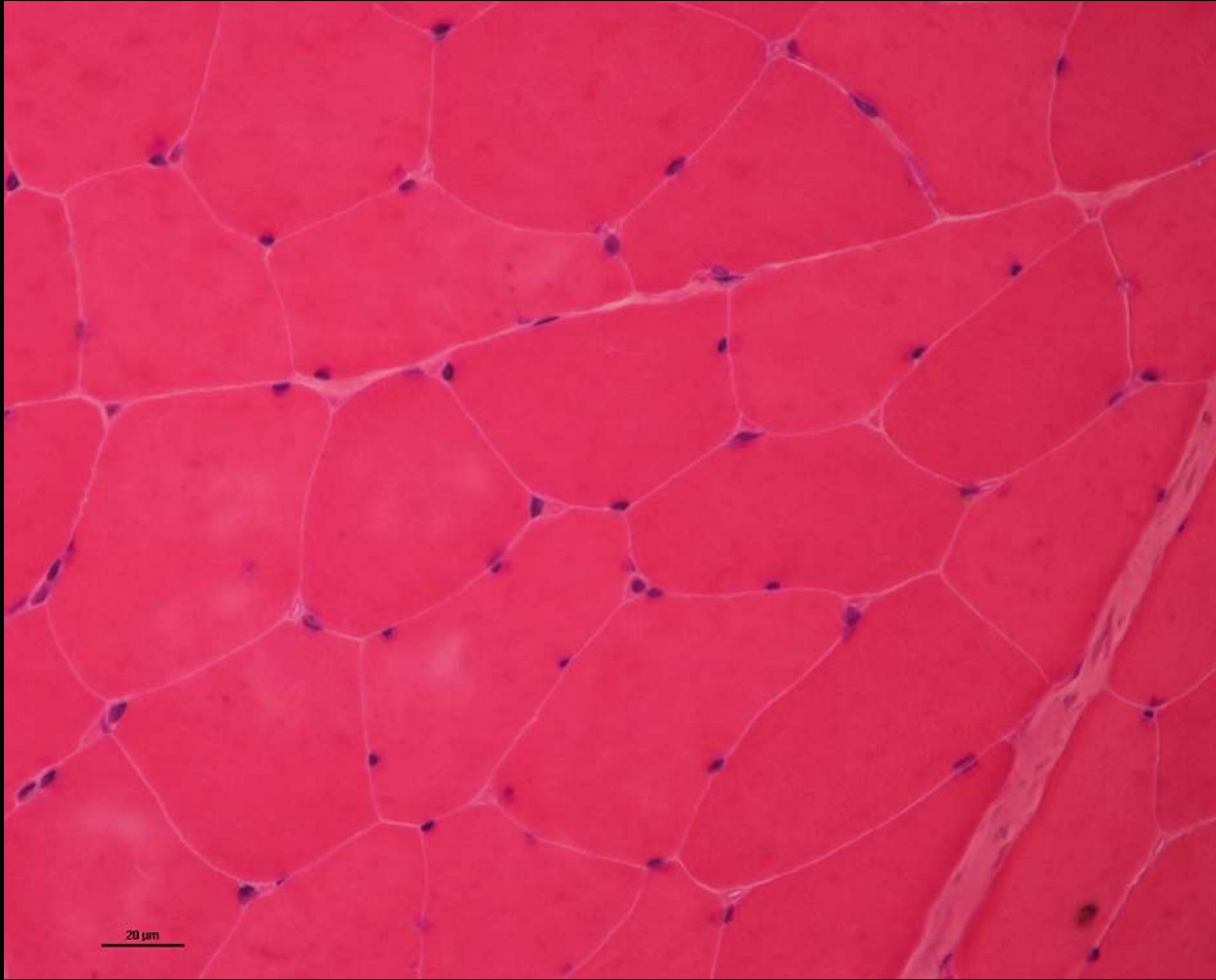
- ・ 脳神経内科における外科病理診断。
- ・ 患者をよりよく知る上で、理解が重要。
- ・ 自己抗体とMRIのみで筋炎を診断するのは無理で、筋生検が診断には必須。
- ・ GBS, CIDPの病態解明に限界があるのは、病理評価が限定的で、研究リソースが少ないため。
- ・ 剖検時の神経・筋評価を合わせることで、病態理解が深まる点に注意。

# 筋肉病理

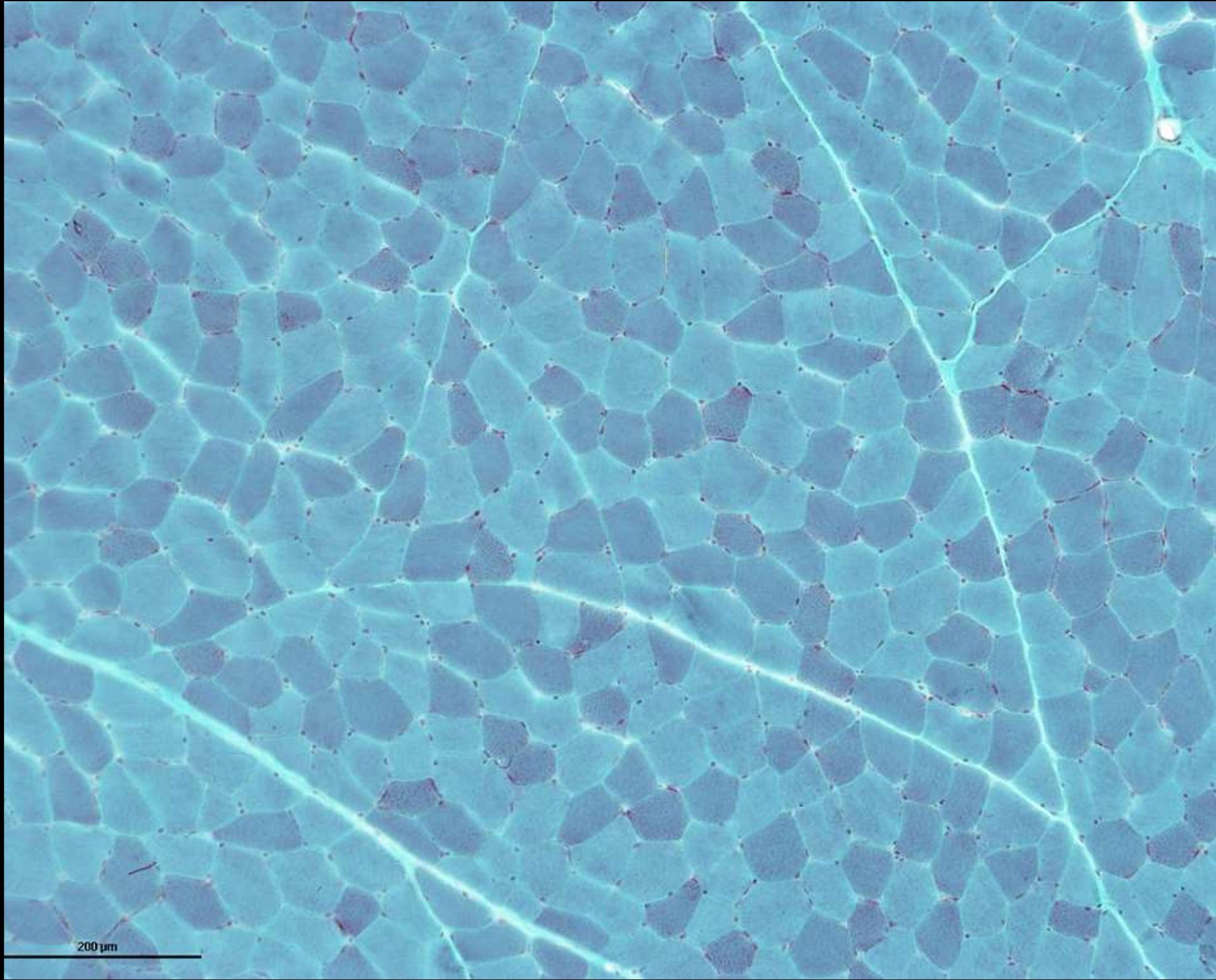
1. 腫瘍病理は神経内科的に問題となることは少ない(悪性リンパ種、鑑別としてのサルコイドーシス等)。
2. 筋肉の解剖・生理学的特徴の理解が必要。  
極めて長い合胞体  
収縮が生理的役割
3. 遺伝性筋疾患の場合、核を含む筋構成蛋白に加え、筋周膜支持構造の異常が関与する。
4. 孤発性疾患の場合、筋炎が最重要。
5. 凍結横断標本が国際標準。



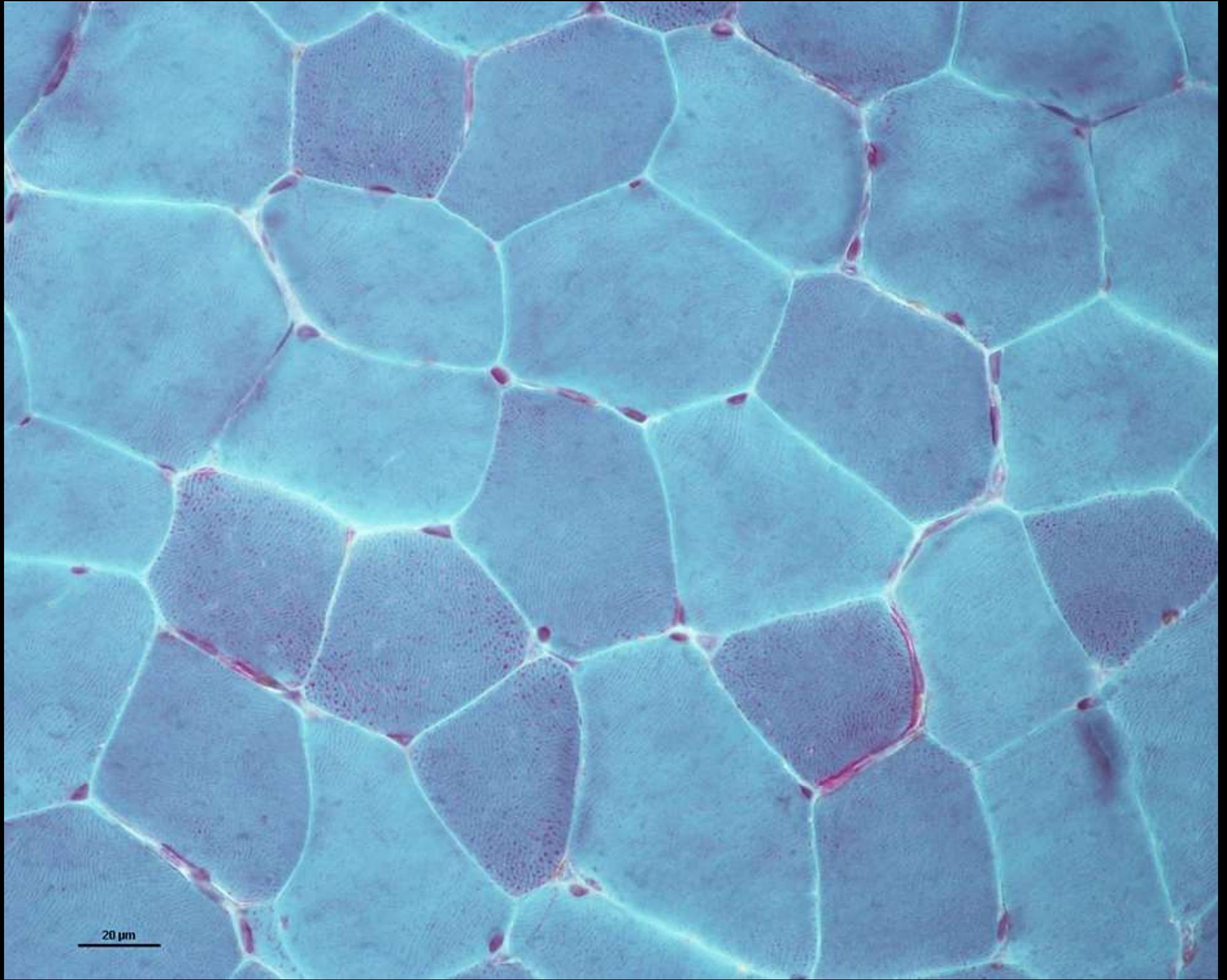
200  $\mu\text{m}$

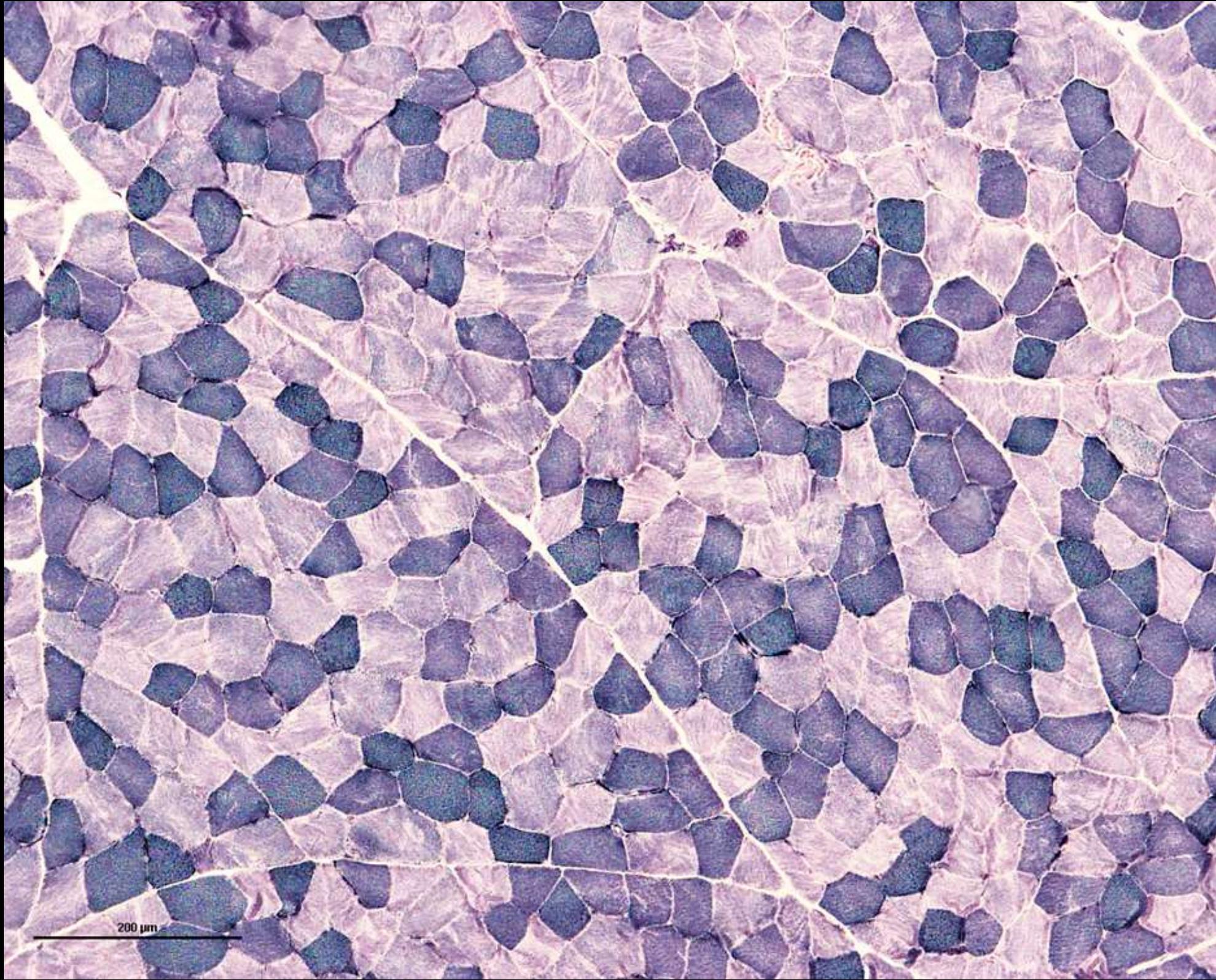


20 μm



200  $\mu$ m

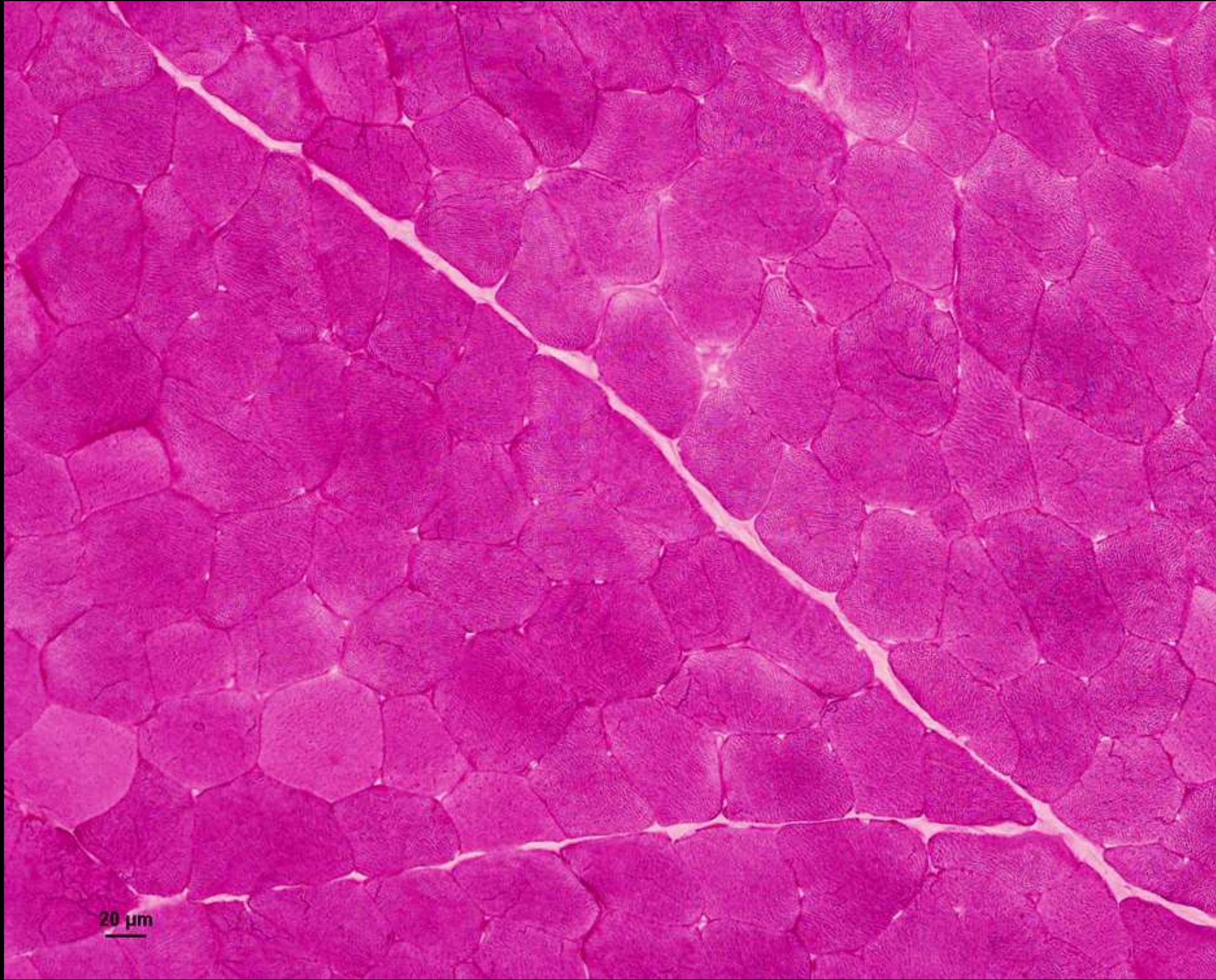




200 μm



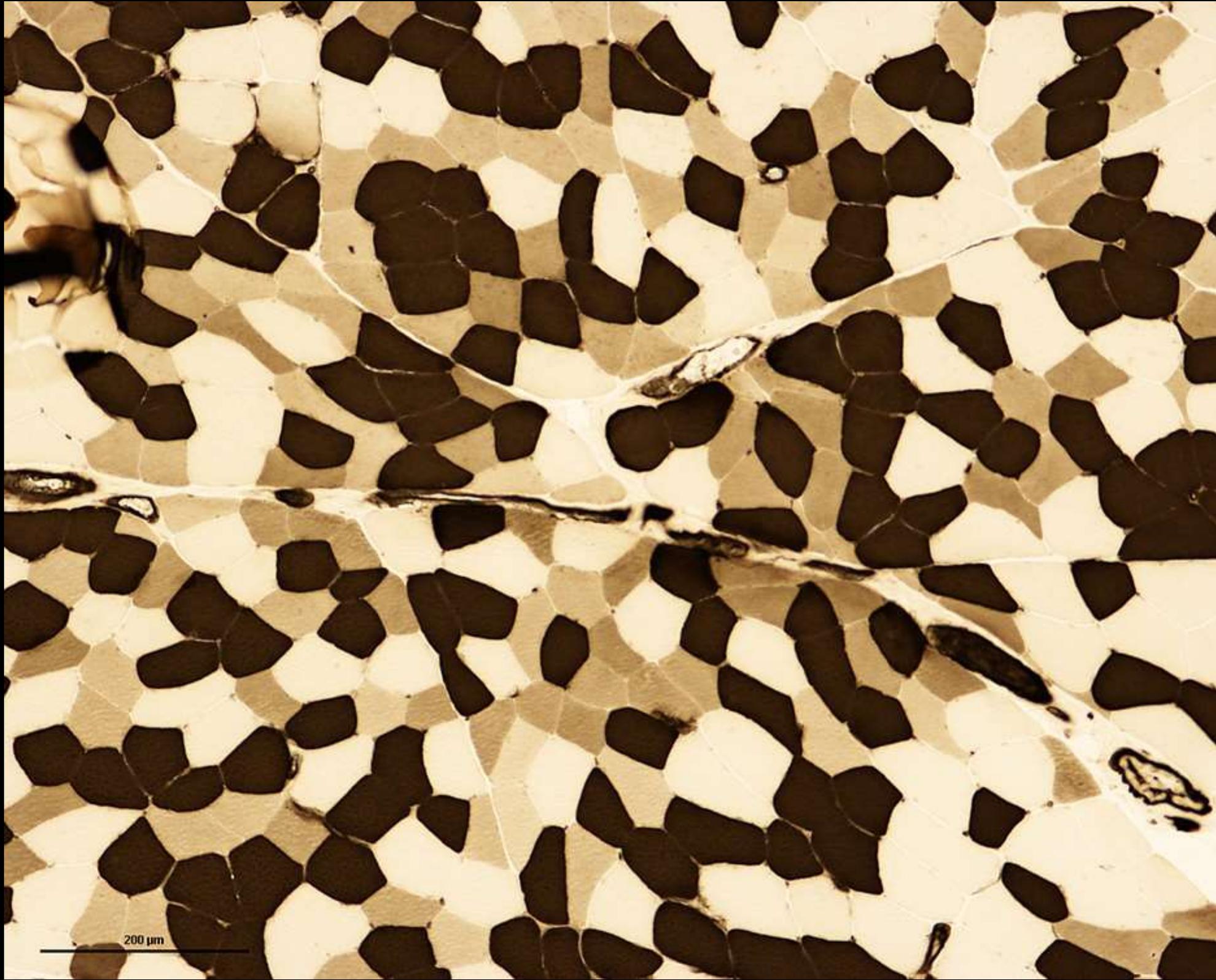
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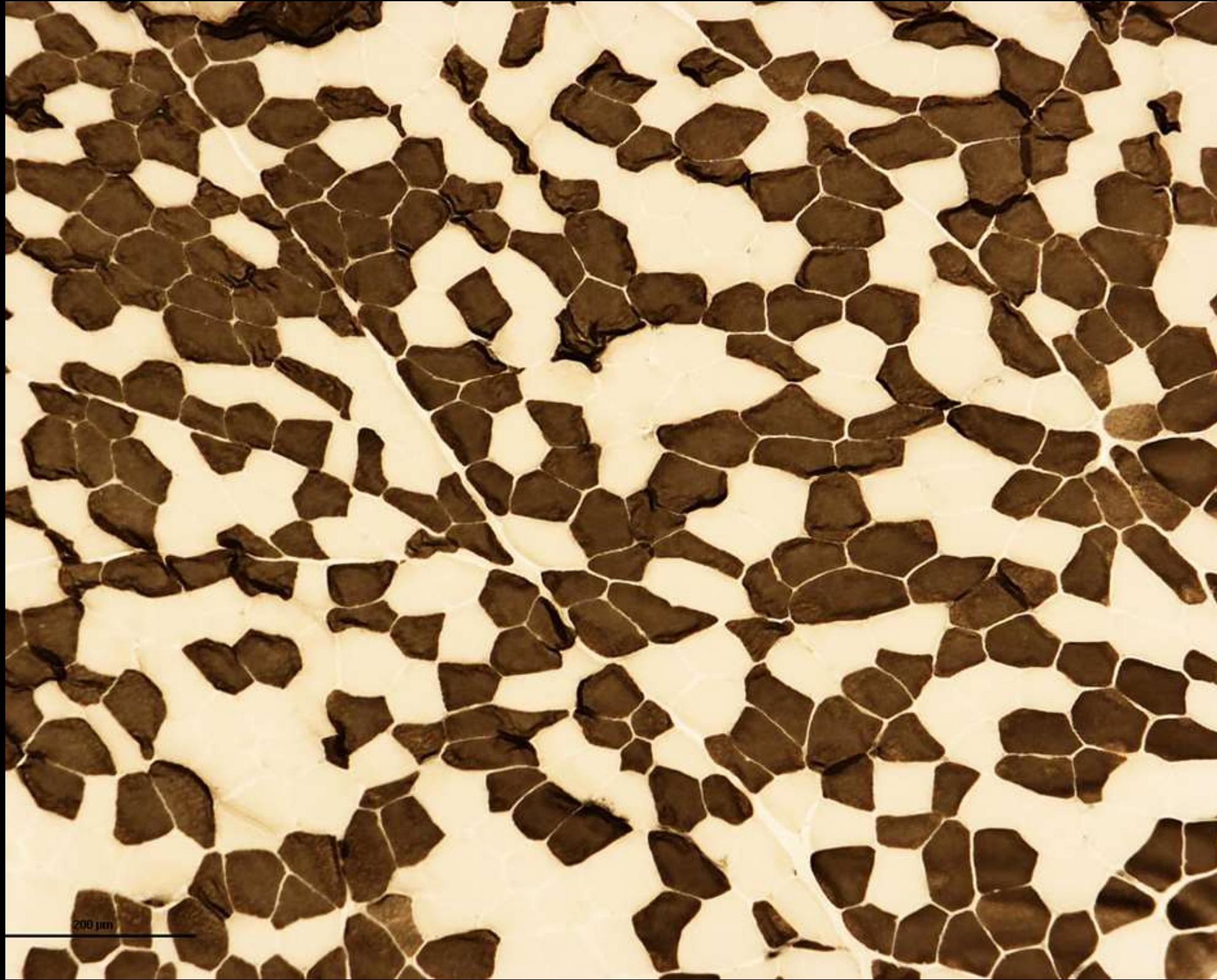
20  $\mu$ m



200  $\mu\text{m}$



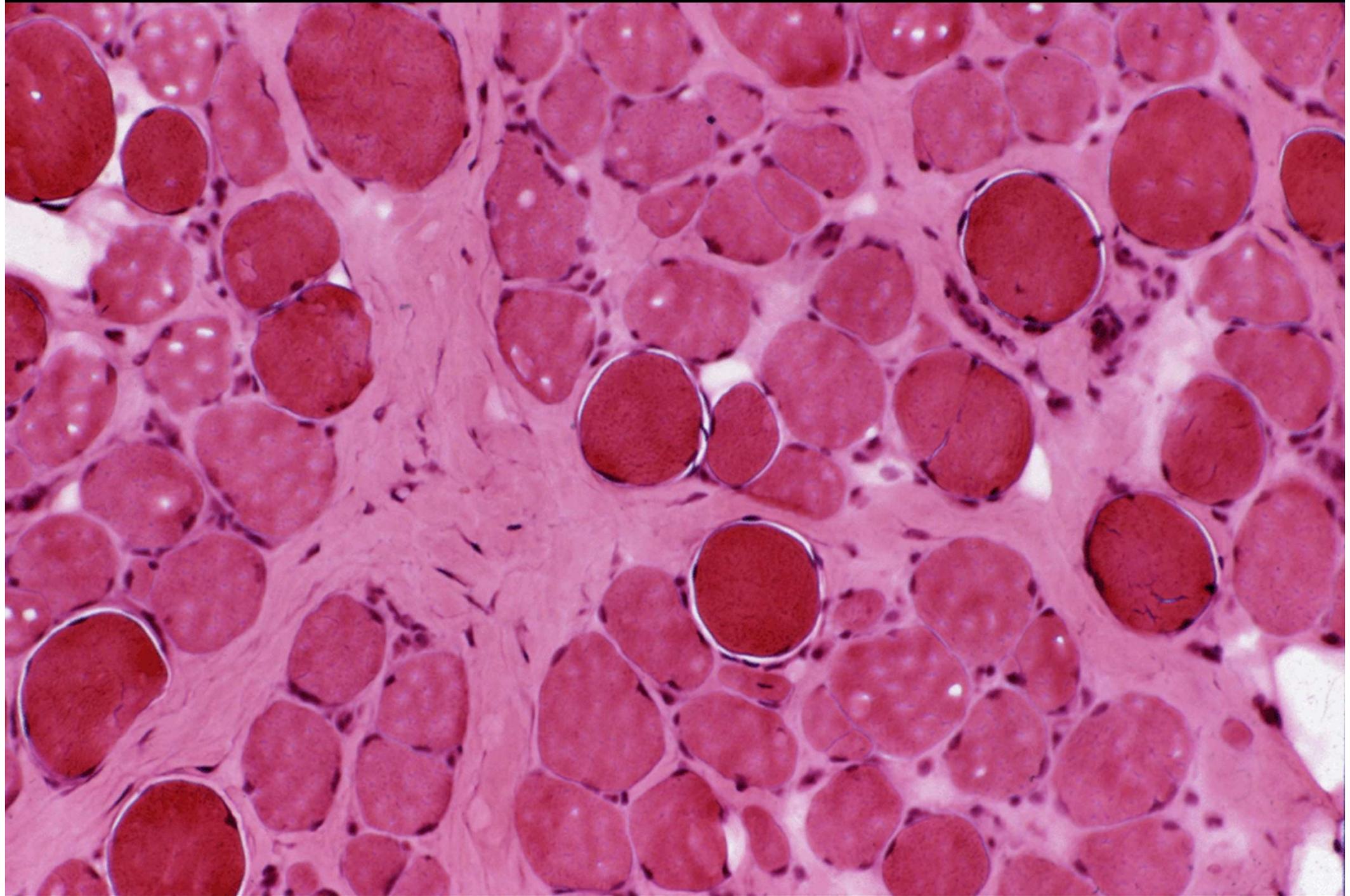
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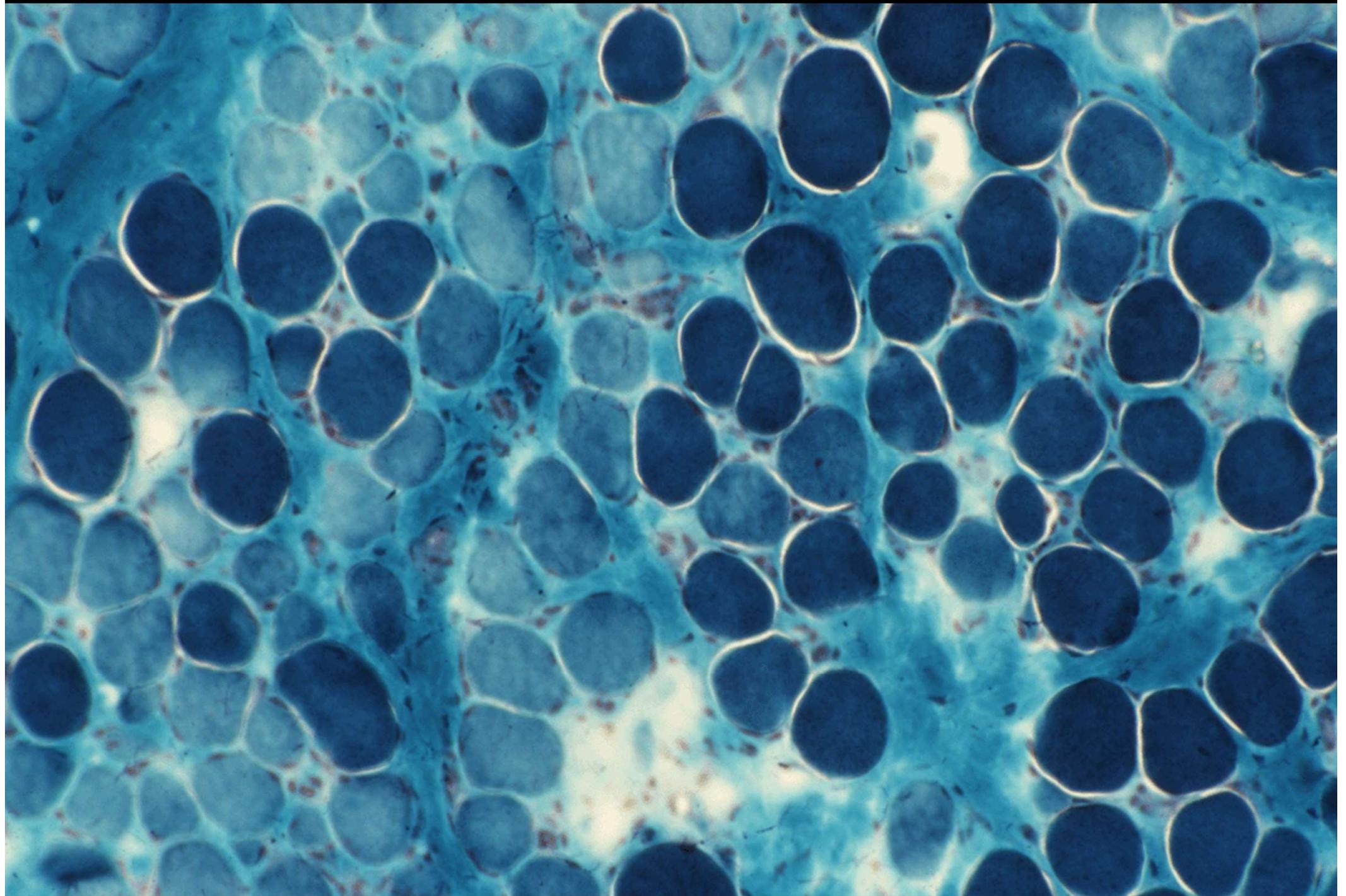


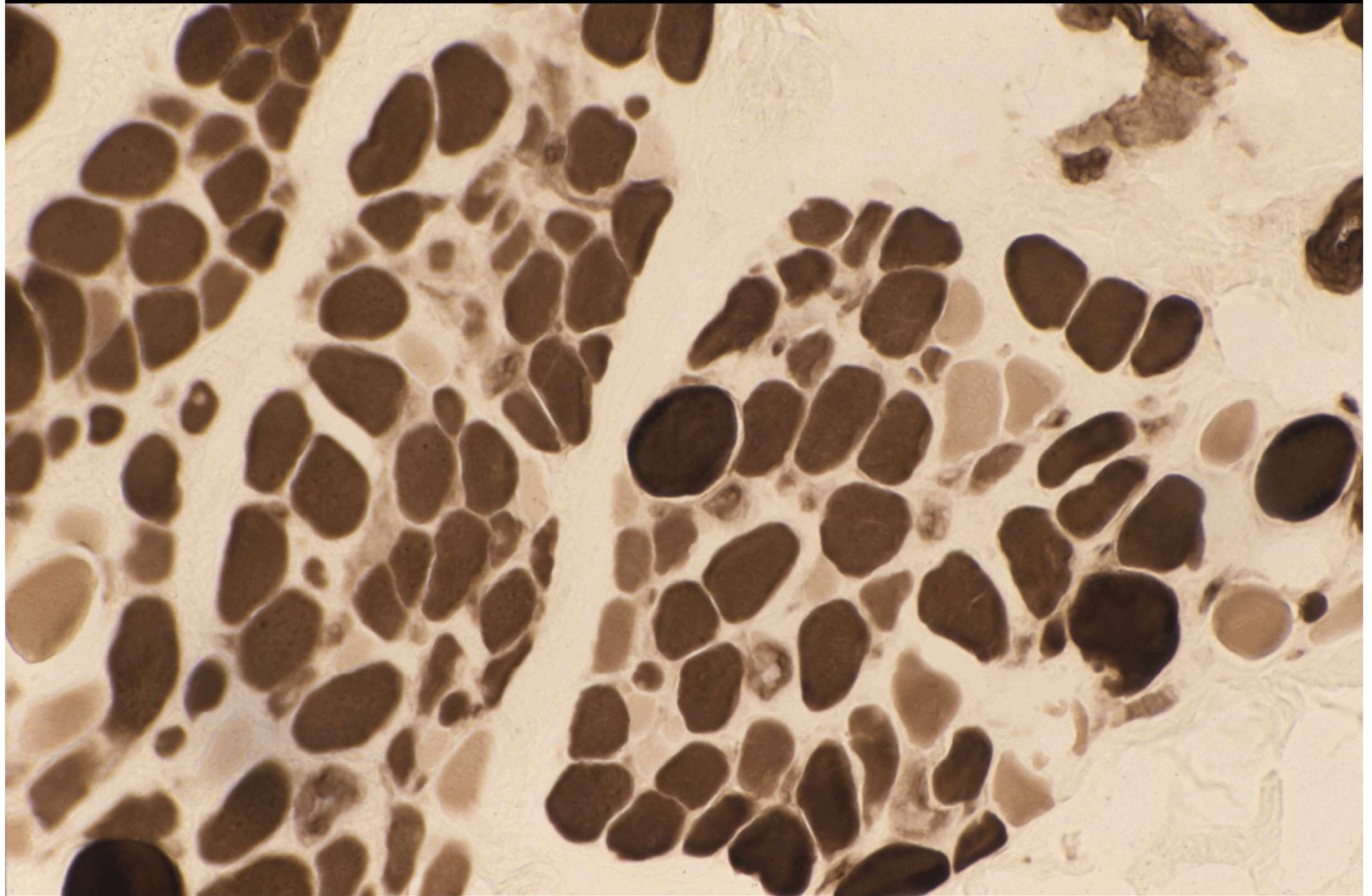
200 μm

# 筋ジストロフィー

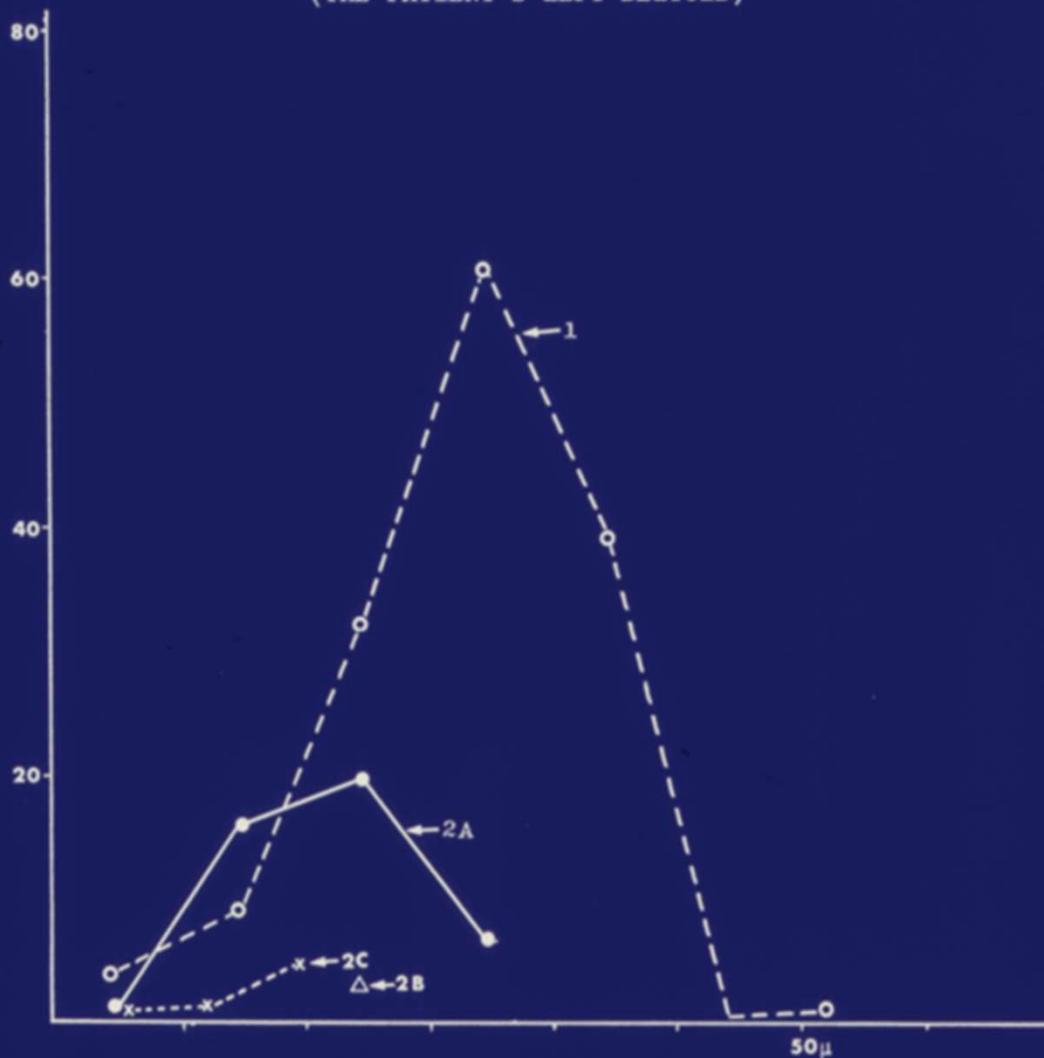
- ・ 筋構成構造蛋白、酵素、筋周膜支持構造、核膜保持蛋白、核蛋白の異常が関与。
- ・ 遺伝性進行性で筋壊死・再生を伴うことが埜中先生による古典的定義。



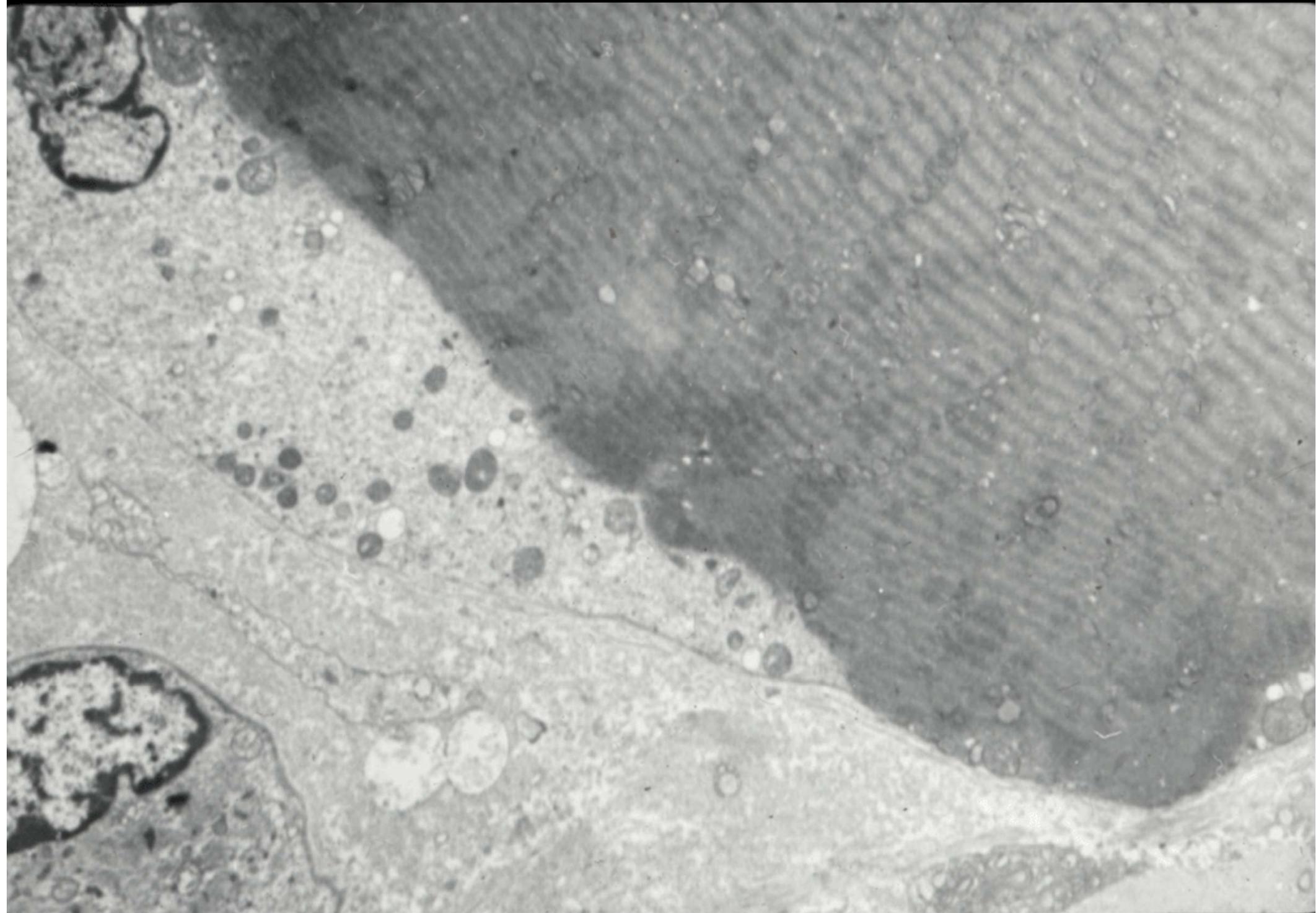


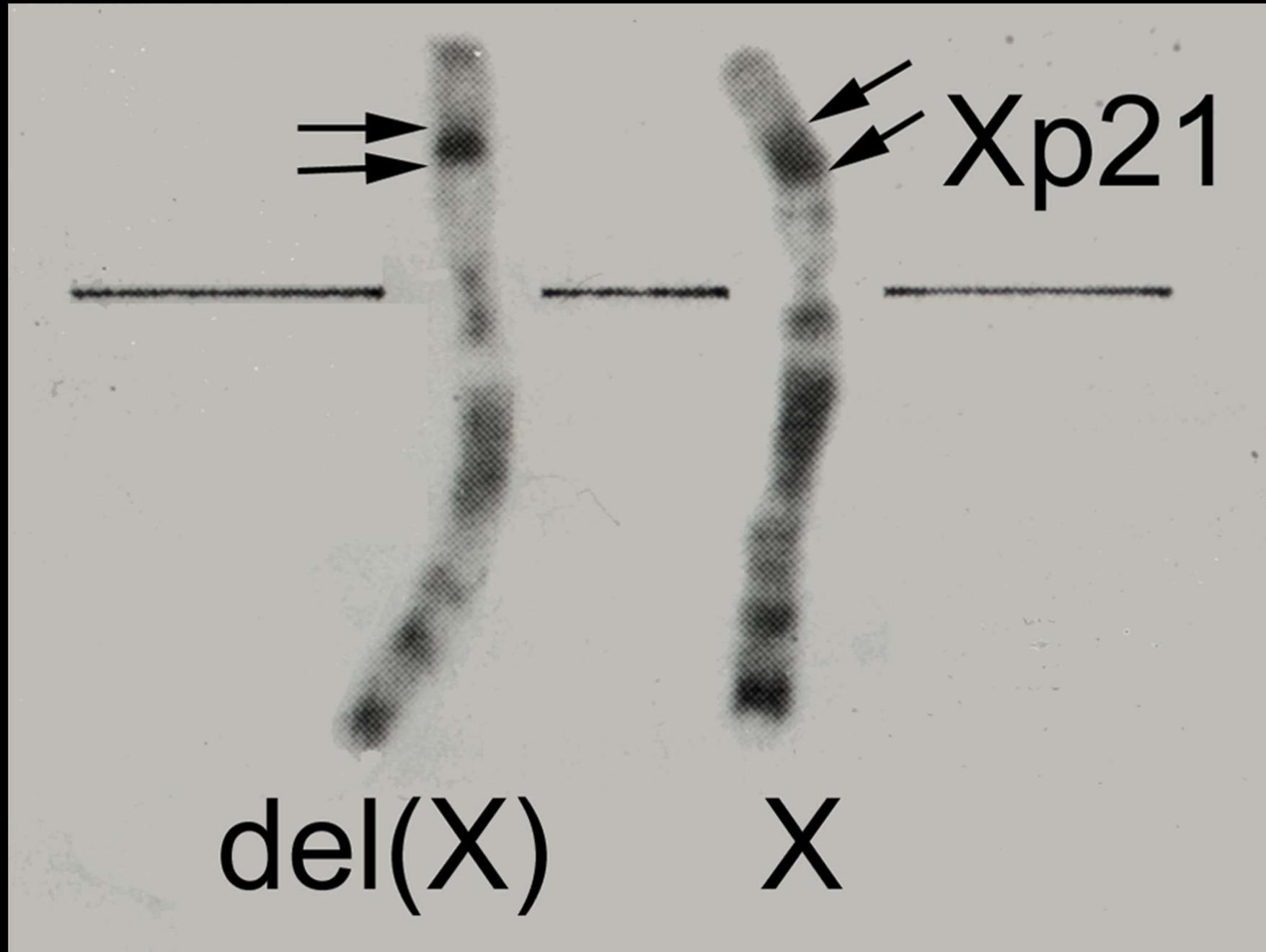


FIBER DIAMETER HISTOGRAM  
 (THE PATIENT'S LEFT DELTOID)

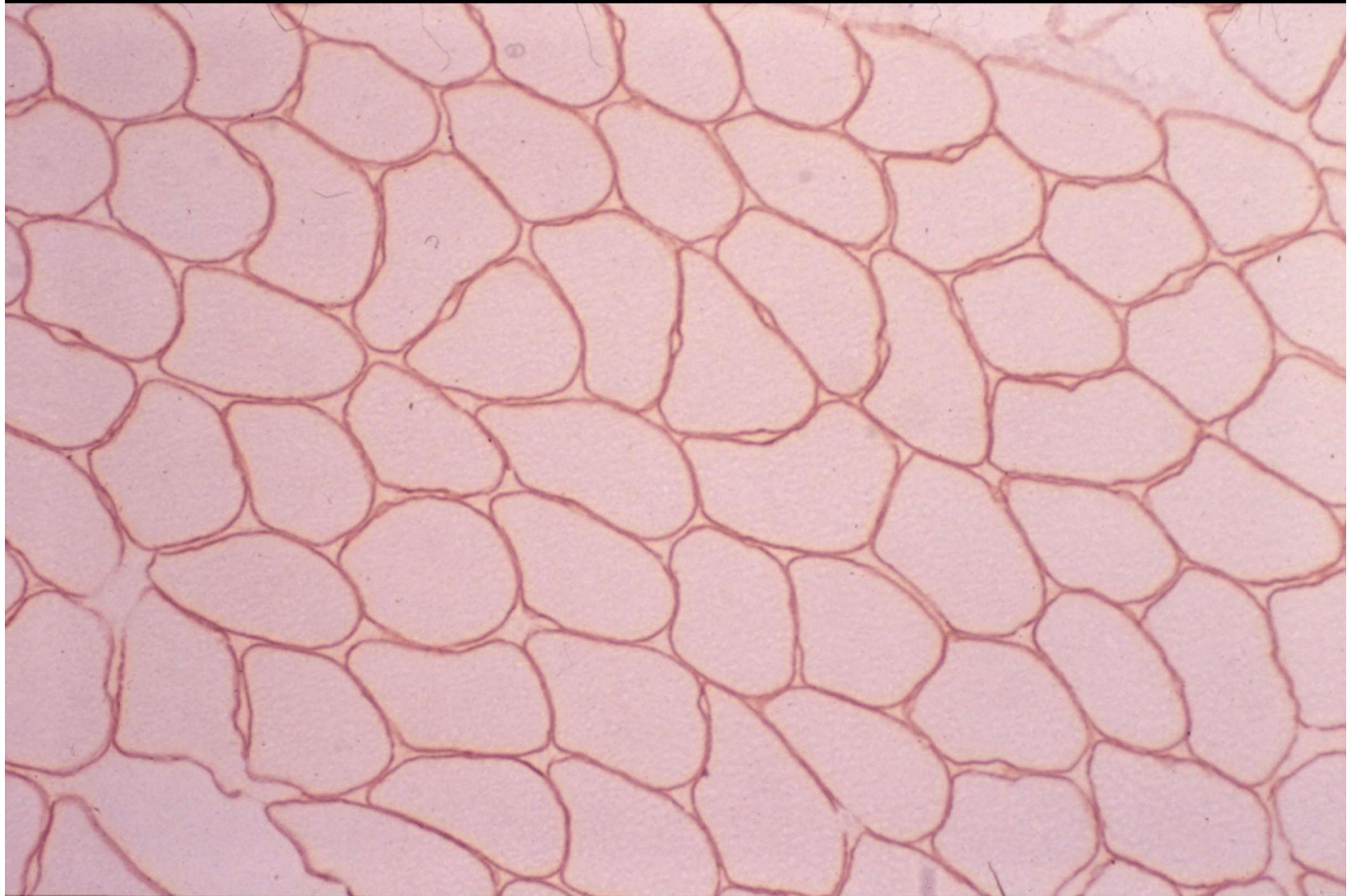


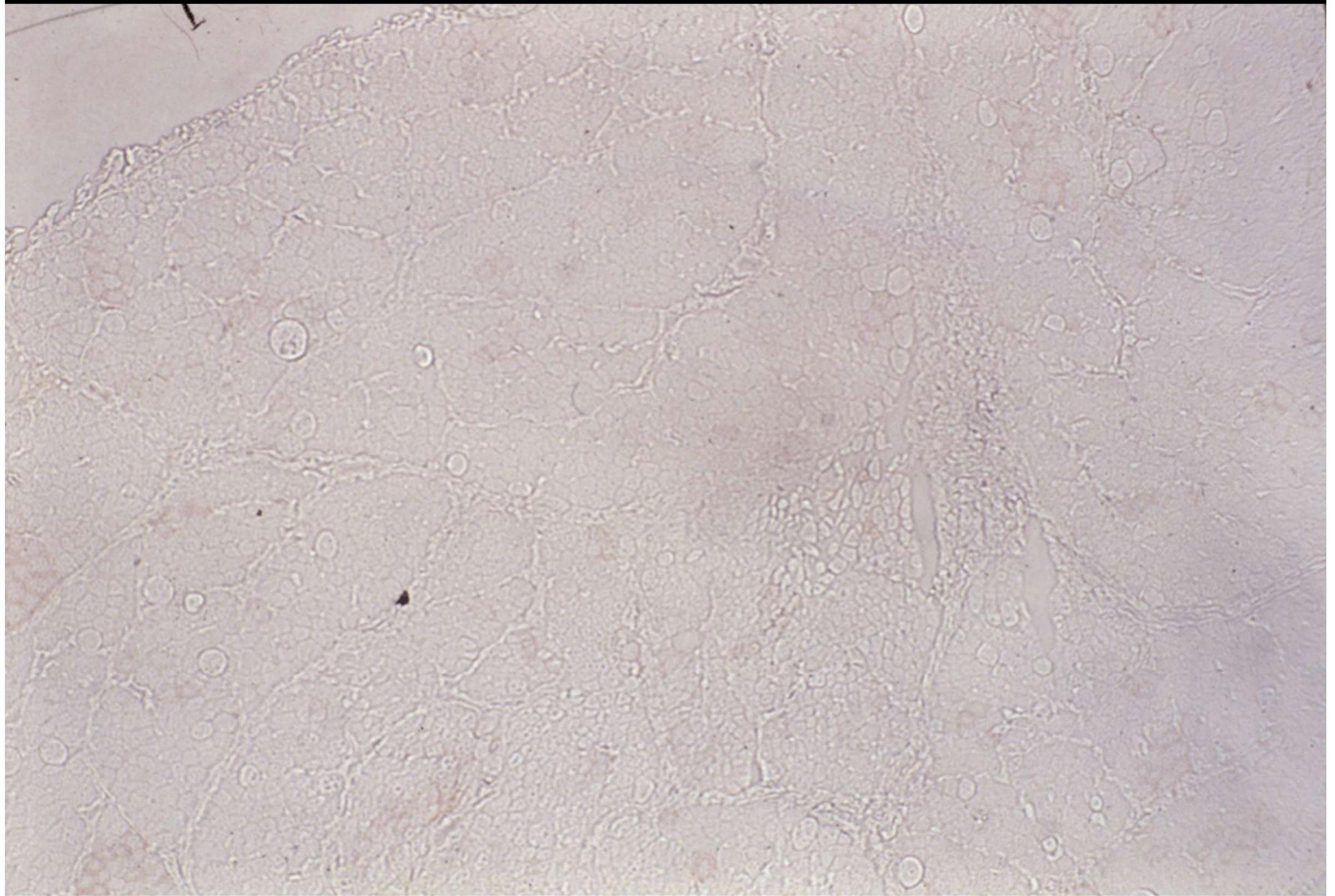
MUSCLE FIBER TYPE	I	IIA	IIB	IIC
MEAN DIAMETER	33.0	39.9	24	19
STANDARD DEVIATION	9.82	5.78	1.94	7.57
ATROPHY FACTOR	1,151	2,250	2,000	2,429
HYPERTROPHY FACTOR	0	0	0	0
PERCENTAGE OF FIBERS	73	22	1.5	3.5

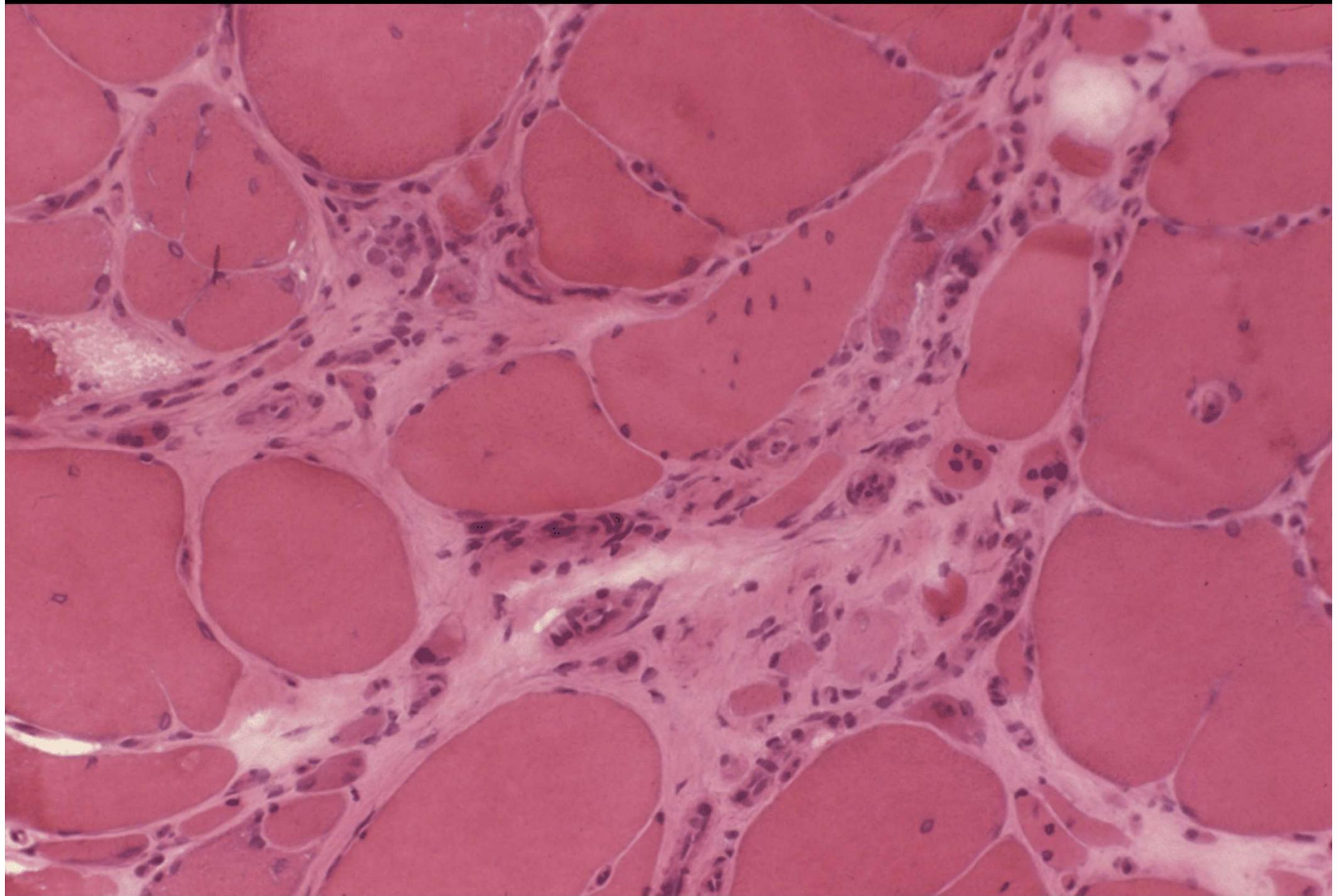


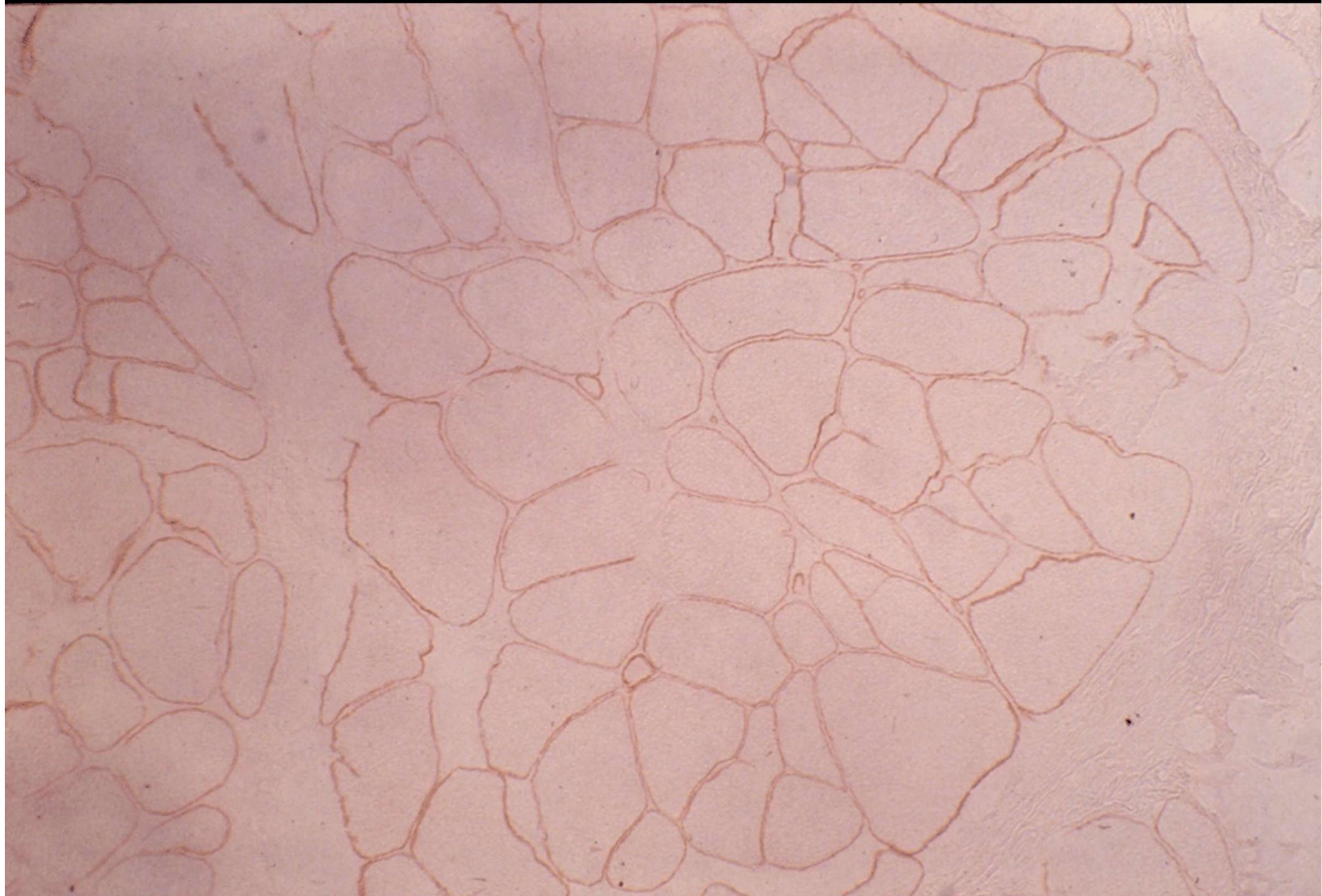


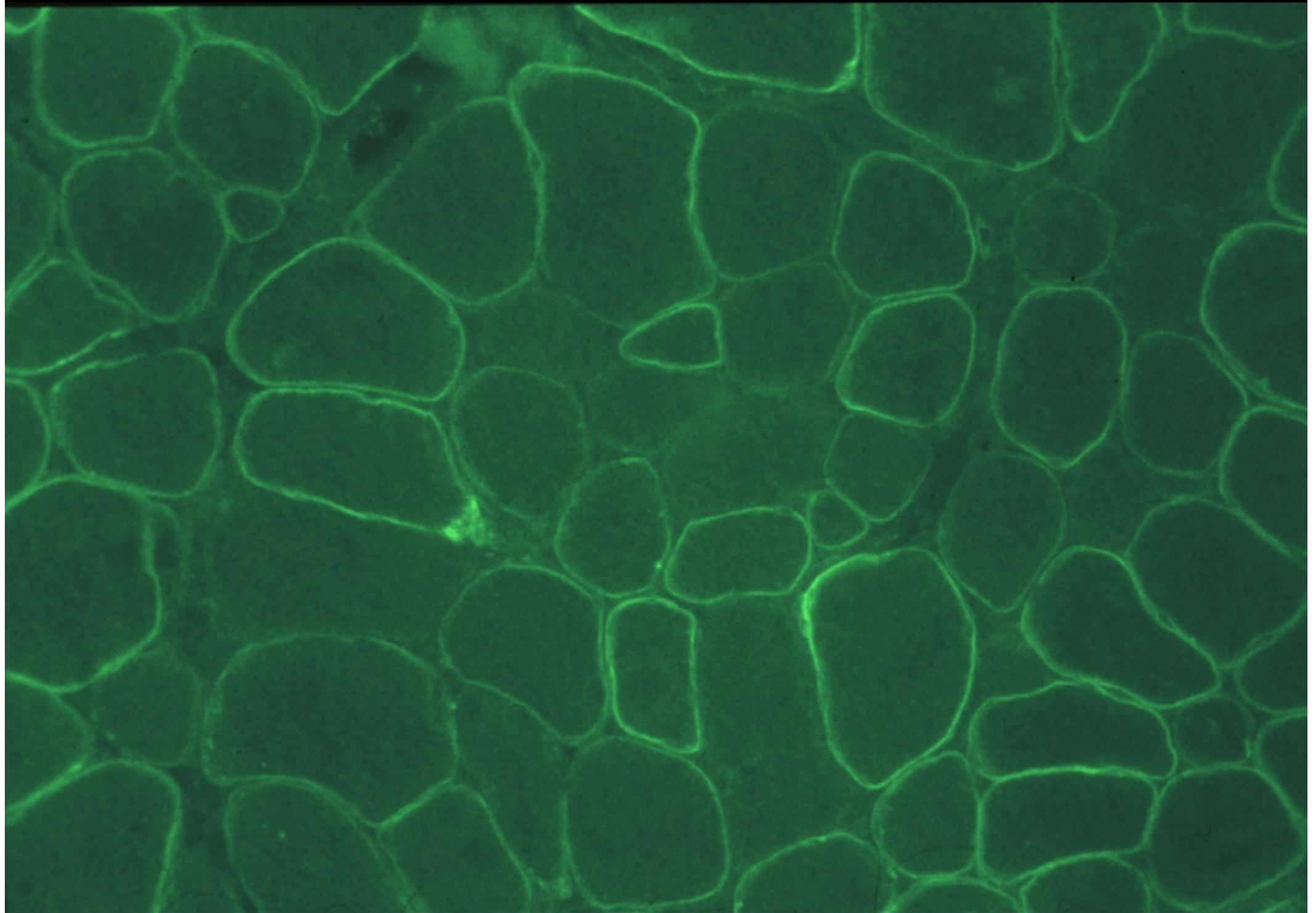
Saito F, 3 authors, Murayama S, two authors: Inherited Xp21 deletion in a boy with complex glycerol kinase deficiency syndrome. Clin Genet 1986,

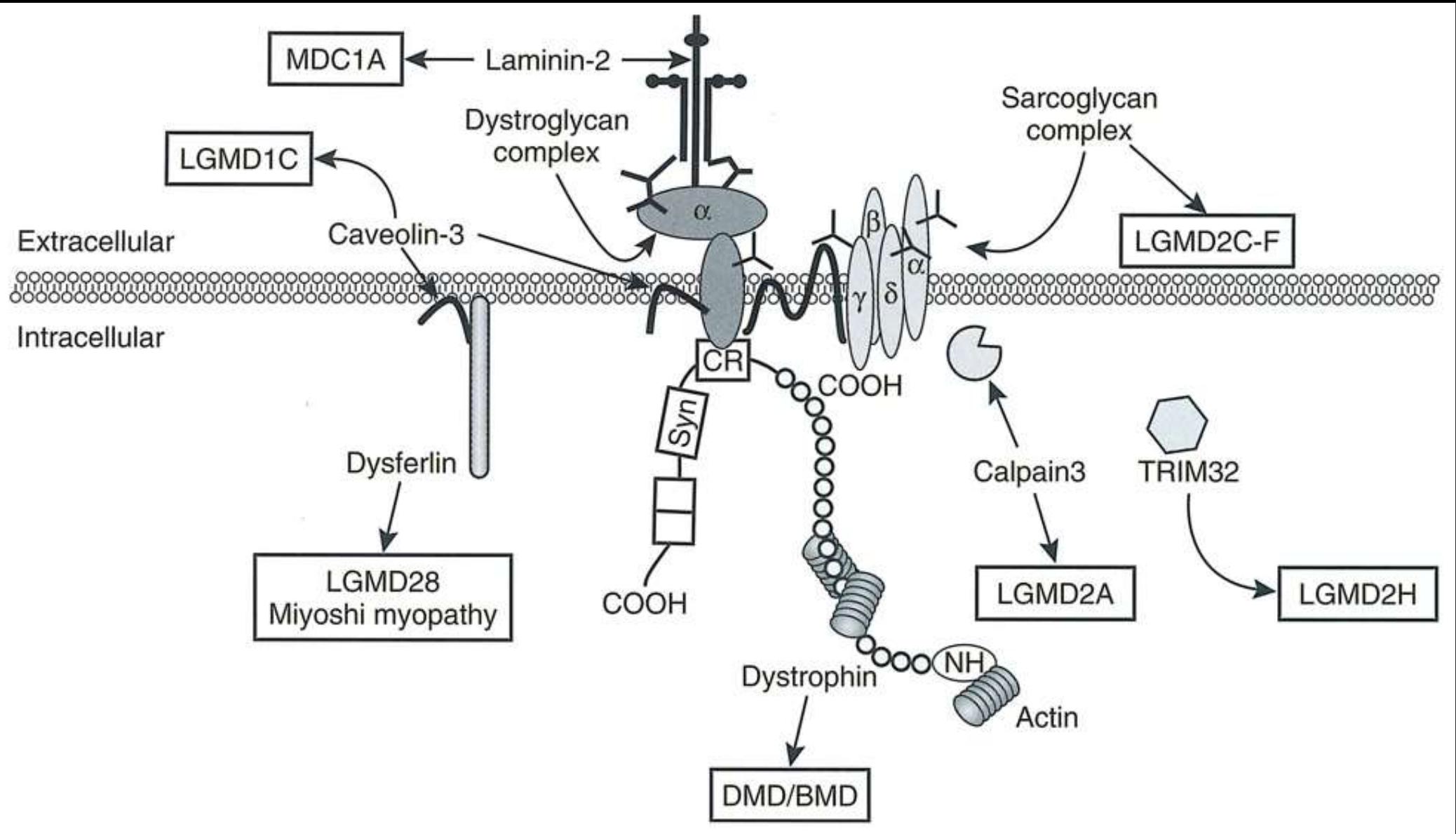


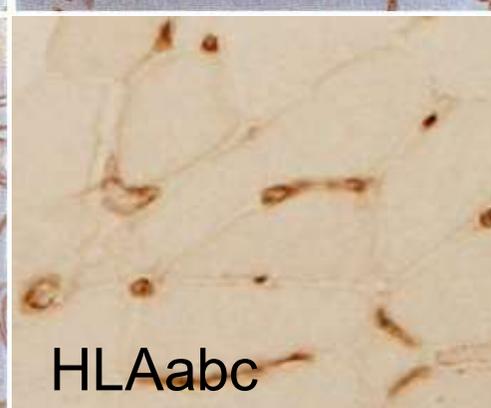
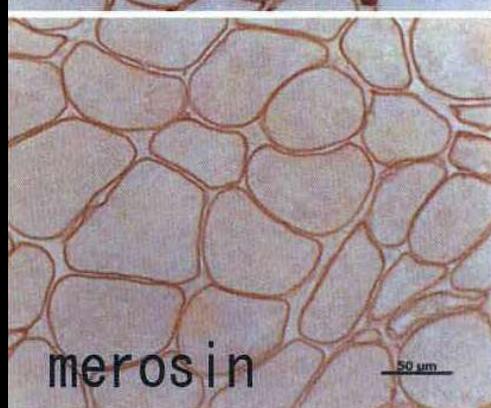
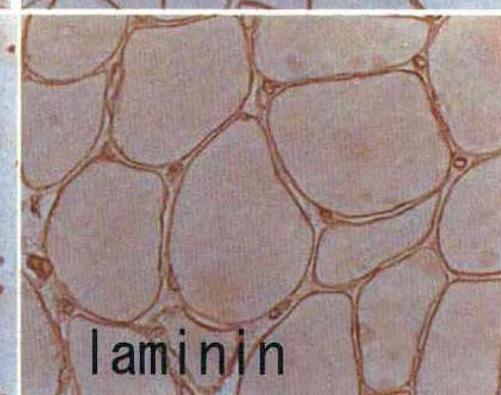
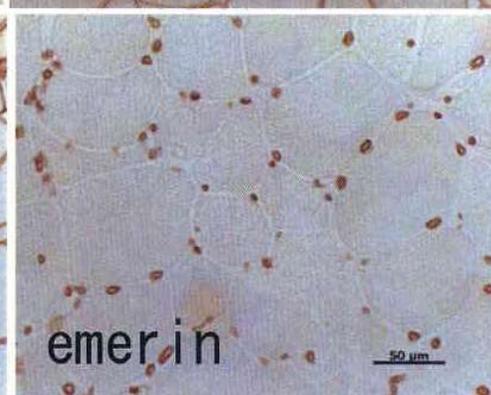
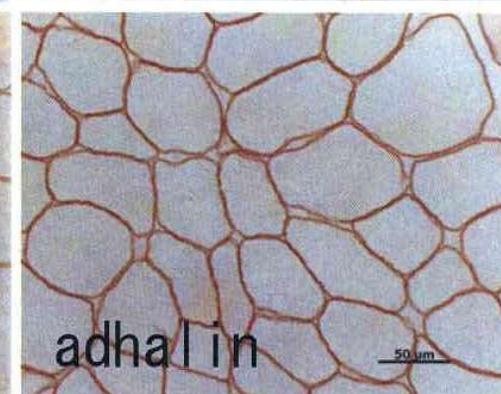
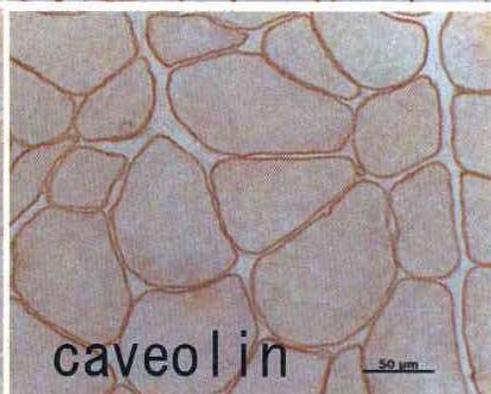
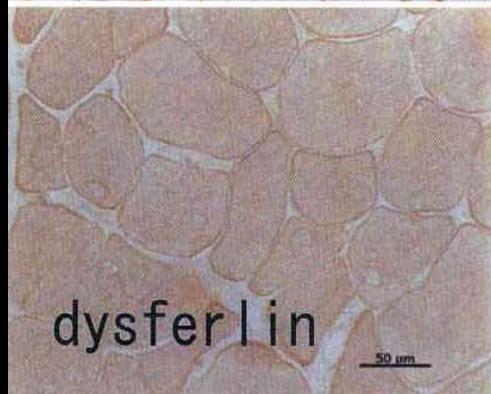
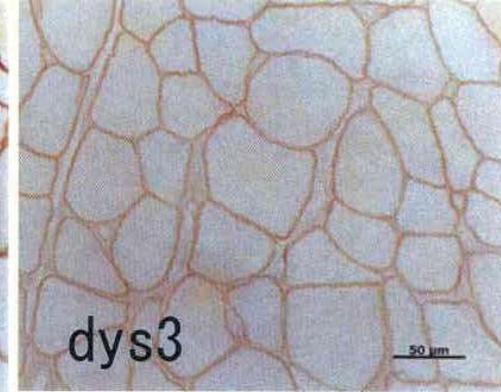
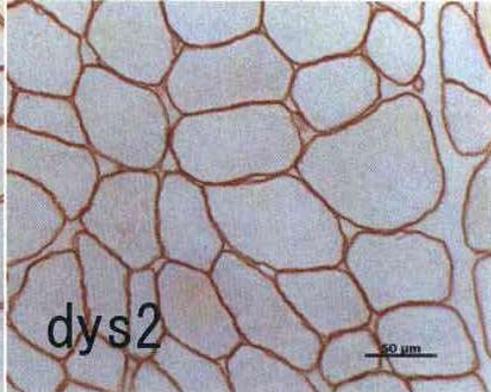
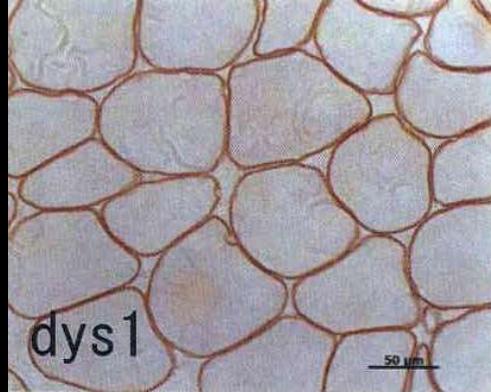






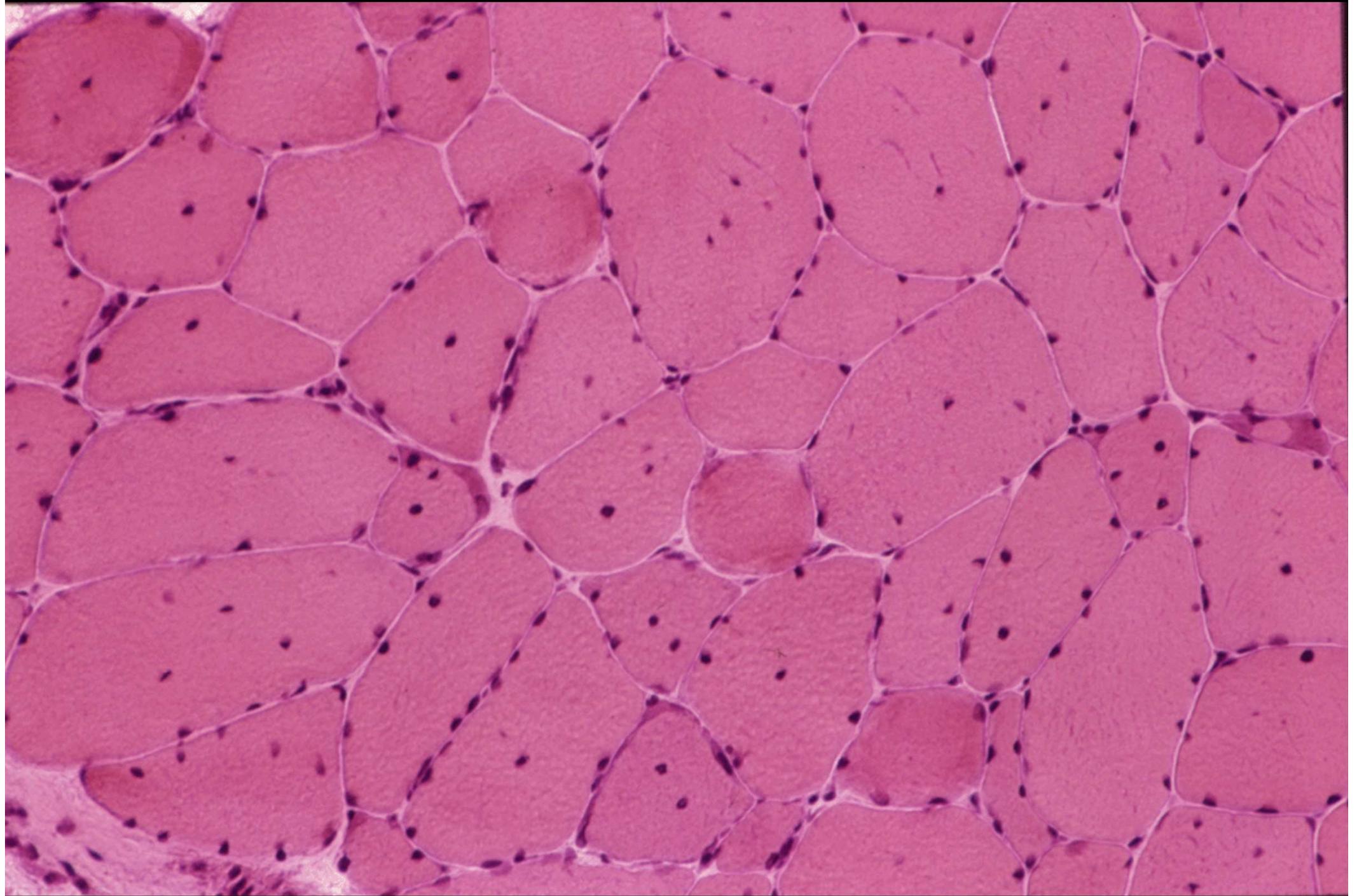


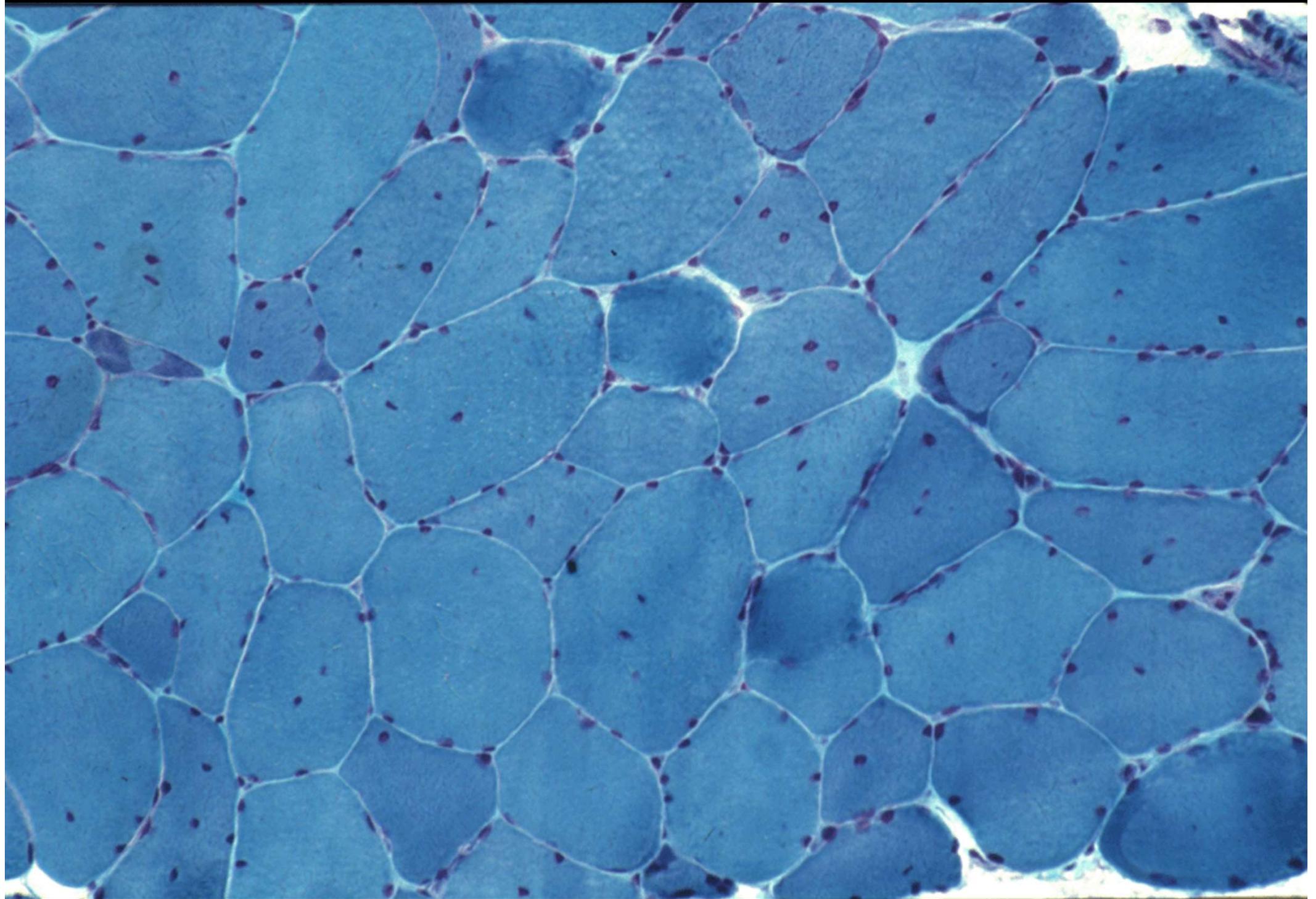


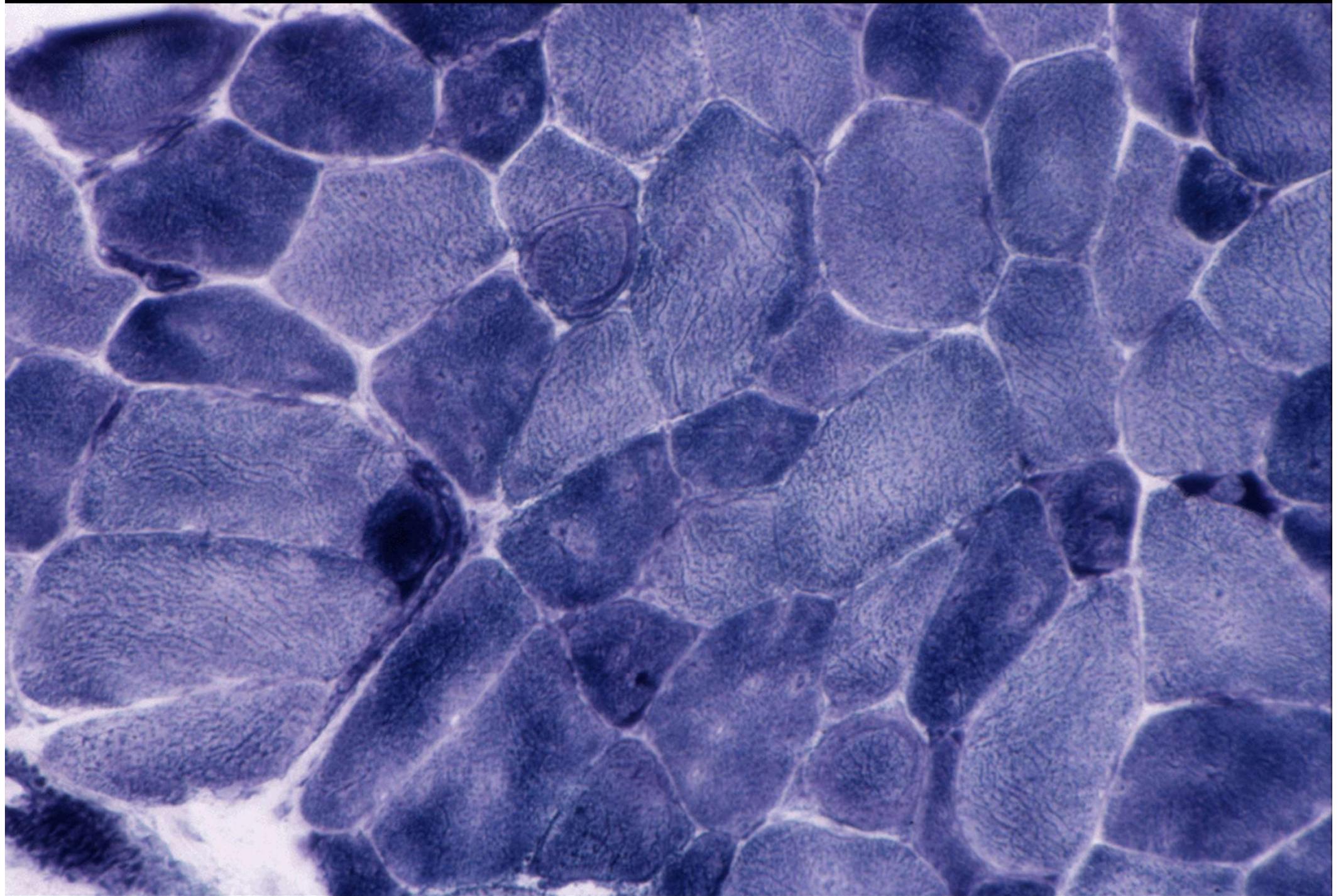


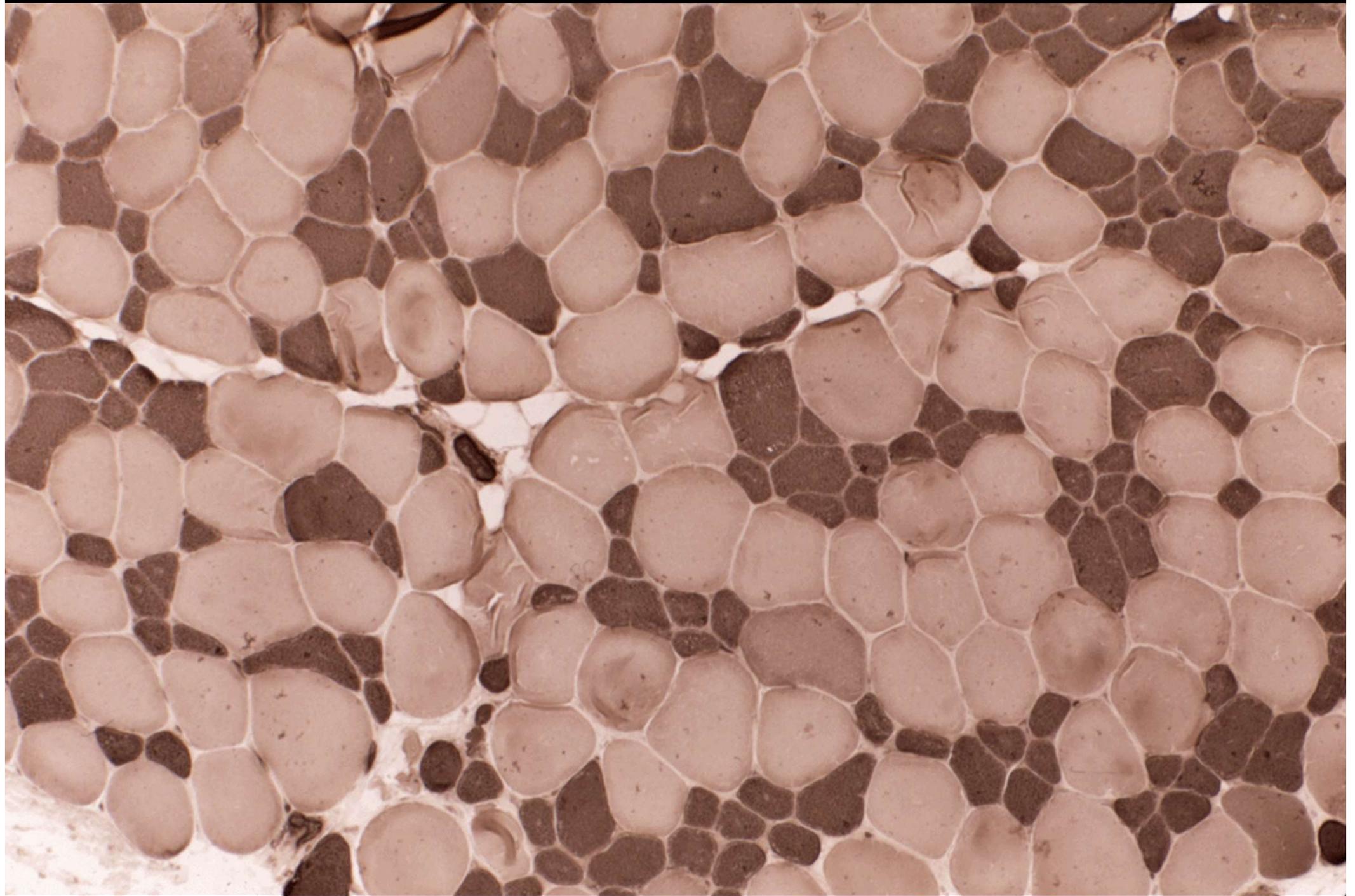
**Table 13-4.** Classifications and Characteristics of Limb Girdle Muscle Dystrophies

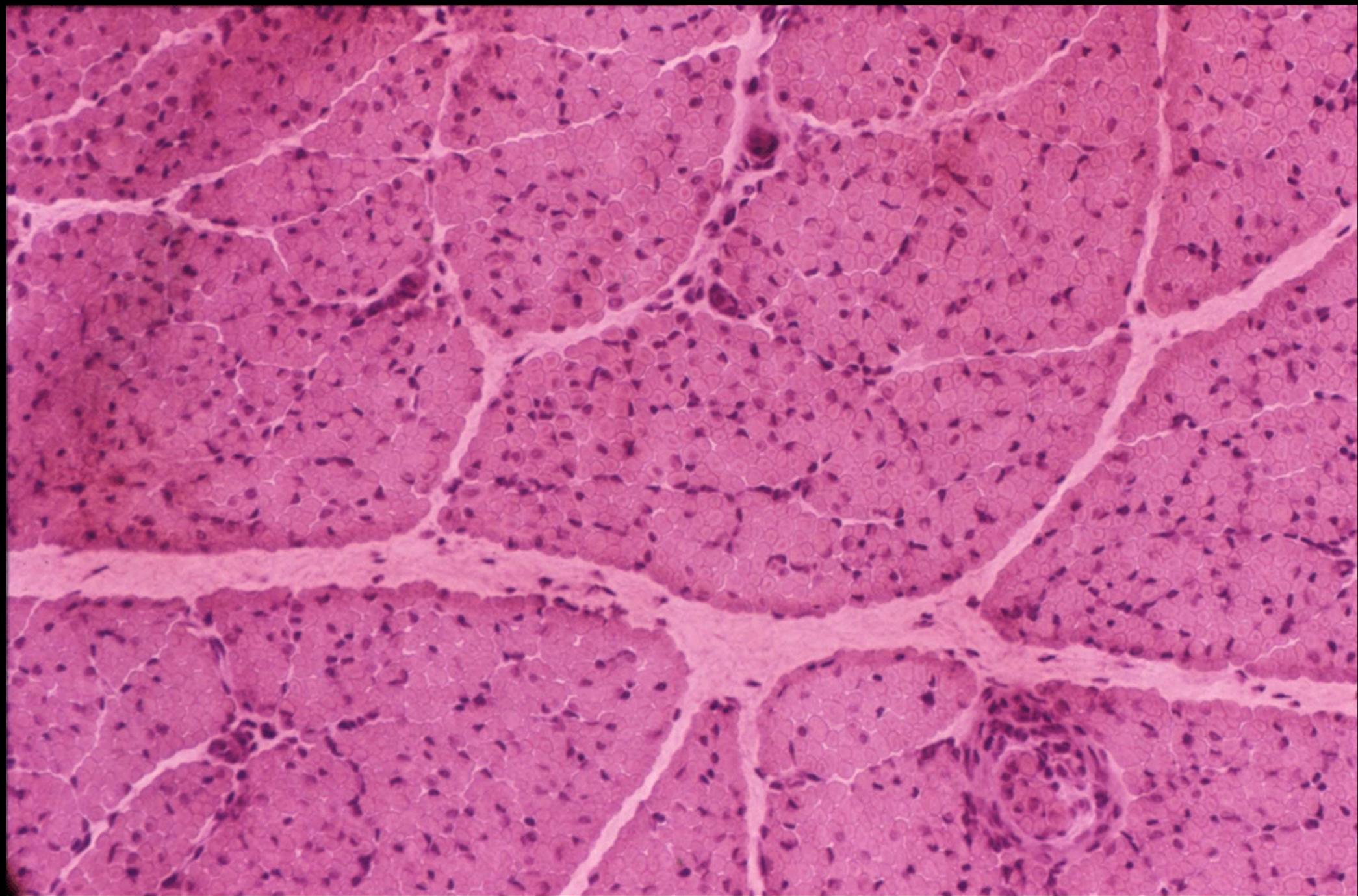
Subtype	Gene Product	Gene Localization	Characteristic Feature
<b>Limb Girdle Dystrophies: Autosomal Dominant</b>			
LGMD 1A	Myotilin	5q31	Nasal dysarthric speech
LGMD 1B	Lamin A/C	1q21	Dilated cardiomyopathy, conduction defects
LGMD 1C	Caveolin-3	3p25	Childhood onset, cramps, rippling muscle disease
LGMD 1D		6q23	
LGMD 1E		7q7-9	
<b>Limb Girdle Dystrophies: Autosomal Recessive</b>			
LGMD 2A	Calpain-3	15q15	Scapular winging; may have contractures and facial weakness late
LGMD 2B	Dysferlin	2p12	Proximal or distal weakness
LGMD 2C	$\gamma$ -Sarcoglycan	13q12	Scapular winging, calf hypertrophy, possibly dilated cardiomyopathy
LGMD 2D	$\alpha$ -Sarcoglycan	17q21	Scapular winging, calf hypertrophy, possibly dilated cardiomyopathy
LGMD 2E	$\beta$ -Sarcoglycan	4q12	Scapular winging, calf hypertrophy, possibly dilated cardiomyopathy
LGMD 2F	$\delta$ -Sarcoglycan	5q33	Scapular winging, calf hypertrophy, possibly dilated cardiomyopathy
LGMD 2G	Telethonin	17q11-12	Anterior distal weakness, rimmed vacuoles
LGMD 2H	TRIM32	9q31-q34.1	Slowly progressive, facioscapulohumeral
LGMD 2I	Fukutin-related protein	19q13.3	Calf hypertrophy, dilated cardiomyopathy
LGMD 2J	Titin	2q31	Proximal and distal weakness; anterior tibial wasting

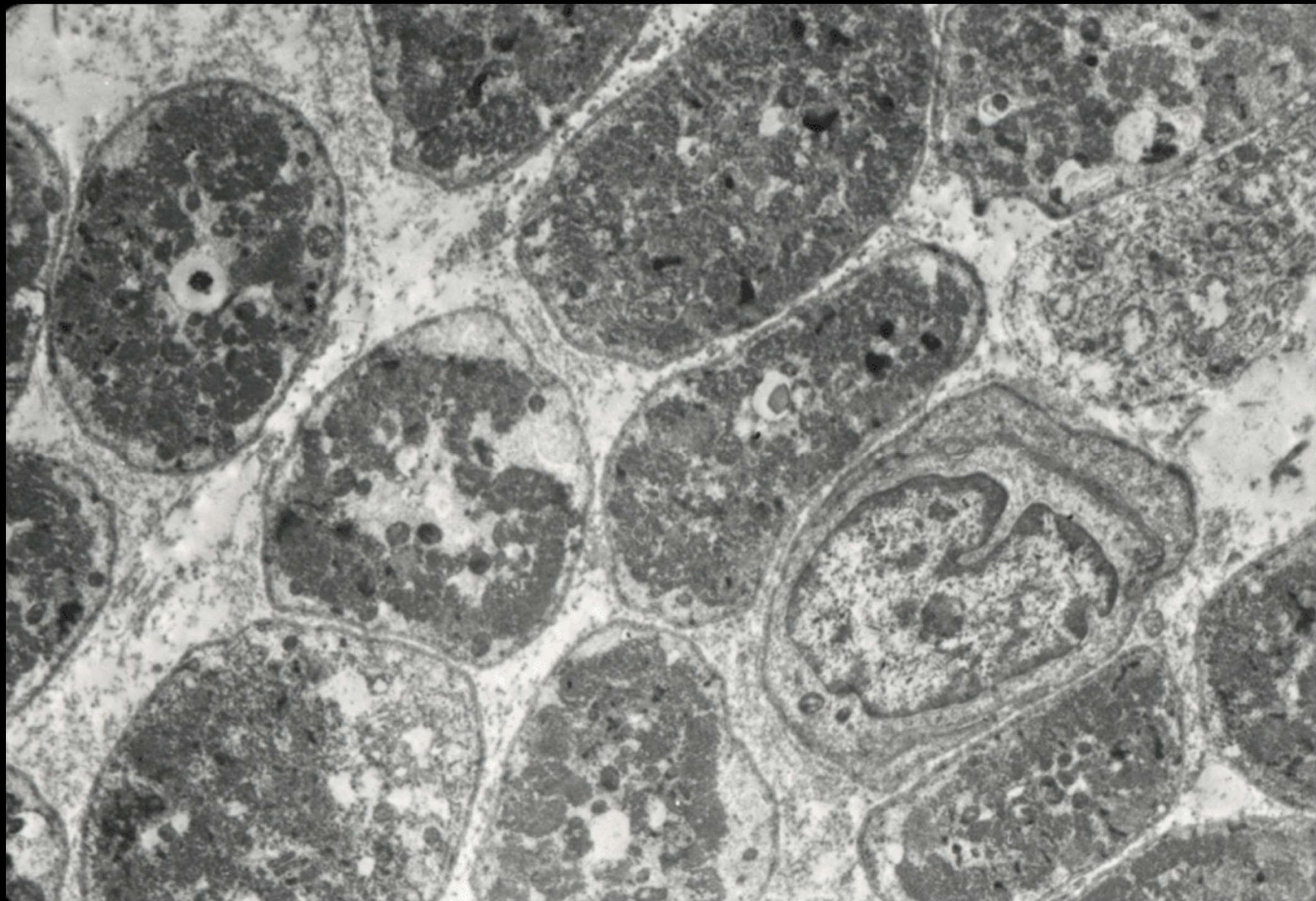






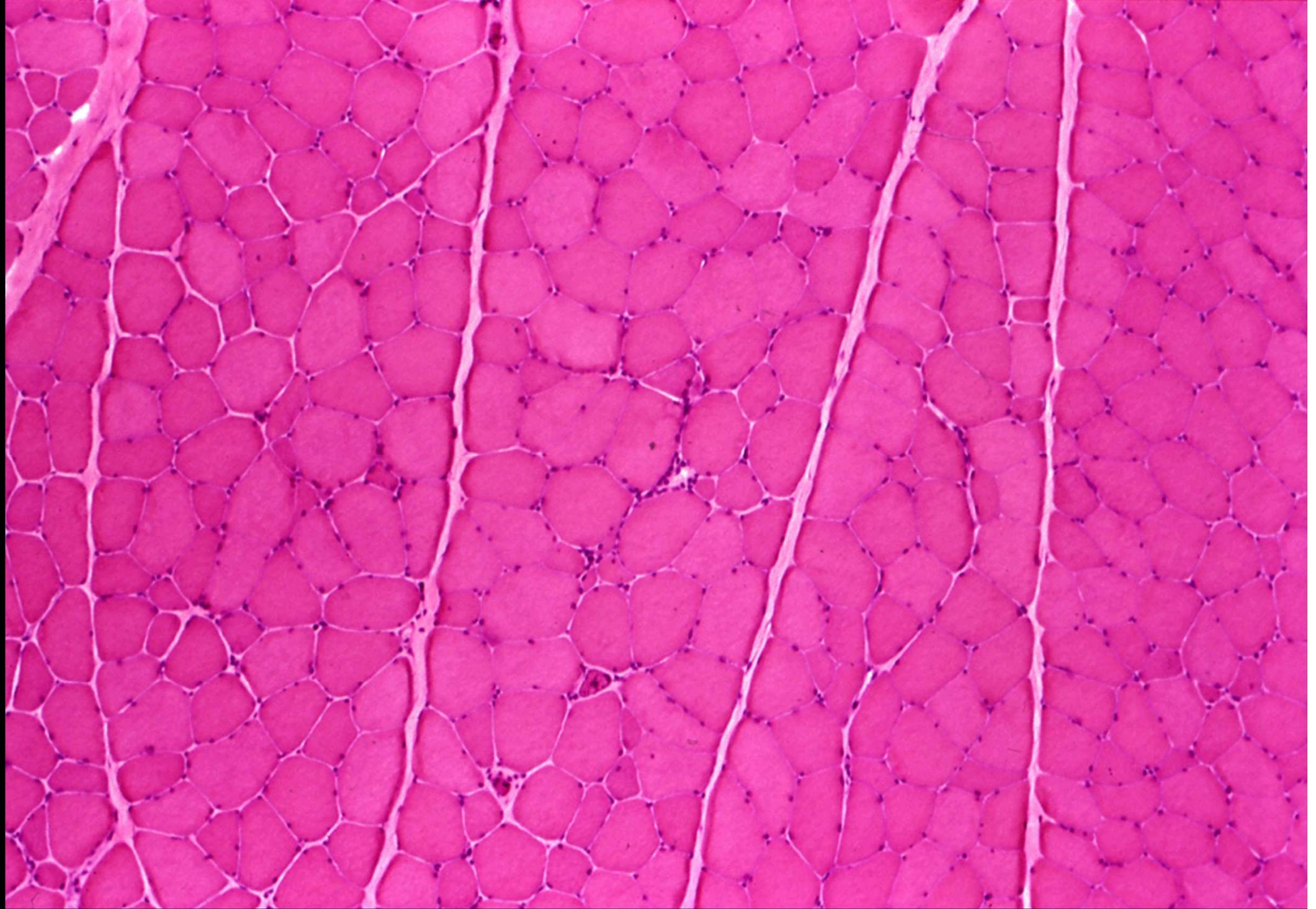




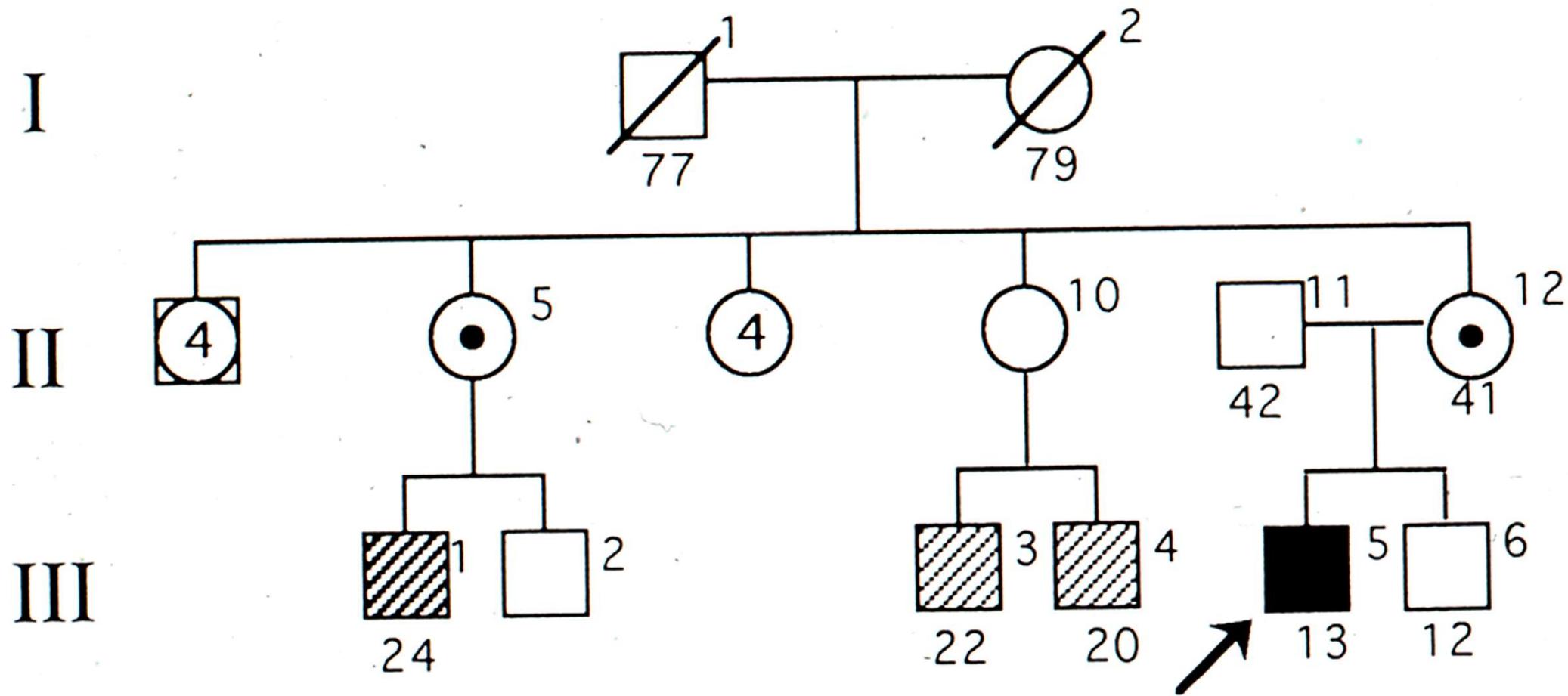


**Table 13-5.** Characteristic Genetic, Clinical, and Pathologic Features of Channel-Disease Myotonia

Disease Name	Gene Name and Locus	Gene Product and Functional Change	Symptoms	Pathology
Myotonia congenita (Becker dystrophy)	CLCN1 7q35	Chloride channel 1; loss of function	Recessive, childhood onset, transient weakness	Muscle hypertrophy
Thomsen disease	Same as above	Chloride channel 1; gain of function	Dominant, second-decade onset	Mild hypertrophy; myofibrillar disarray; loss of 2B fibers
Potassium-aggravated myotonia	SCN4A 17q23	Sodium channel $\alpha$ -subunit; gain of function	Dominant, variable onset, no weakness	
Paramyotonia congenital	SCN4A 17q23	Sodium channel $\alpha$ -subunit; gain of function	Dominant, childhood onset, cold-induced stiffness, weakness	
Hypokalemic periodic paralysis	CACNL1A3	Calcium channel	Dominant, second-decade onset, episodic weakness triggered by carbohydrates or exercise, no myotonia, improved by potassium	Tubular aggregates, debris-filled vacuoles
	SCN4A 17q23	Sodium channel $\alpha$ -subunit; loss of function		
	KCNE3 11q13-14	Potassium channel $\beta$ -subunit; loss of function		
Hyperkalemic periodic paralysis	SCN4A 17q23	Sodium channel $\alpha$ -subunit; loss of function	Dominant, childhood onset, episodic weakness, triggered by rest after exercise, no paramyotonia	Tubular aggregates, debris-filled vacuoles
Malignant hyperthermia (King-Denborough syndrome; Barnes syndrome)	RYR, CACNA1S, SCN4A	Ryanodine receptor; calcium channel; sodium channel $\alpha$ -subunit	Lethal hyperthermia in response to inhalation anesthetics, no weakness	Can be associated with central core myopathy



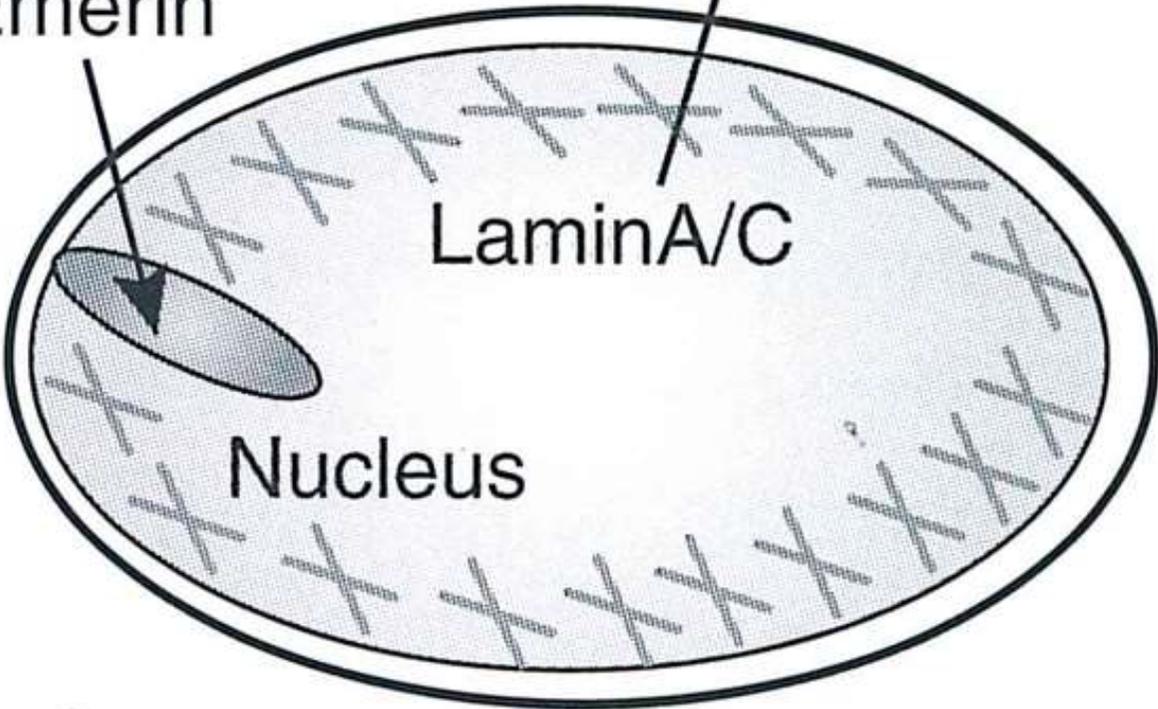
EDM



Emery Dreifuss MD

LGMD1B

Emerin



LaminA/C

Nucleus

# FSH

- Autosomal dominant
- 4/ 10,000,000
- FSH type 1 (FSHMD 1A) 4q35 del



# 筋炎

- (多発筋炎)
- 皮膚筋炎
- 封入体筋炎
- 自己免疫性壊死性筋症
- 抗ARS (tRNA合成酵素) 抗体症候群

# 筋炎特異自己抗体

	皮疹	筋炎	間質性肺炎	悪性腫瘍
ARS	0-2+	0-3+	慢性型	注意
MDA5	2-3+	0-3+	急性進行型	注意
TIF1-g	3+	0-2+	注意	高頻度
Mi-2	3+	1-3+	注意	注意
SRP	0	3+	注意	注意
HMGCR	0	3+	注意	注意

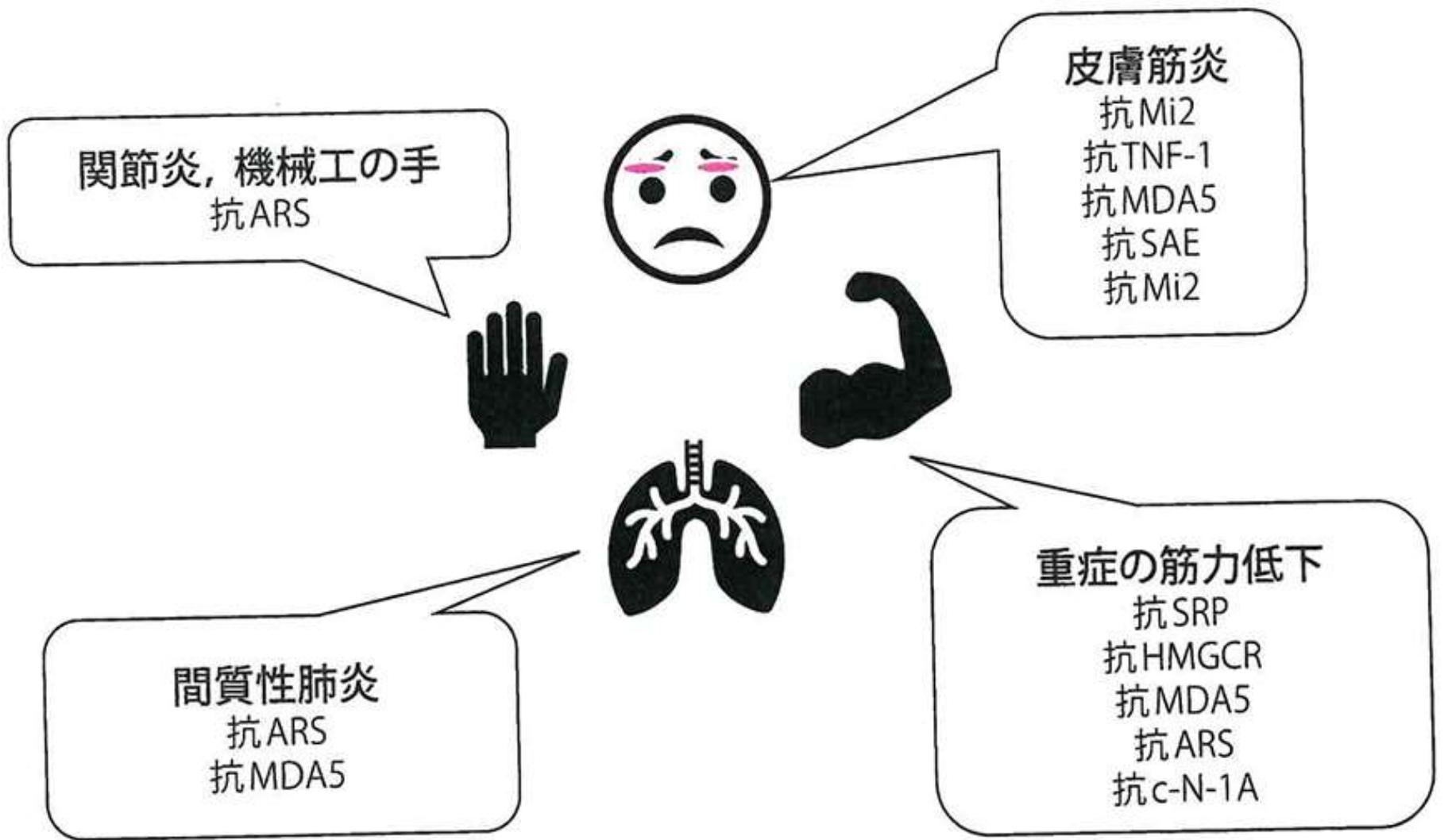
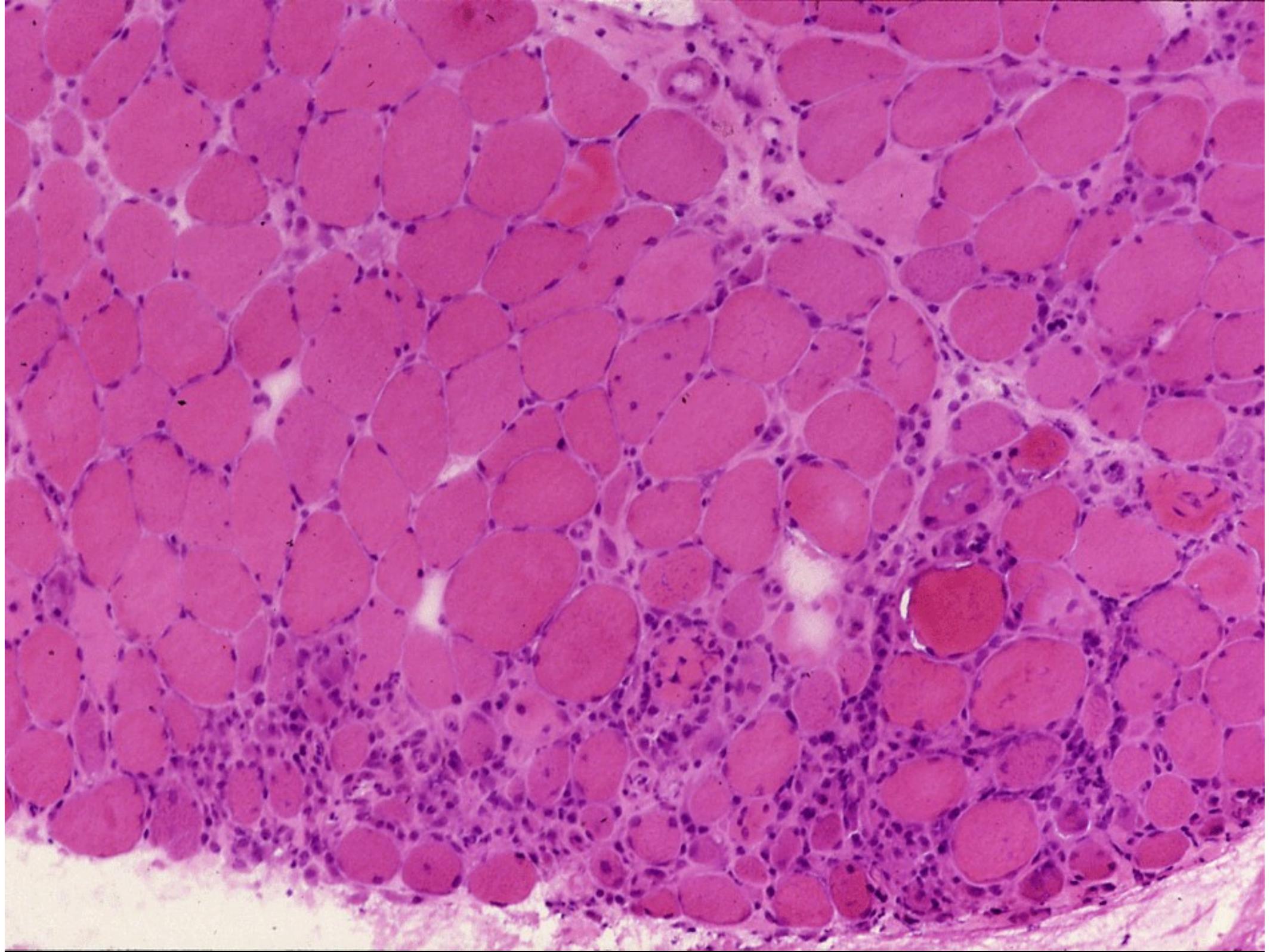
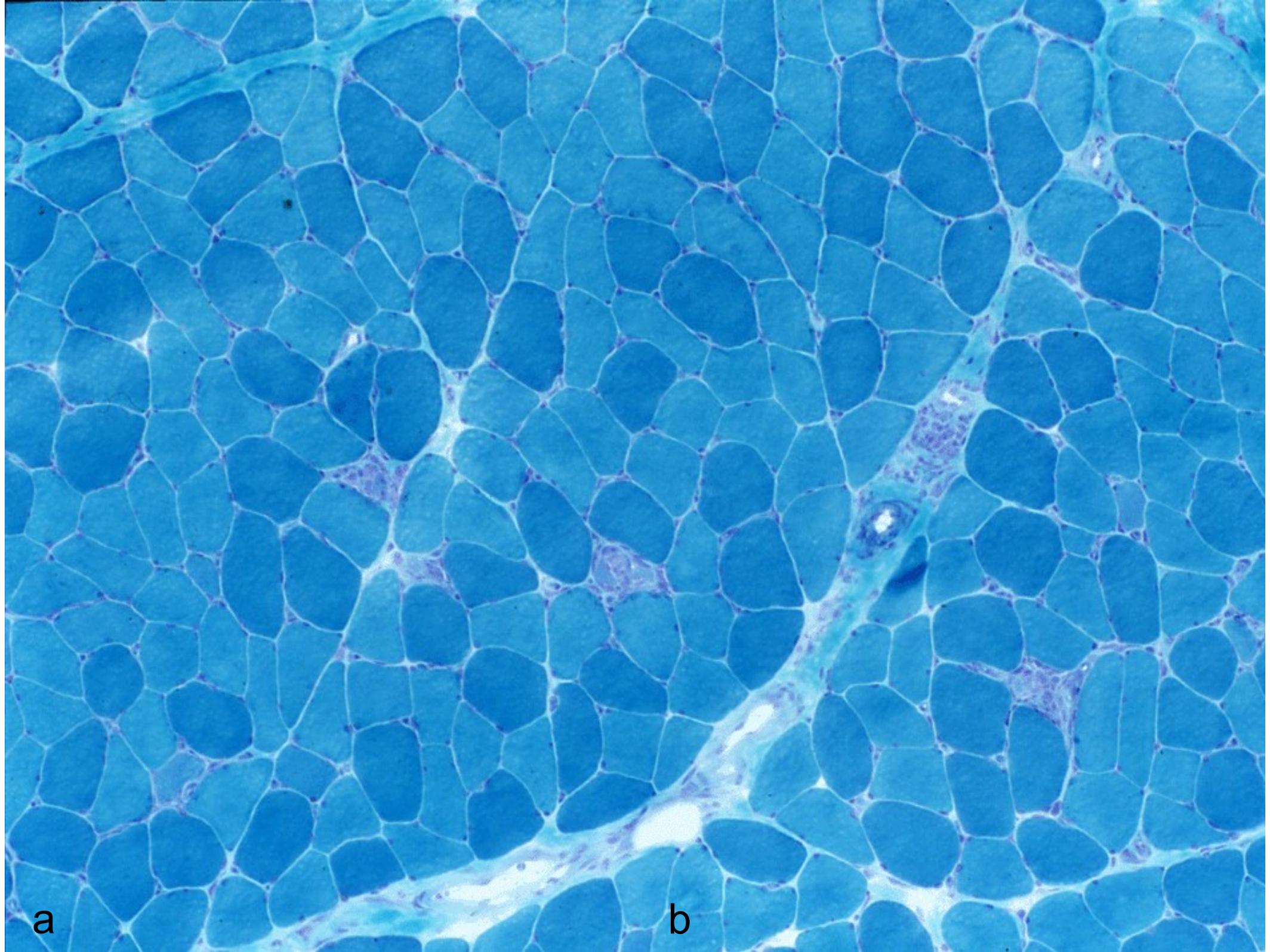


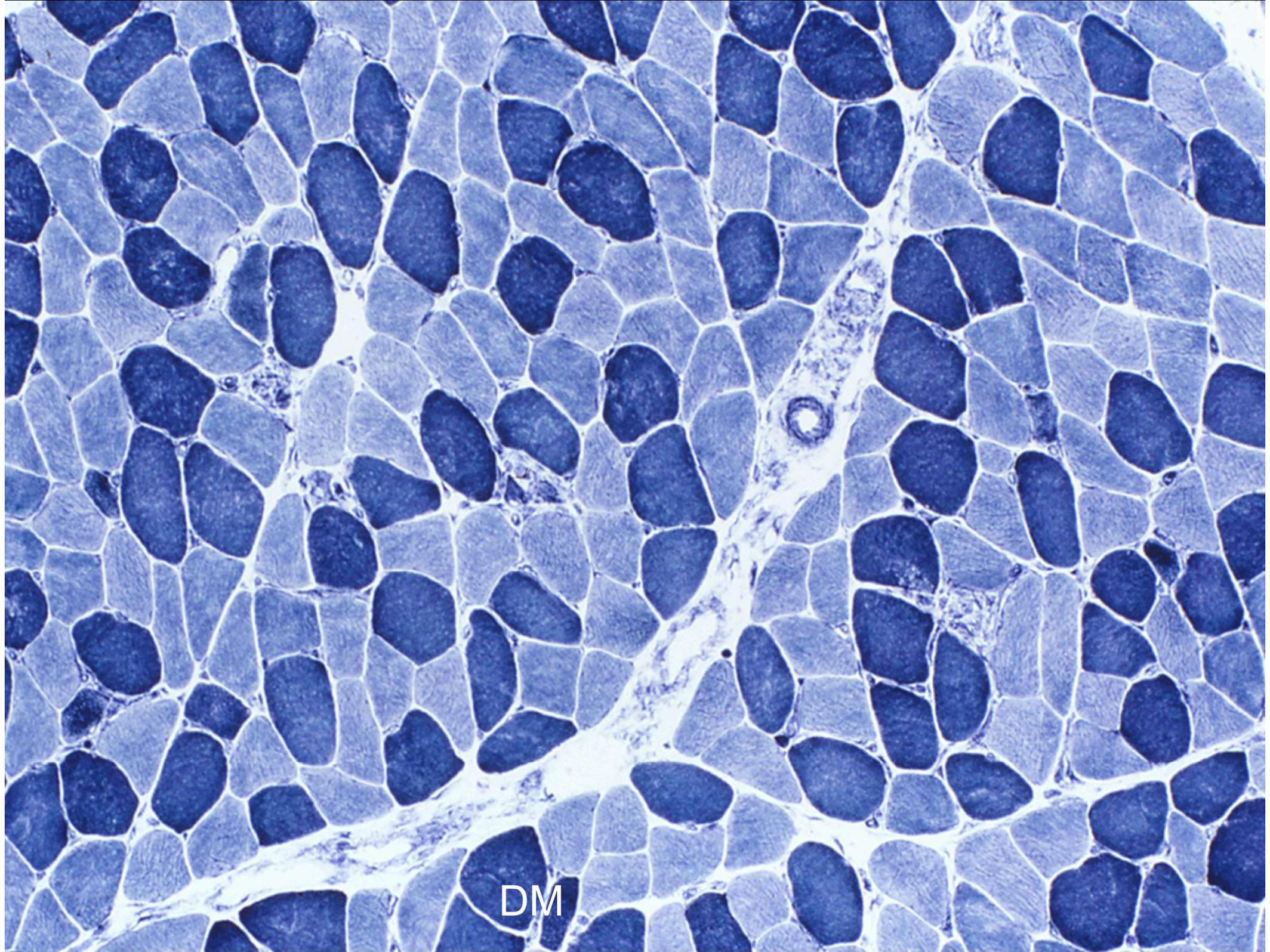
図2 筋炎特異抗体と特徴的な臨床所見との関連



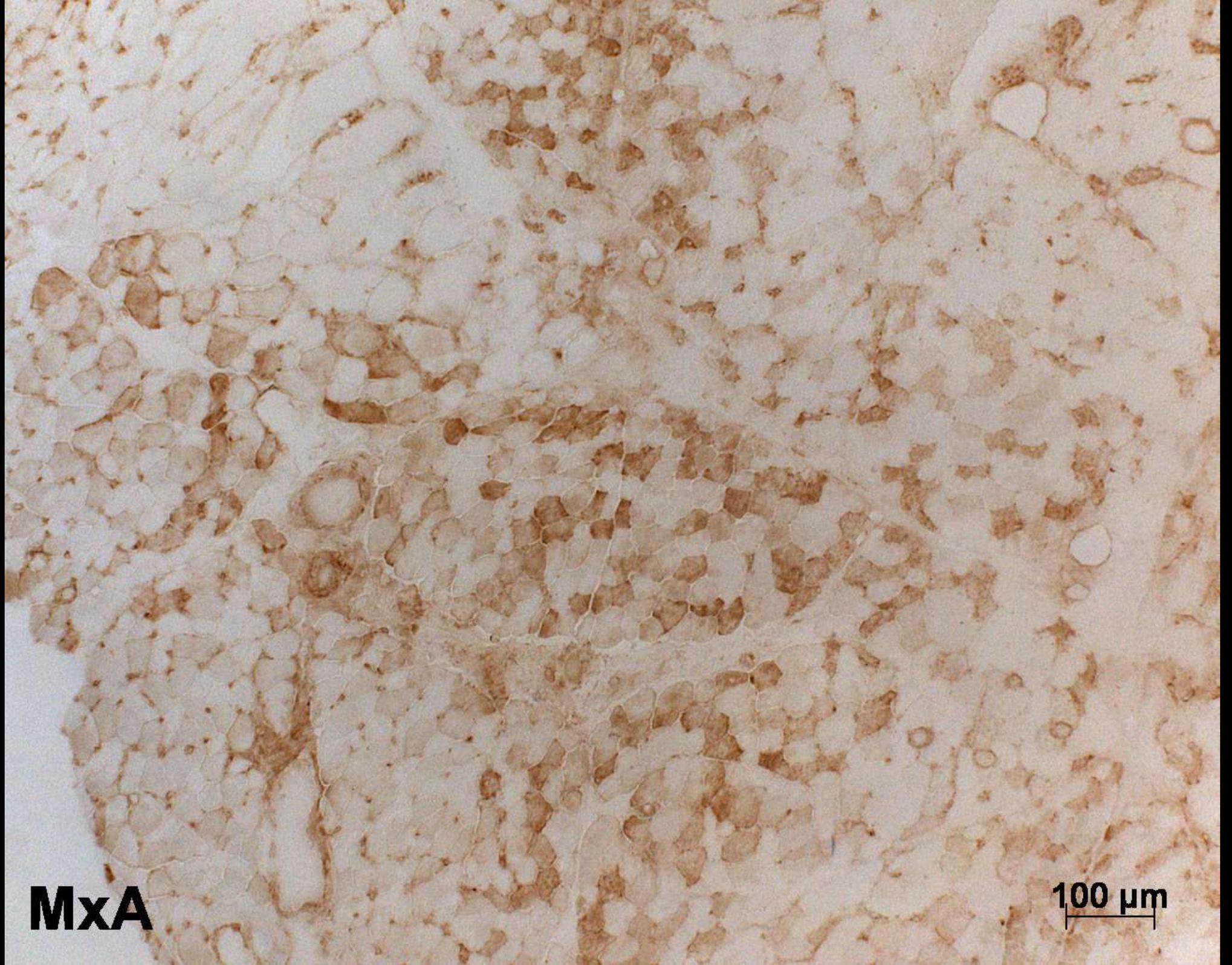


a

b



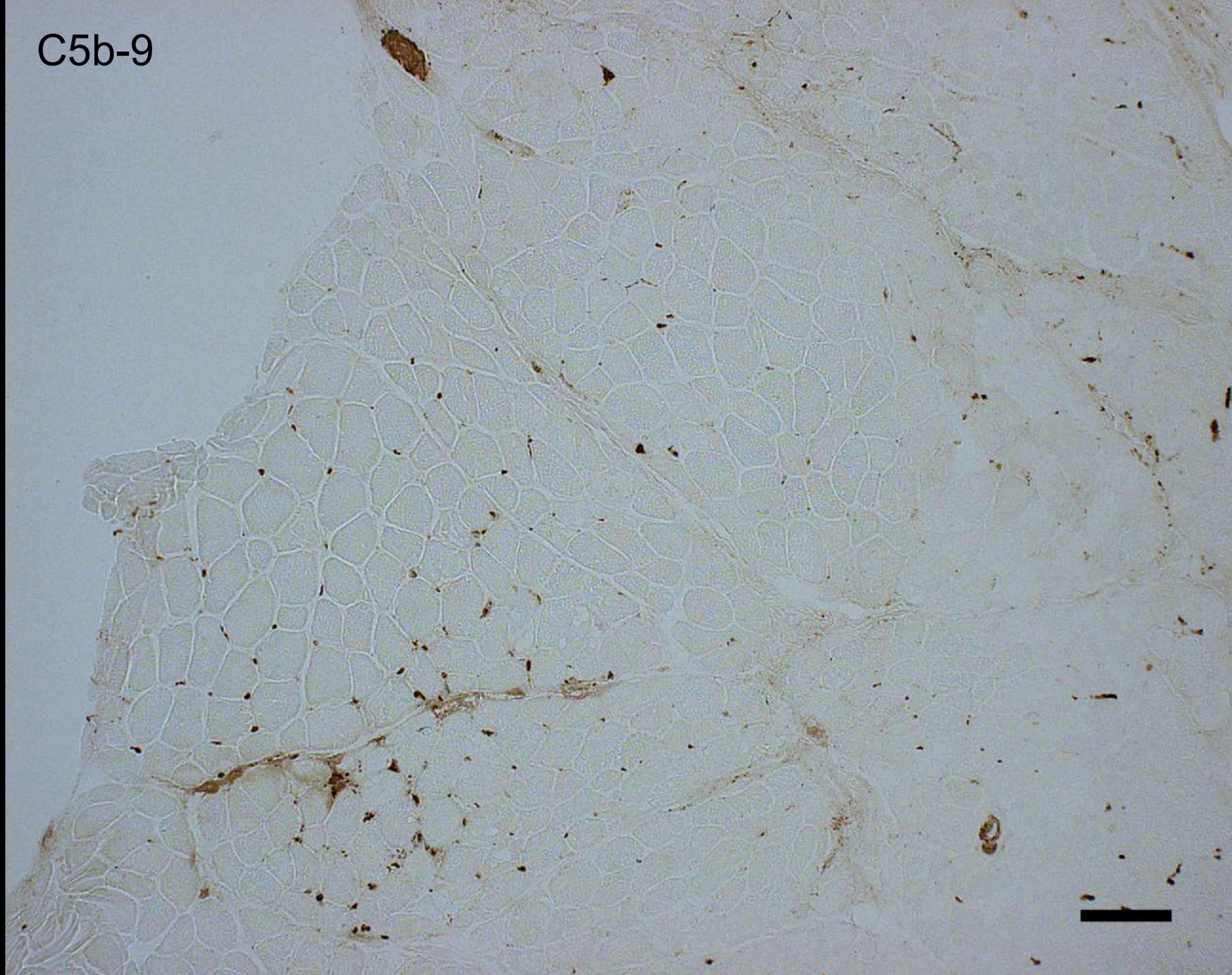
DM

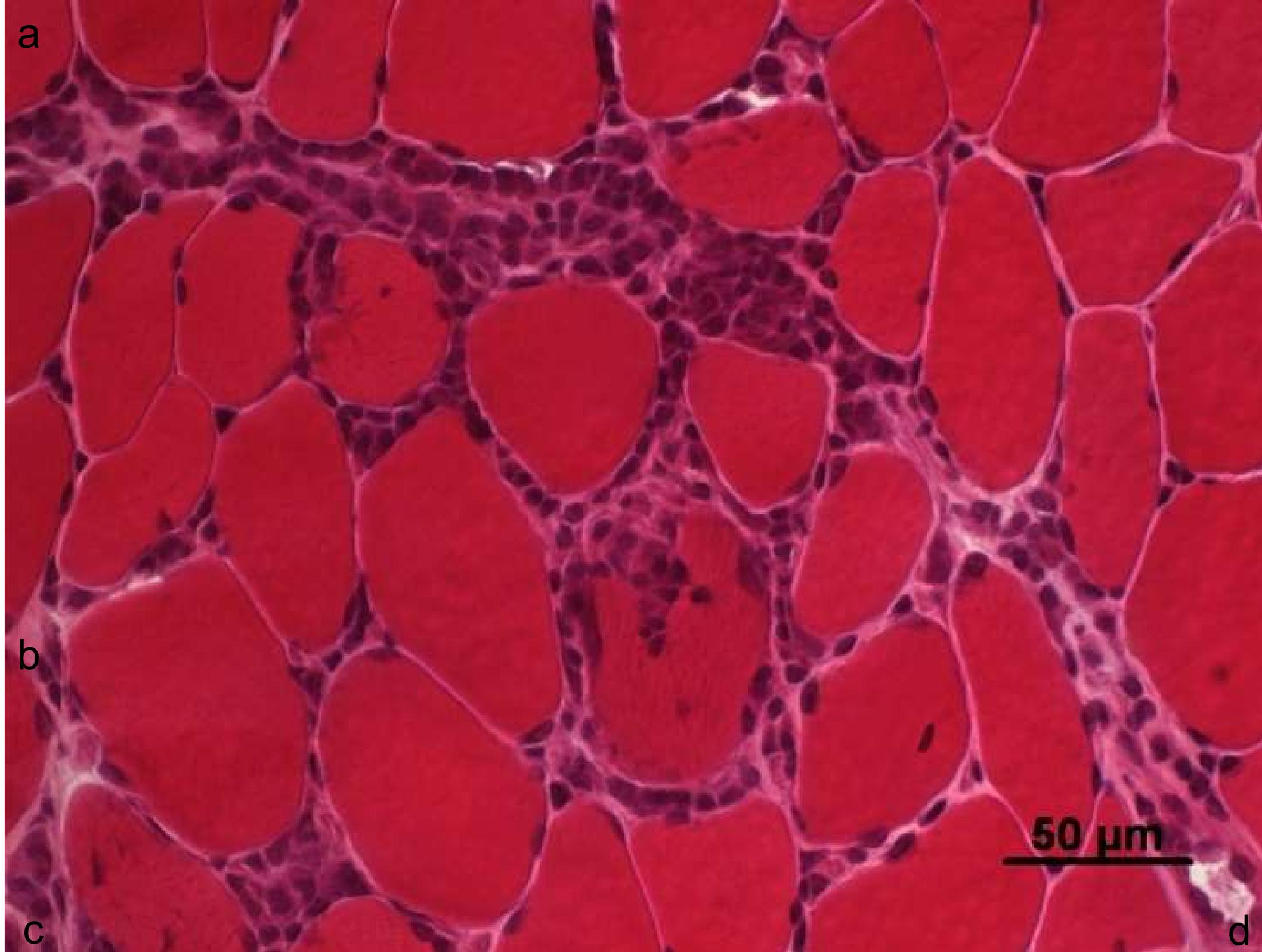


**MxA**

100 μm

C5b-9





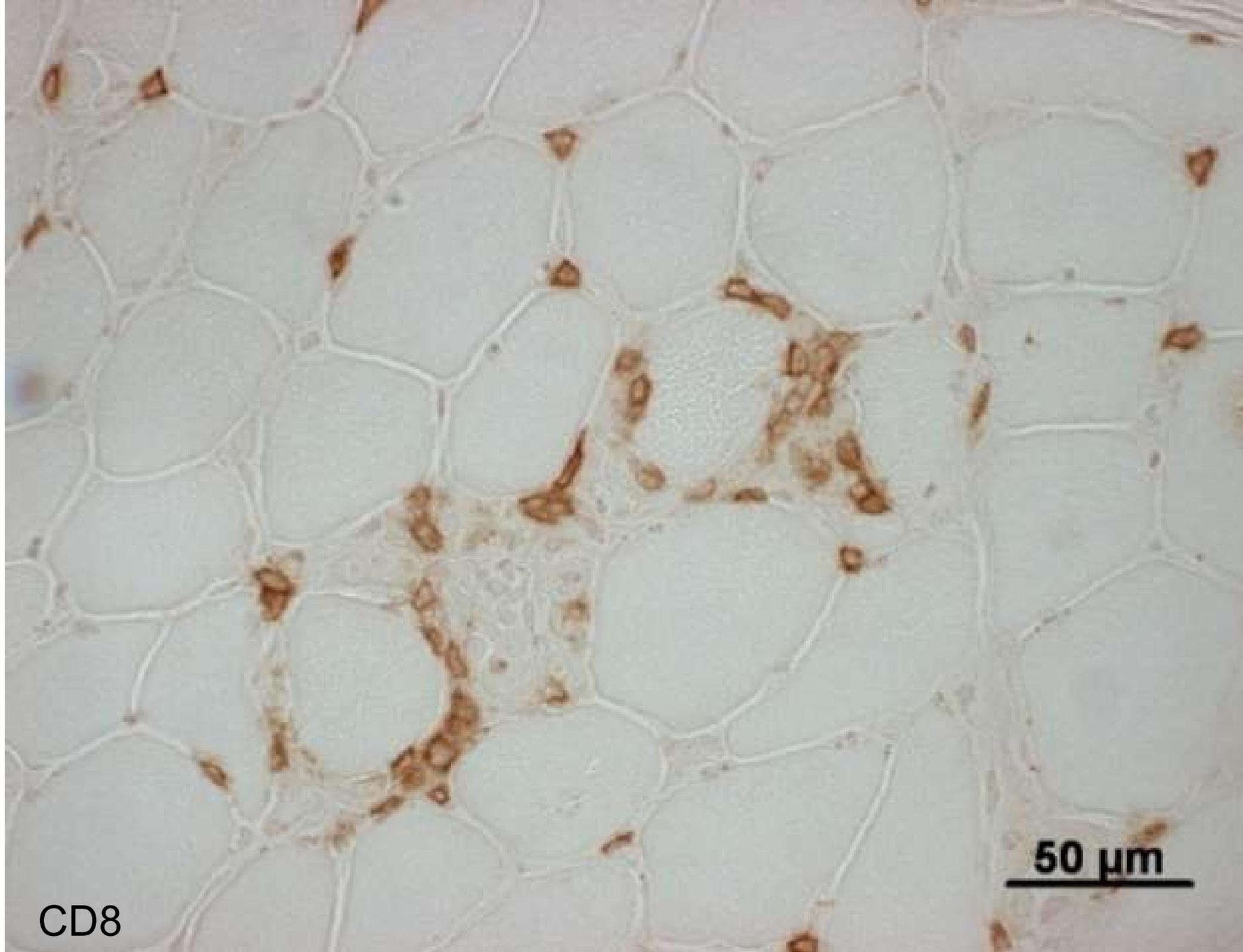
a

b

c

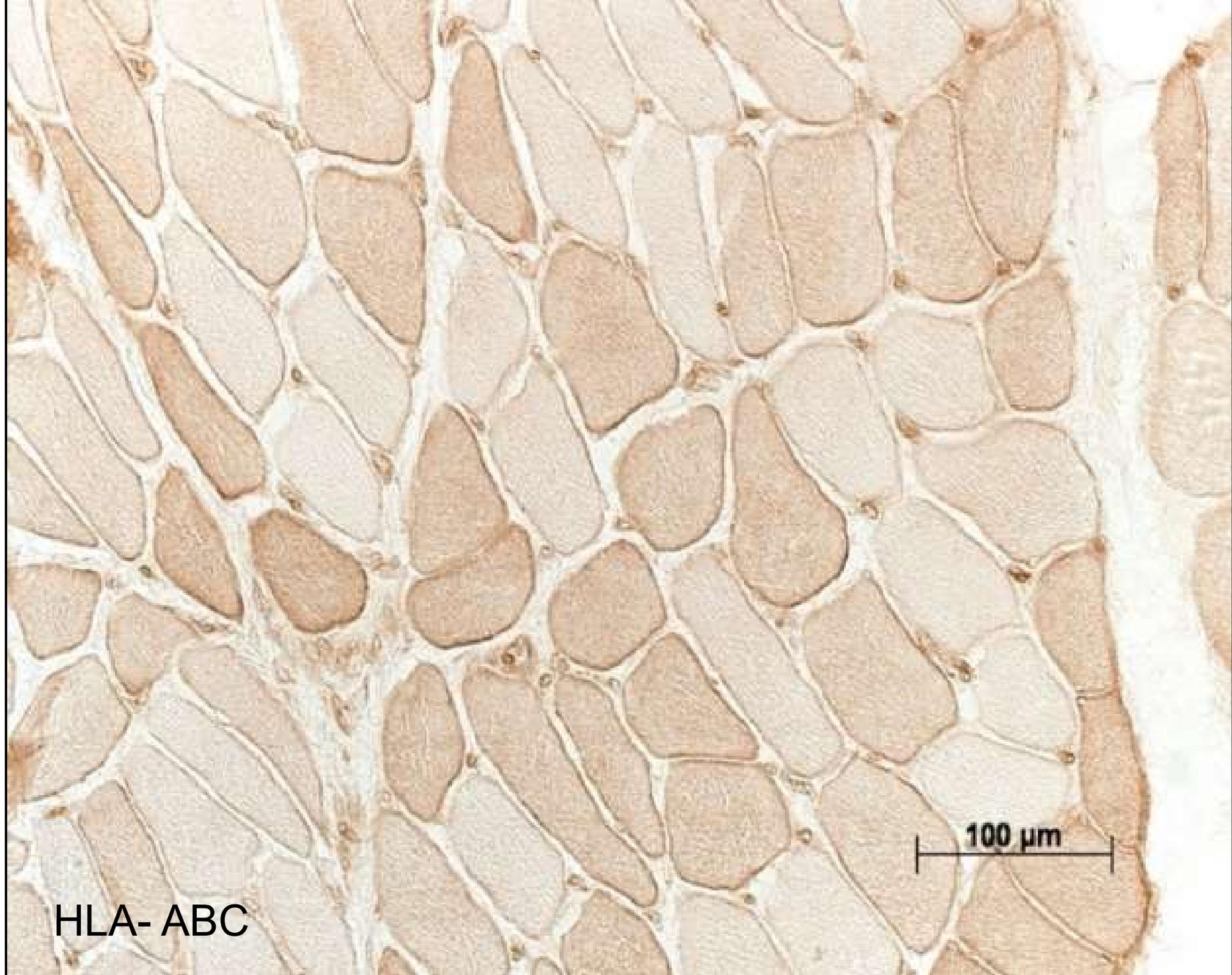
d

50 μm



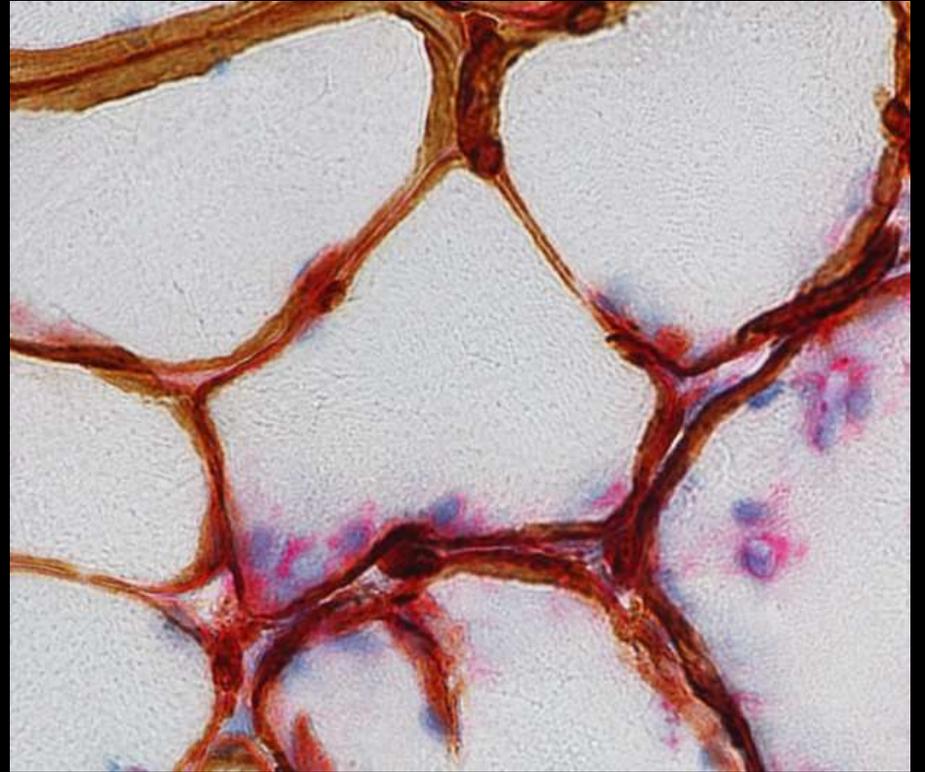
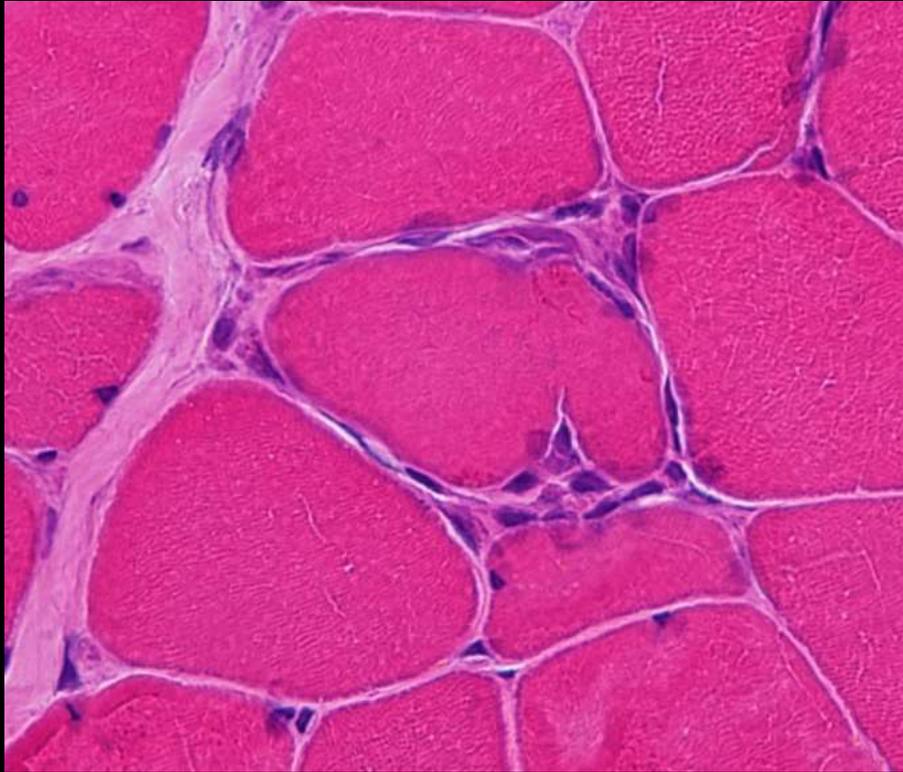
CD8

**50  $\mu$ m**



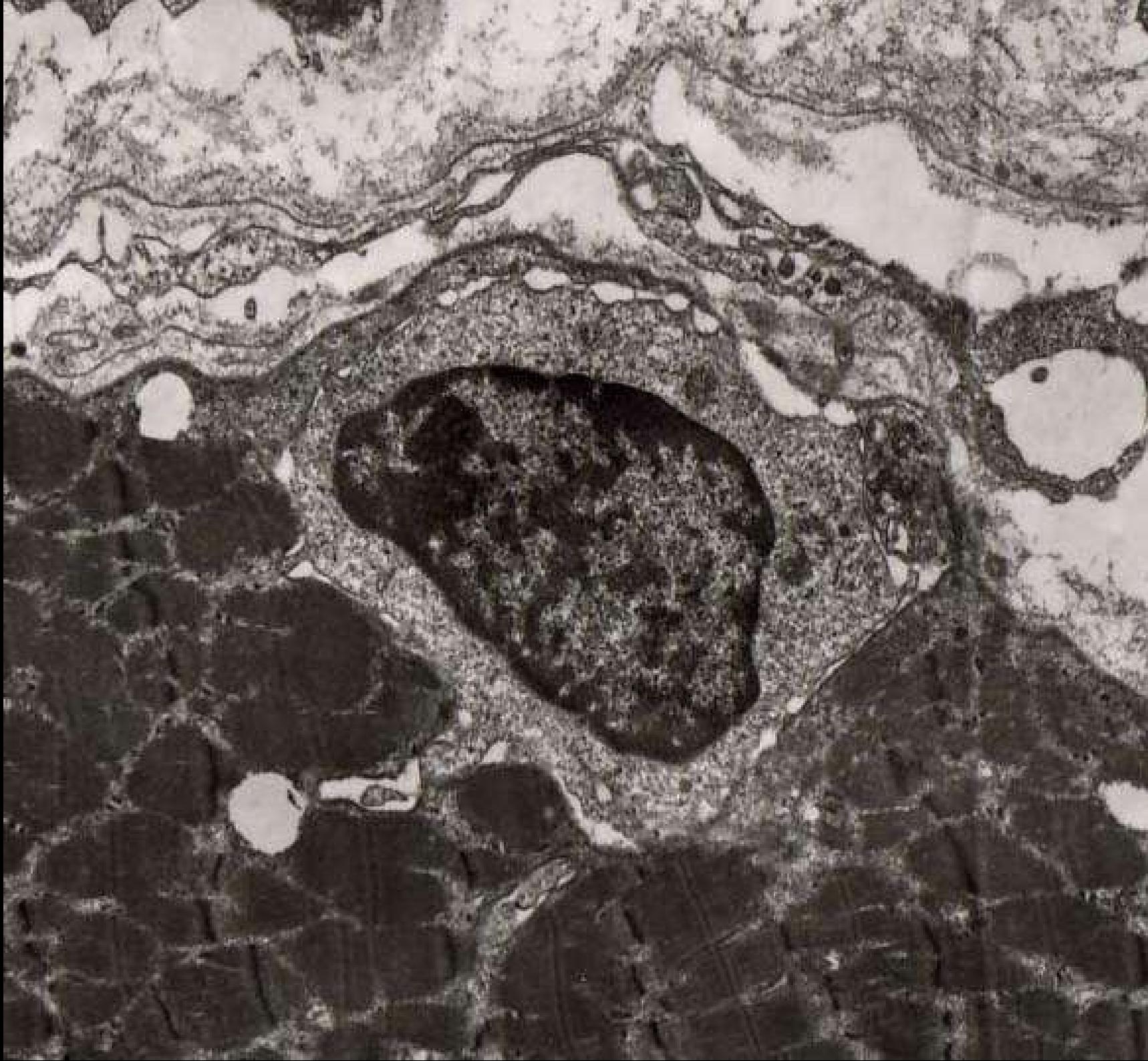
HLA- ABC

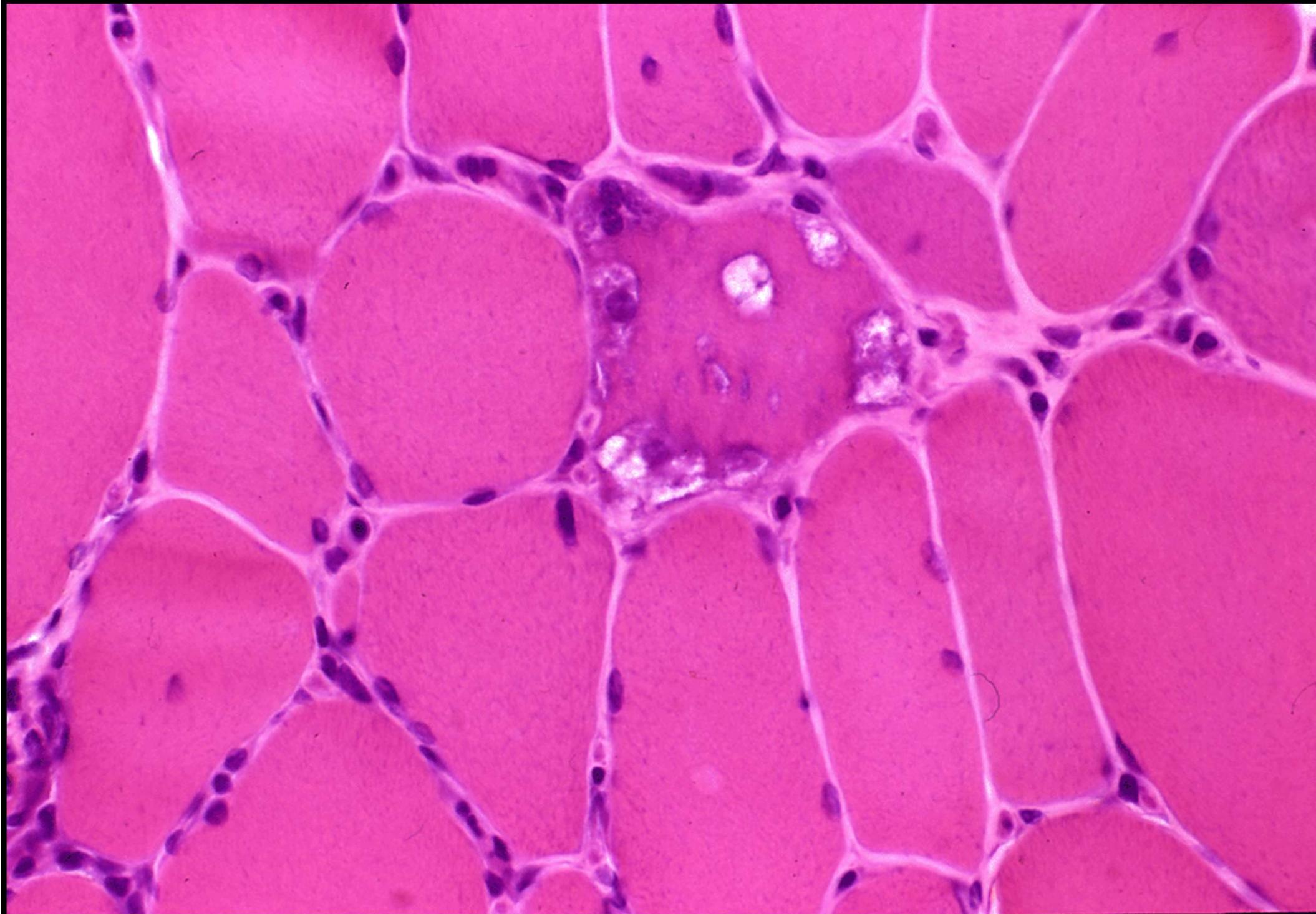
100  $\mu$ m

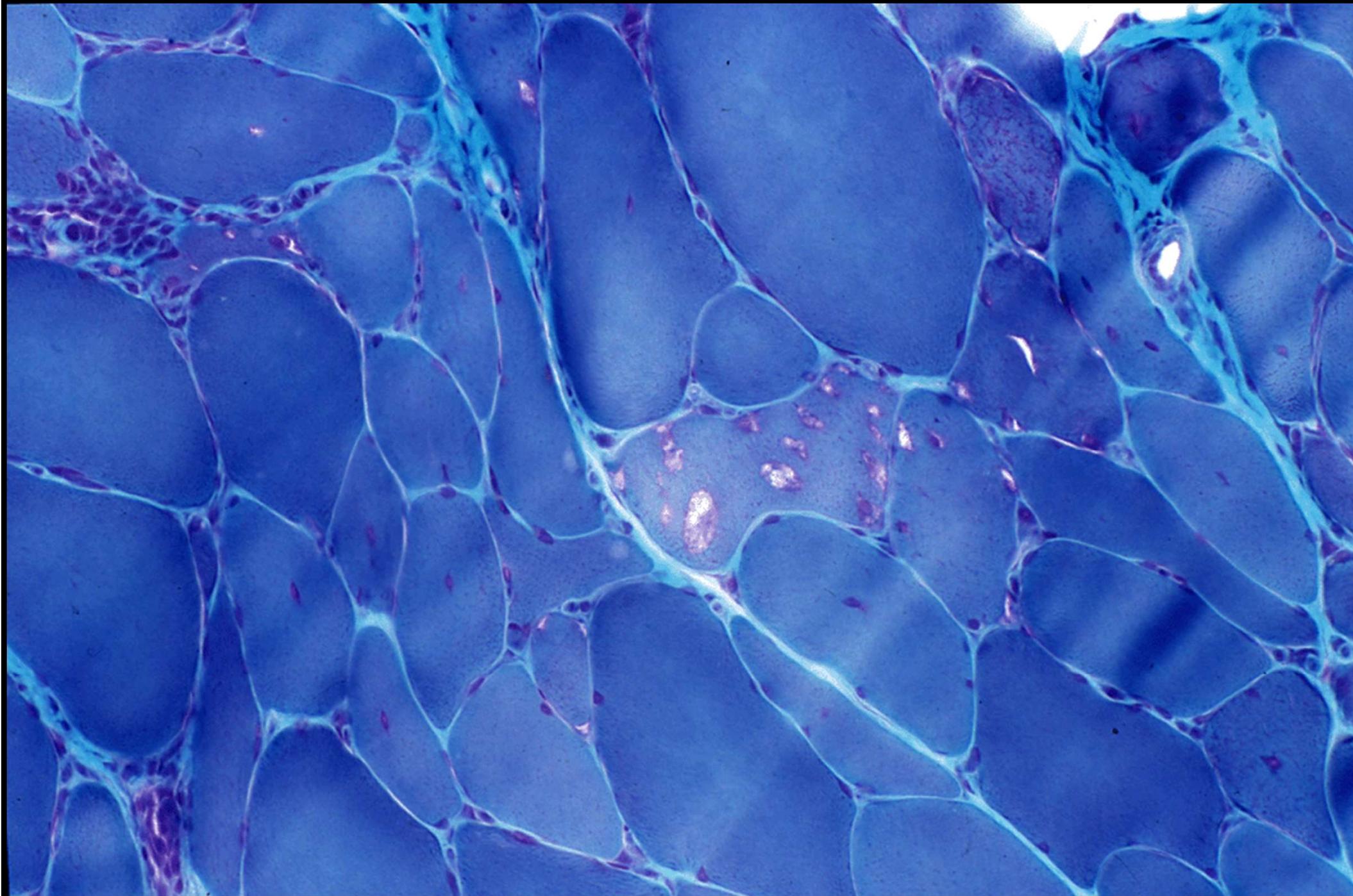


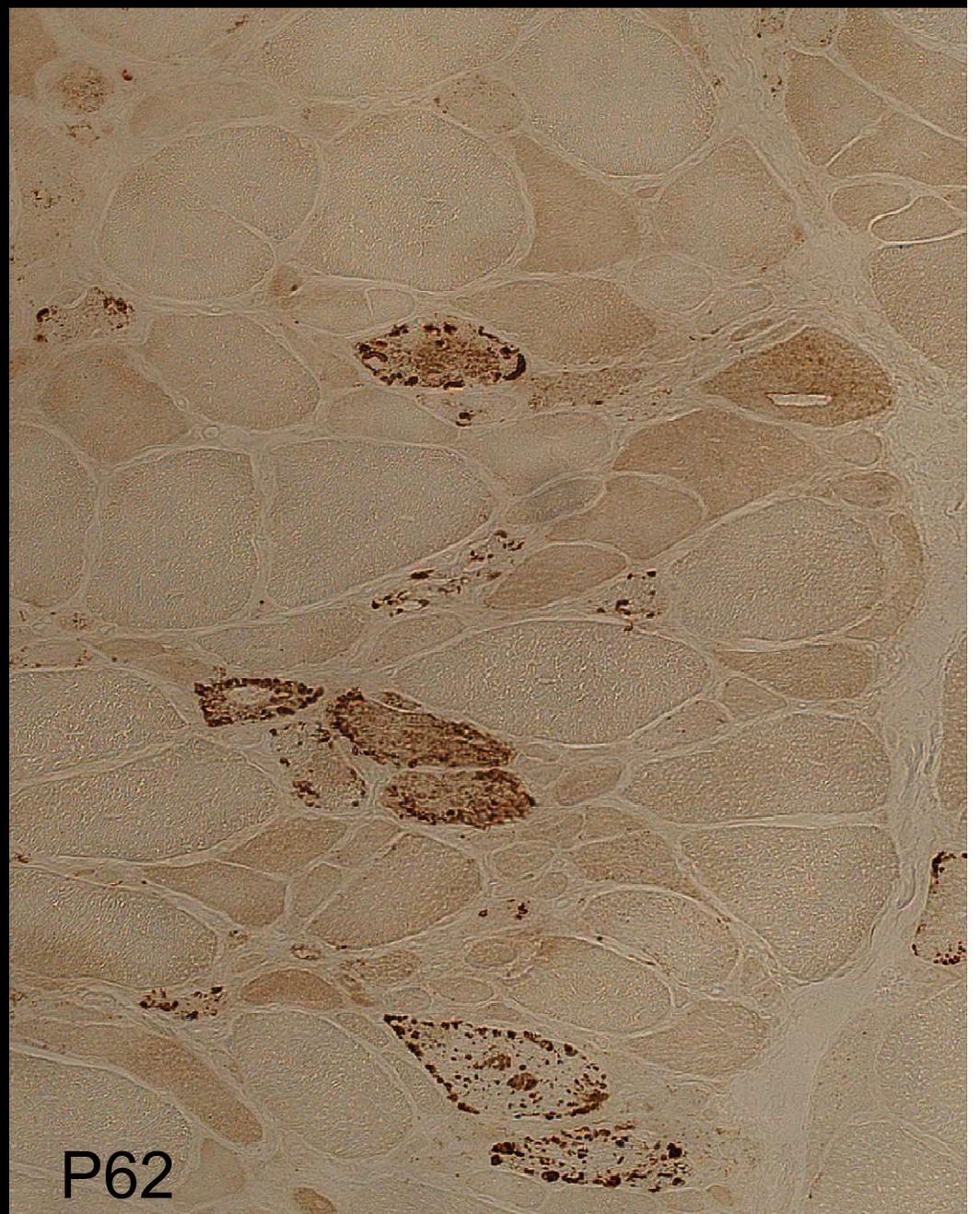
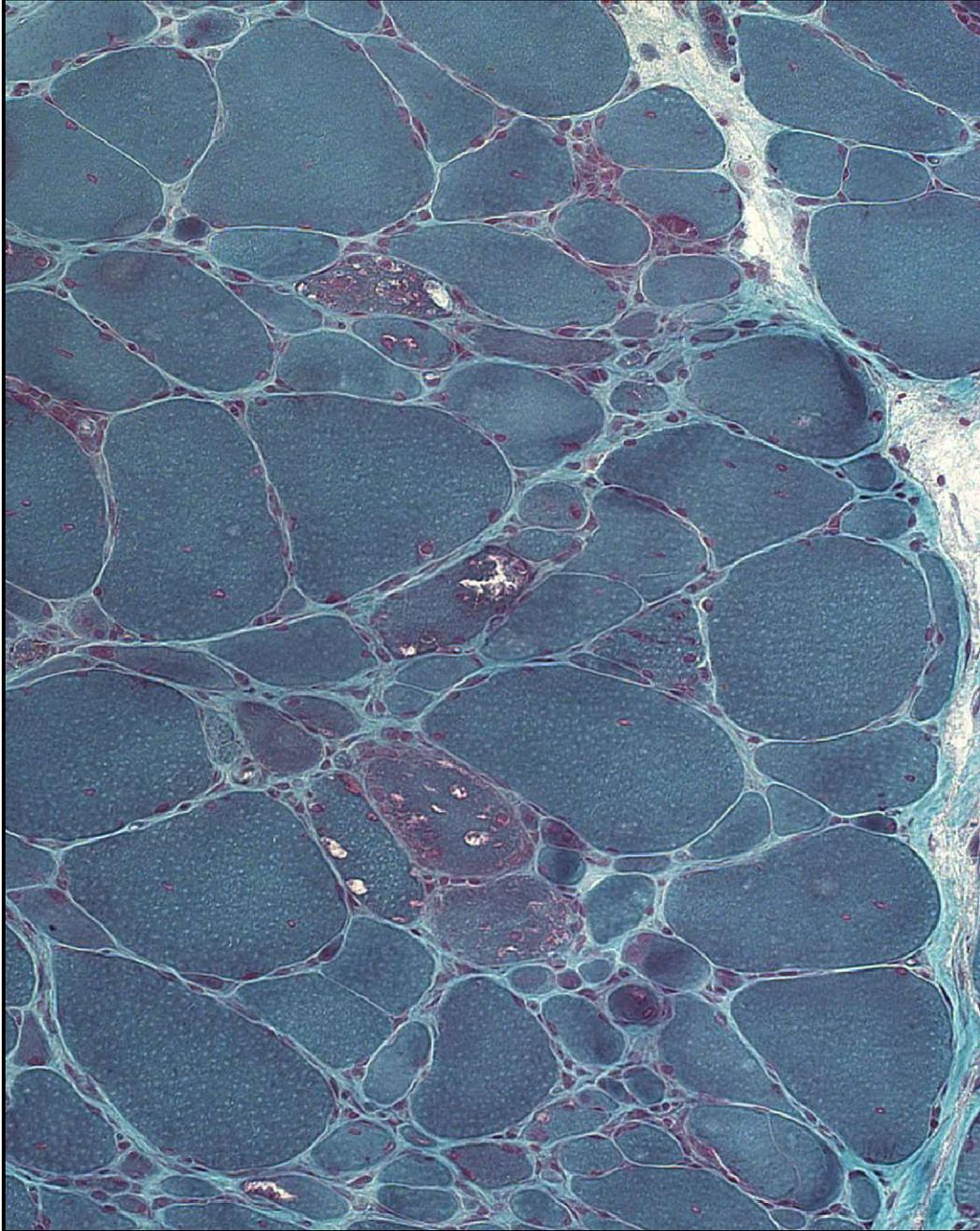
50μm

赤 : CD8  
茶 : collagen IV







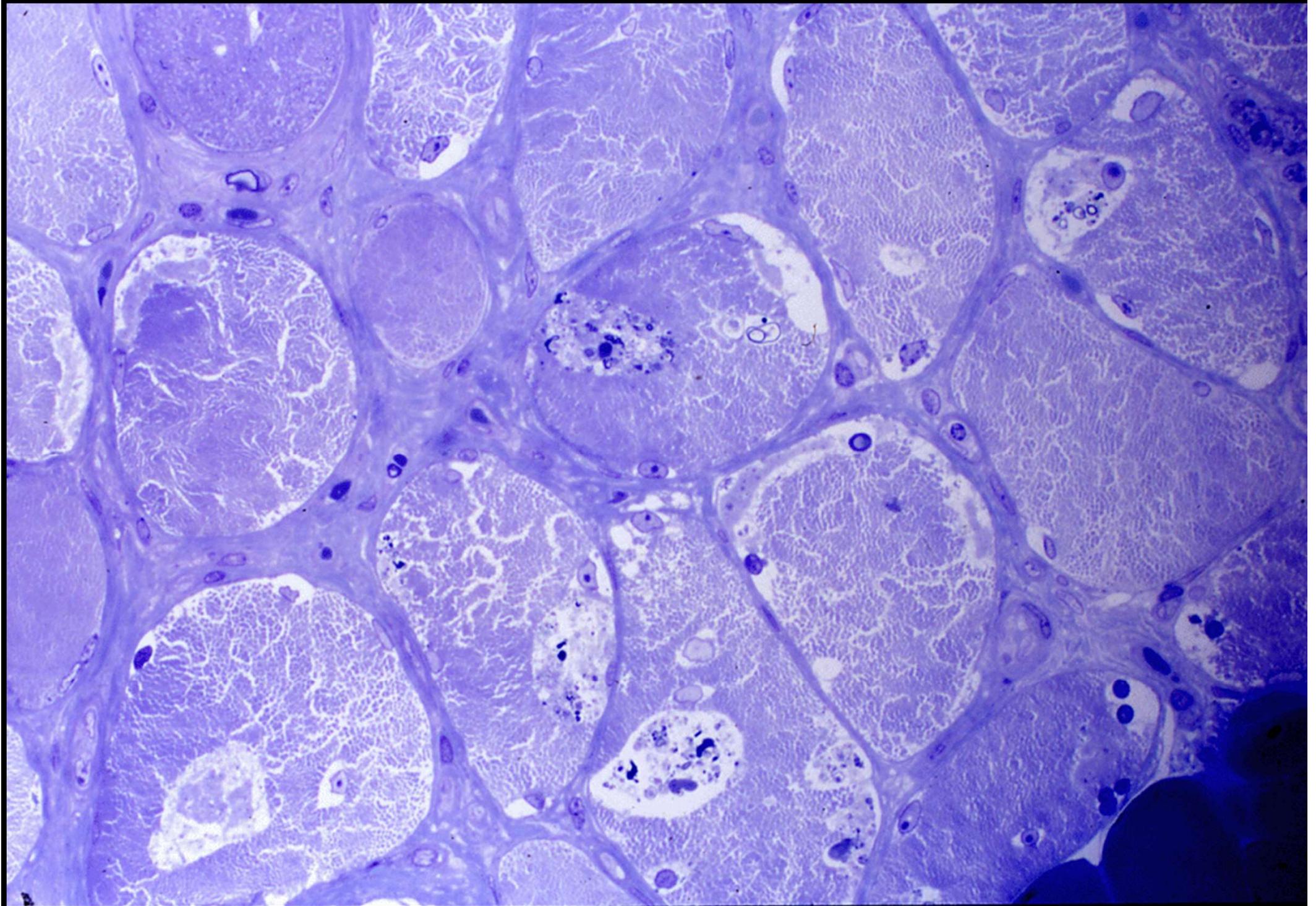


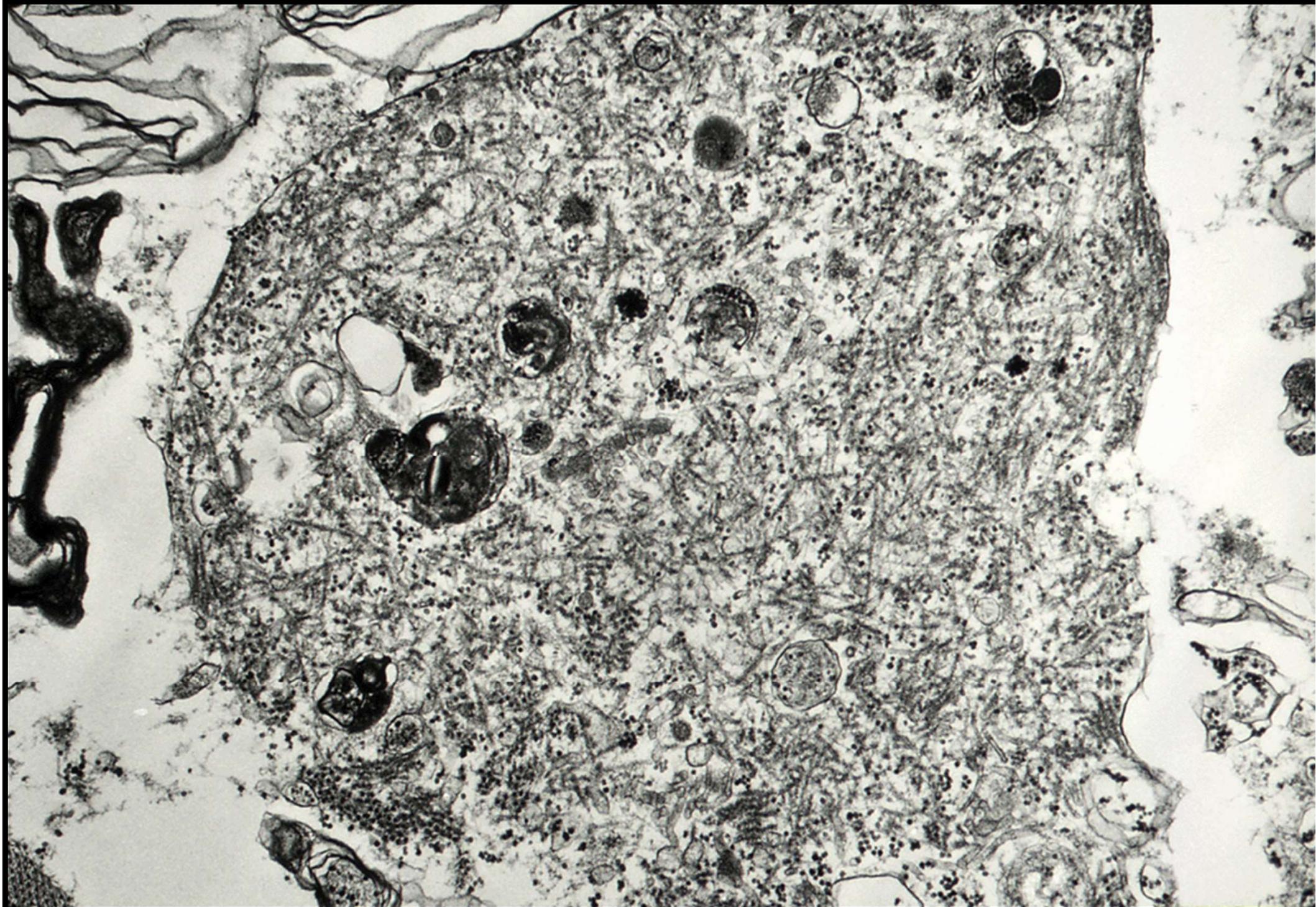
P62

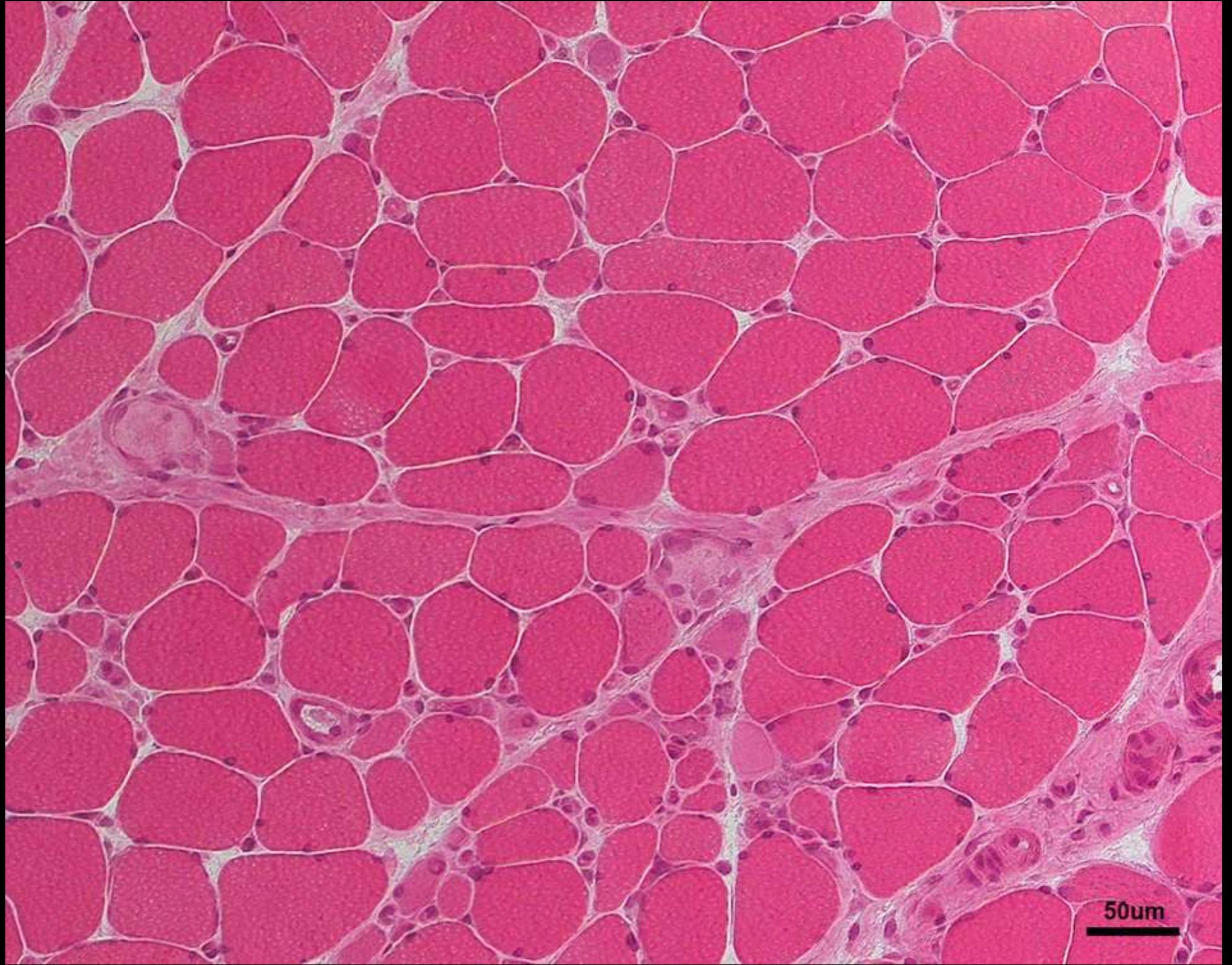


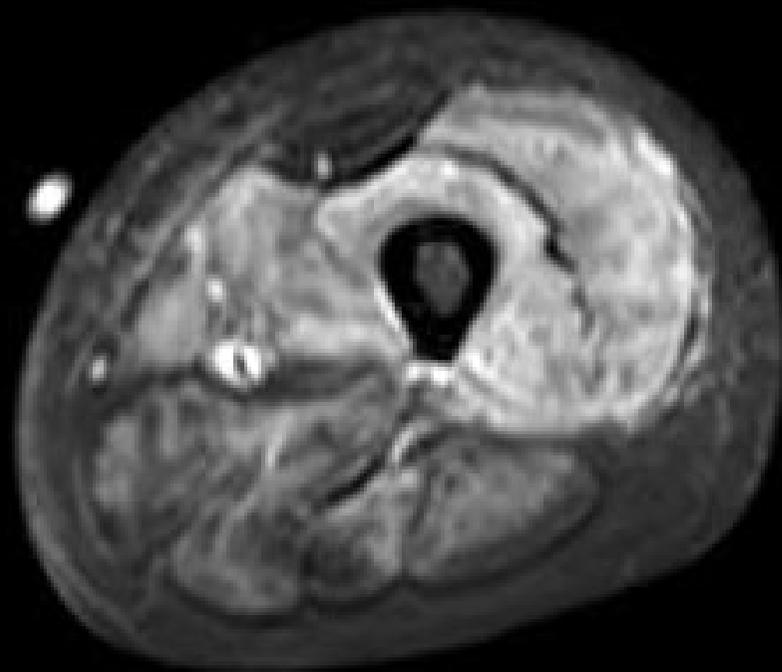
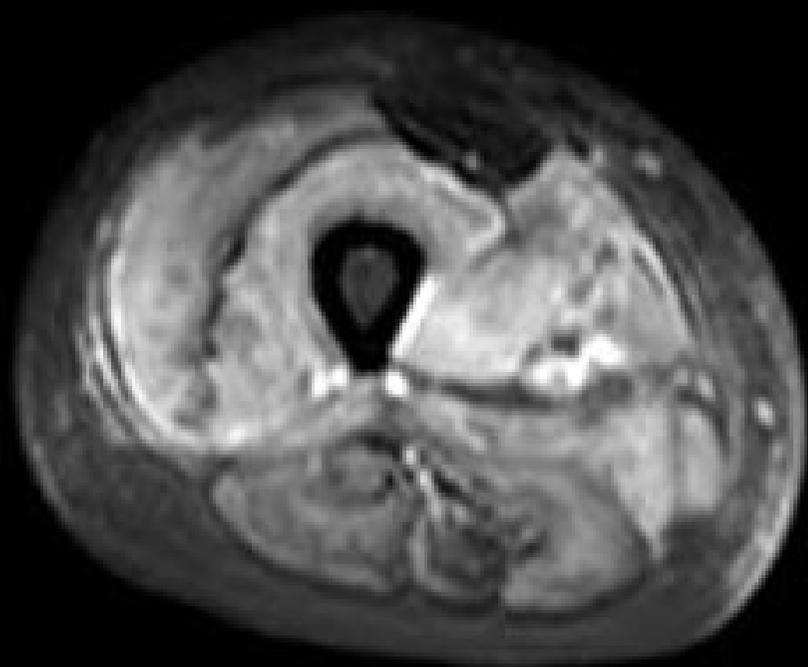


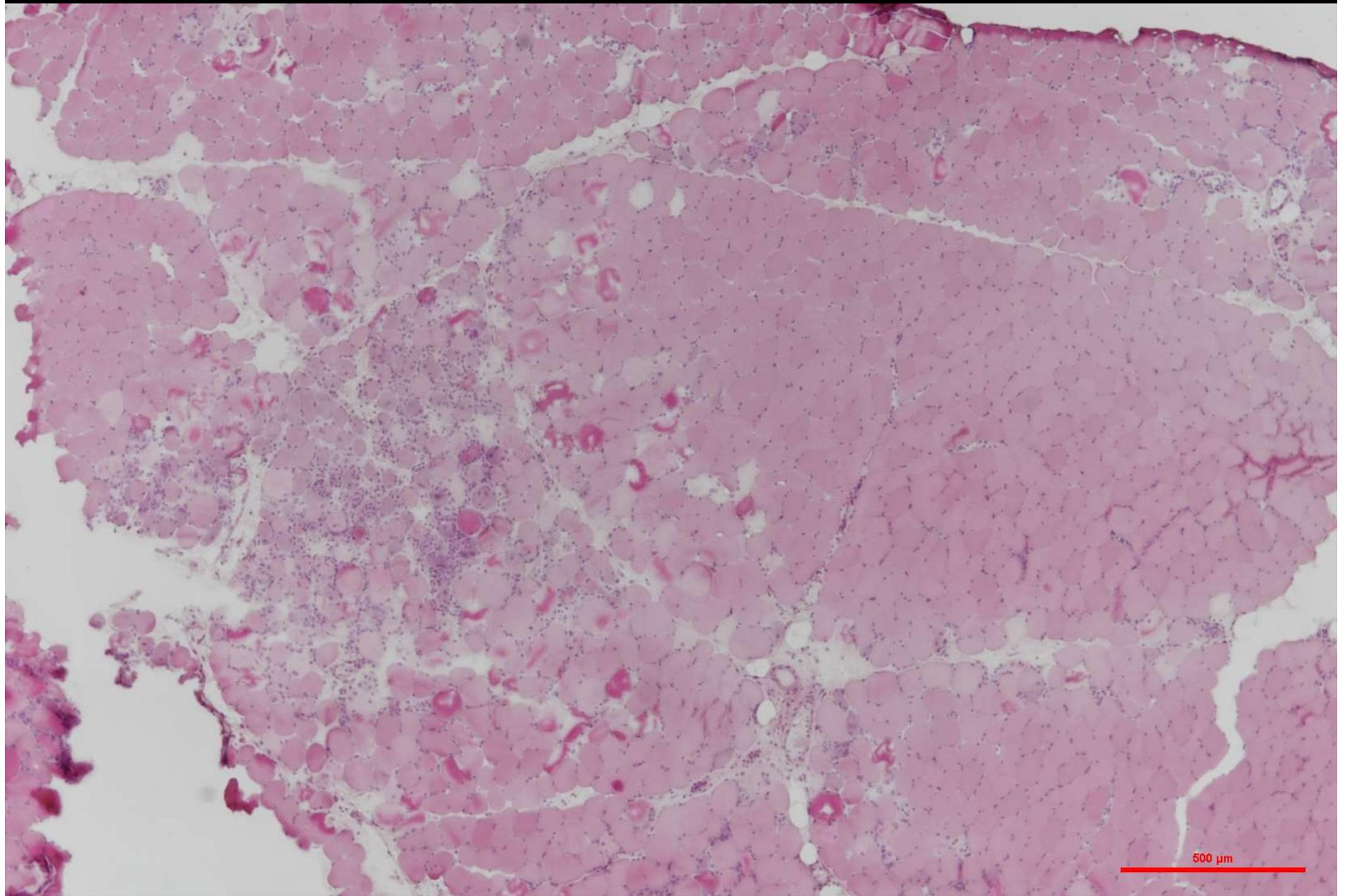
**CD8**

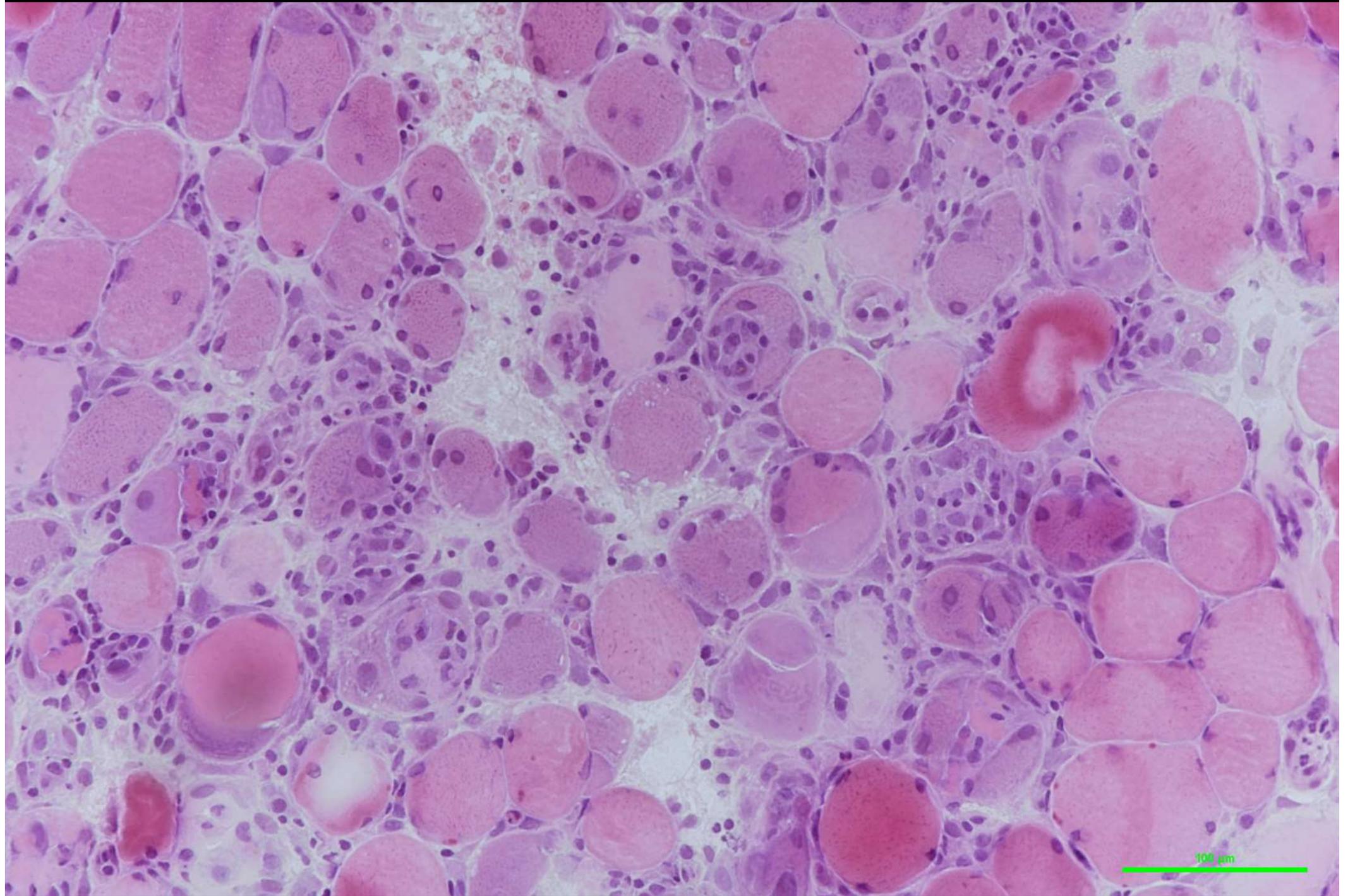


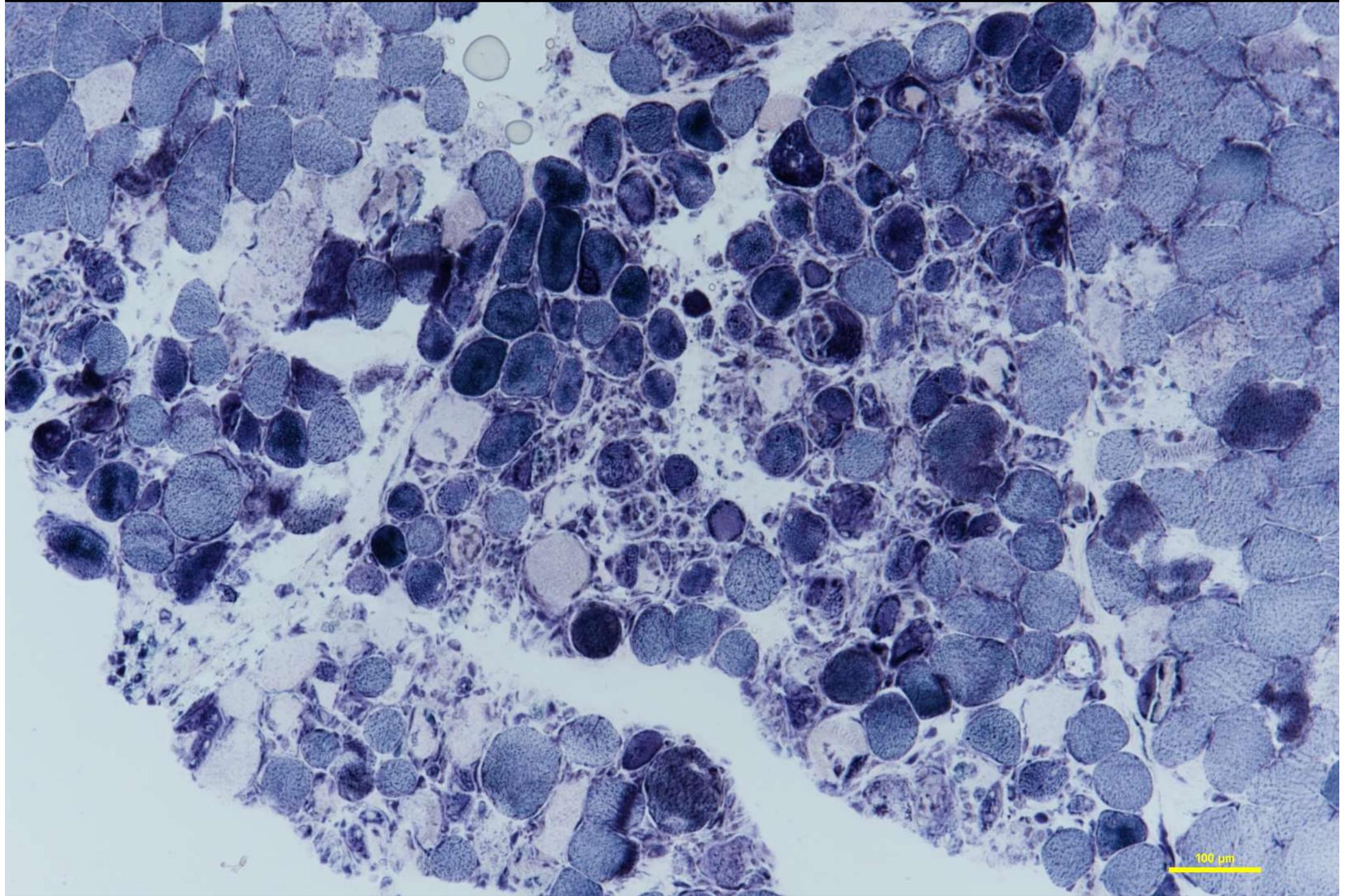


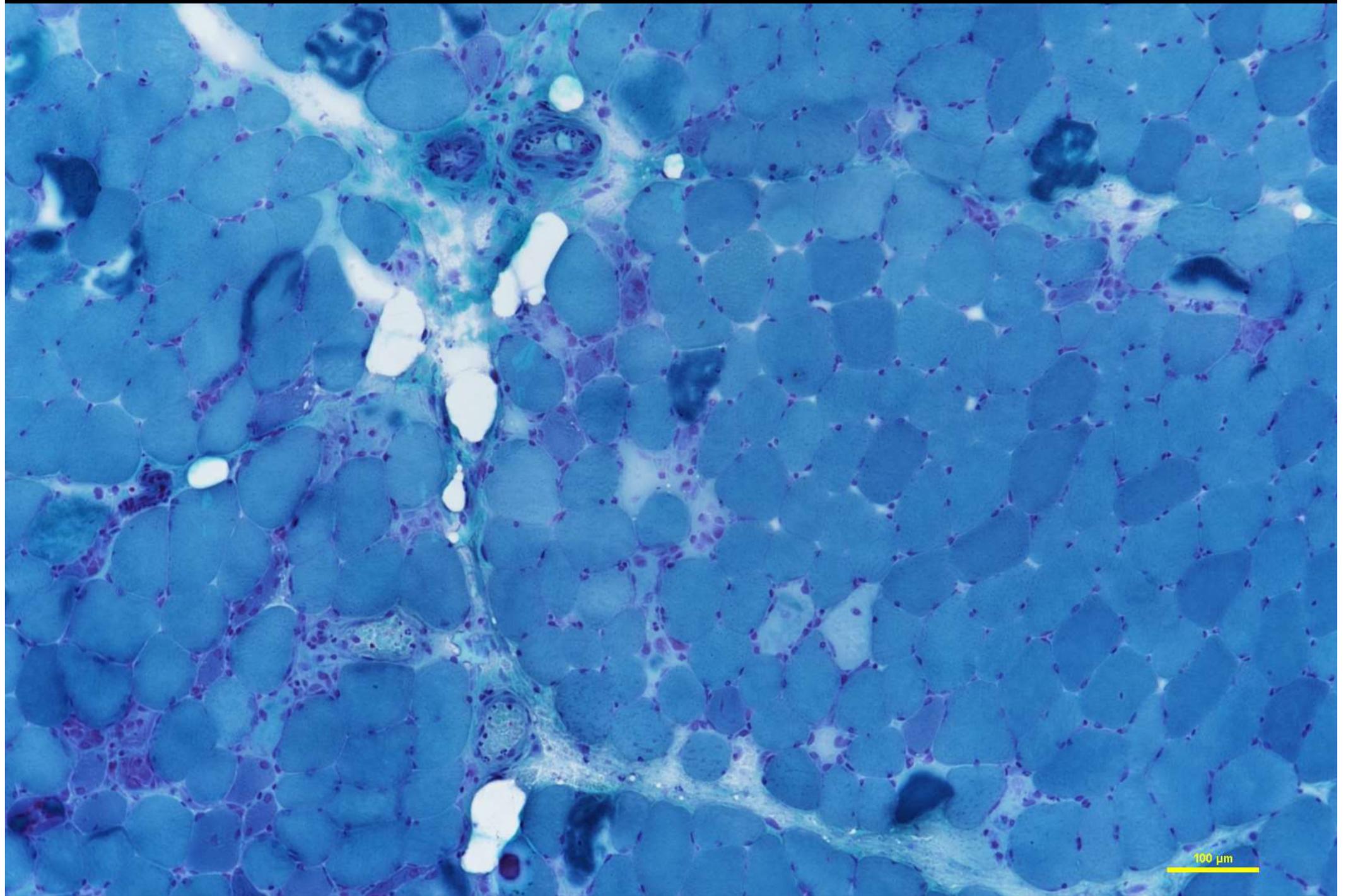


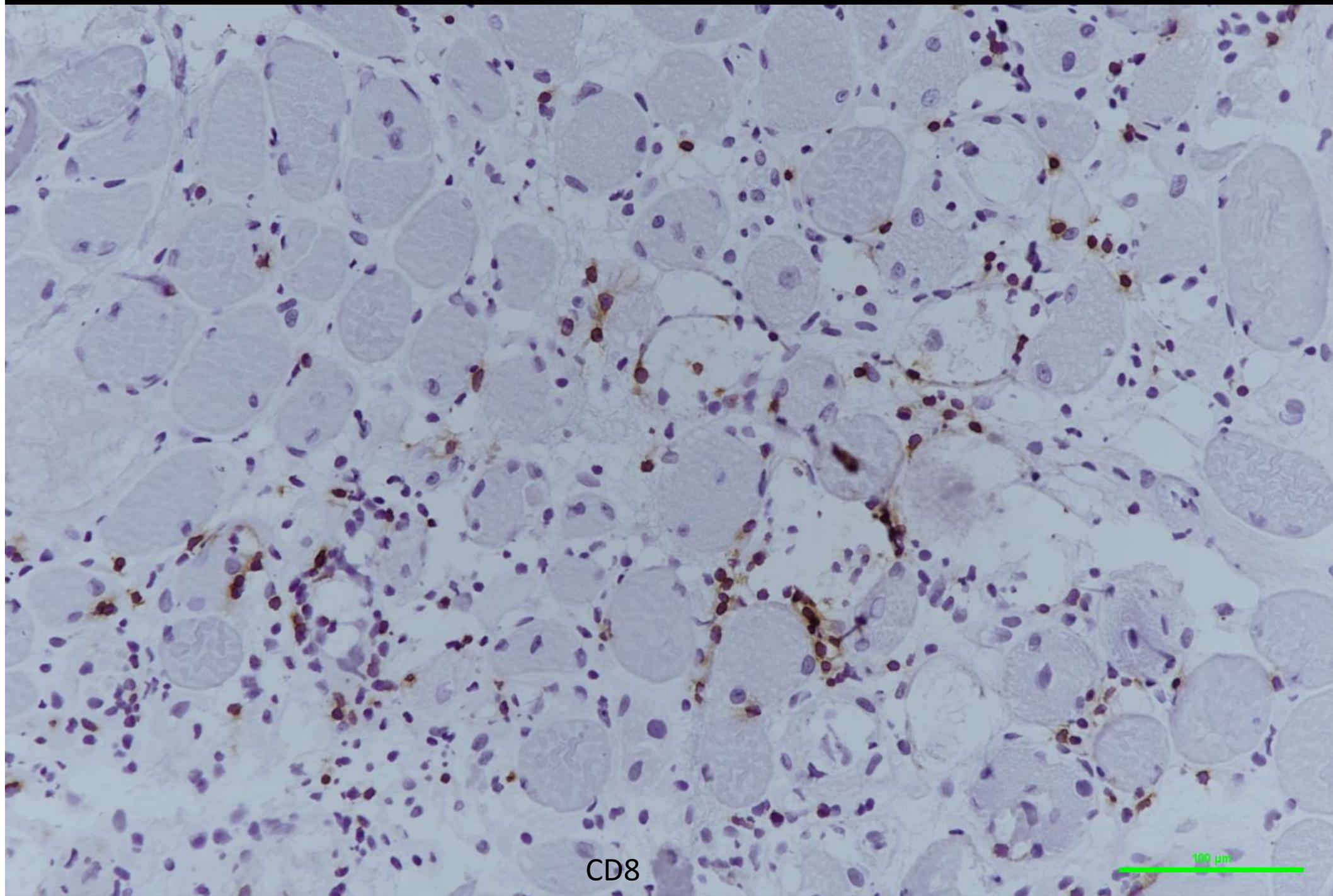






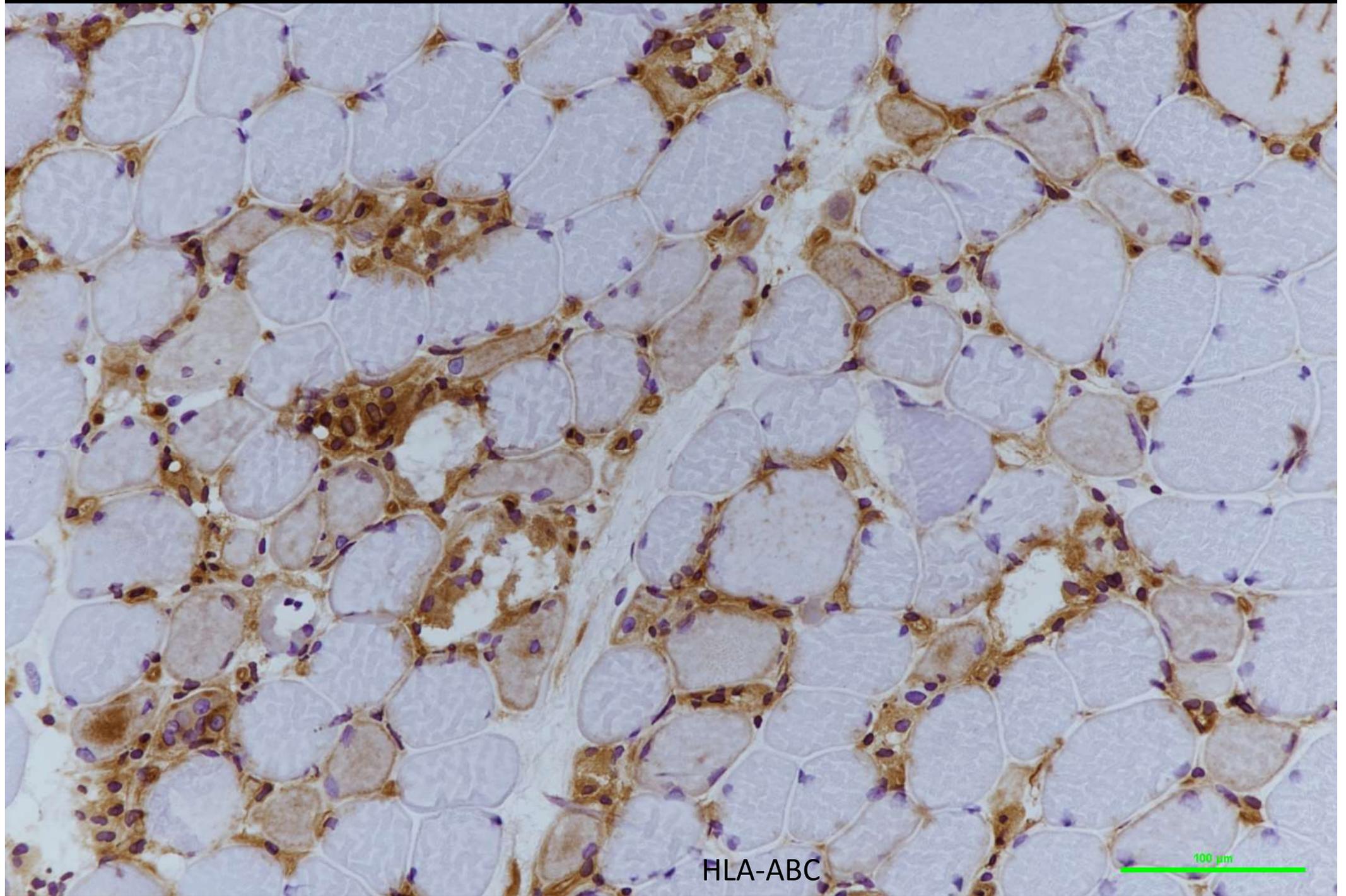






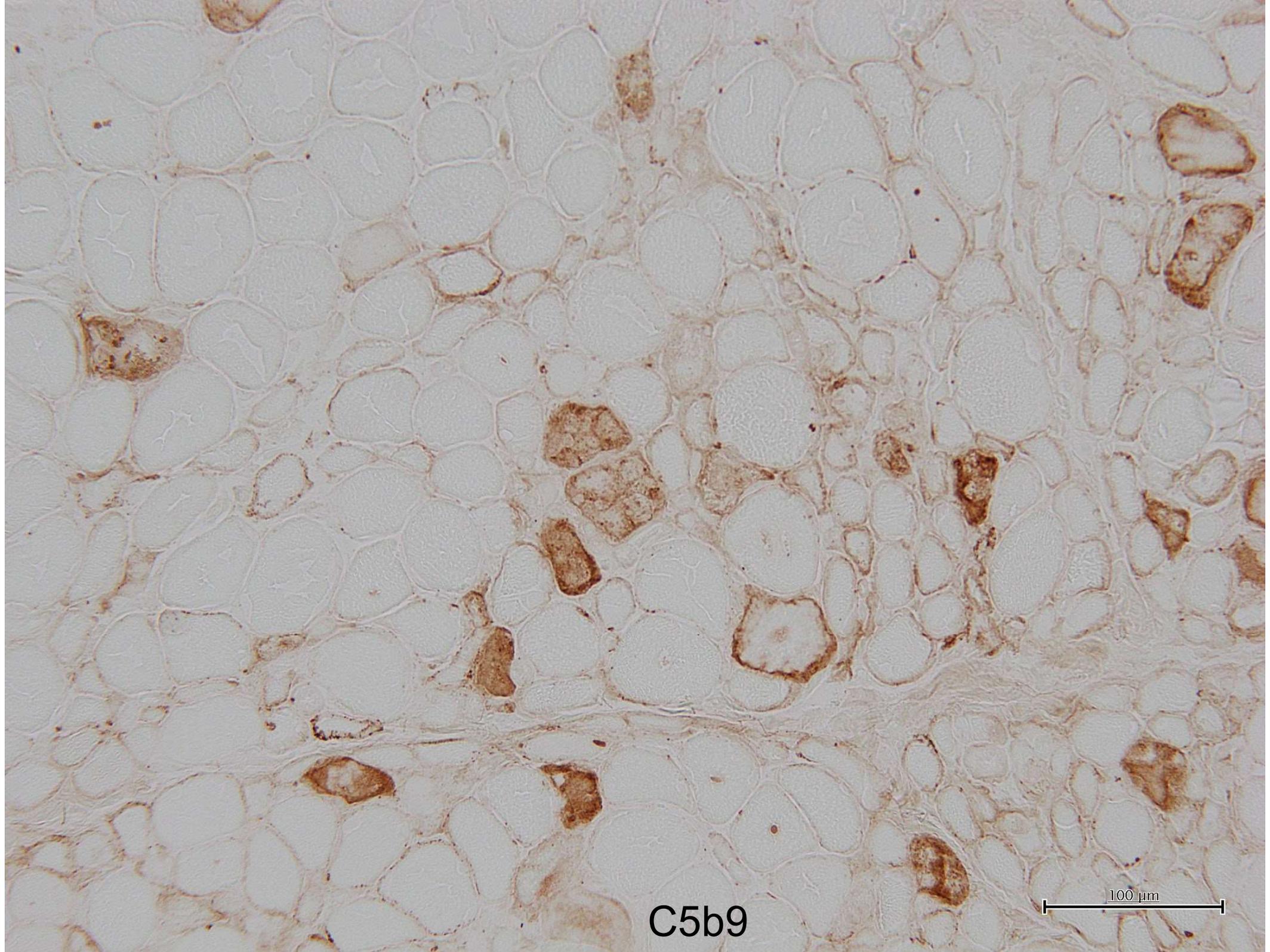
CD8

100  $\mu$ m



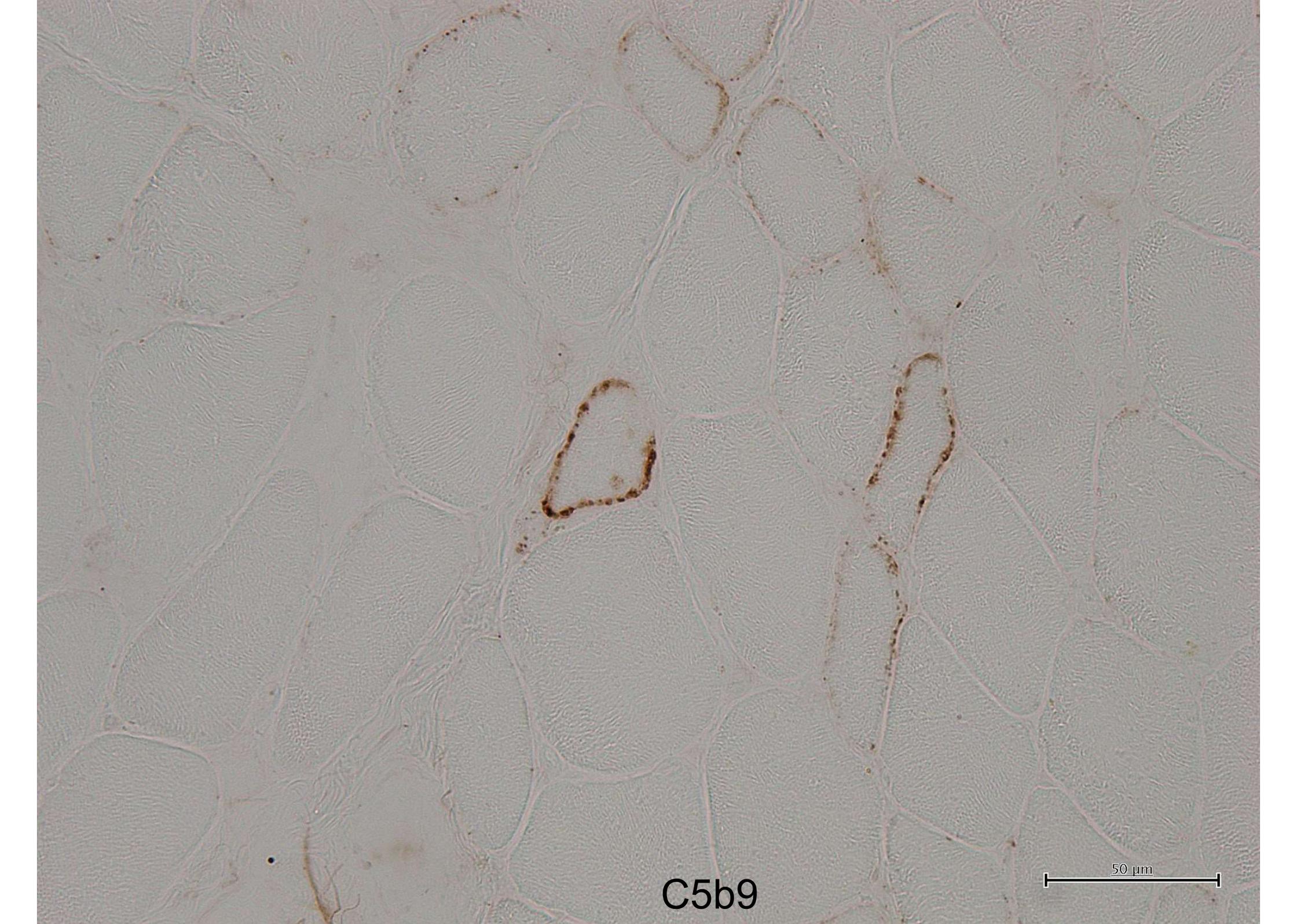
HLA-ABC

100  $\mu$ m



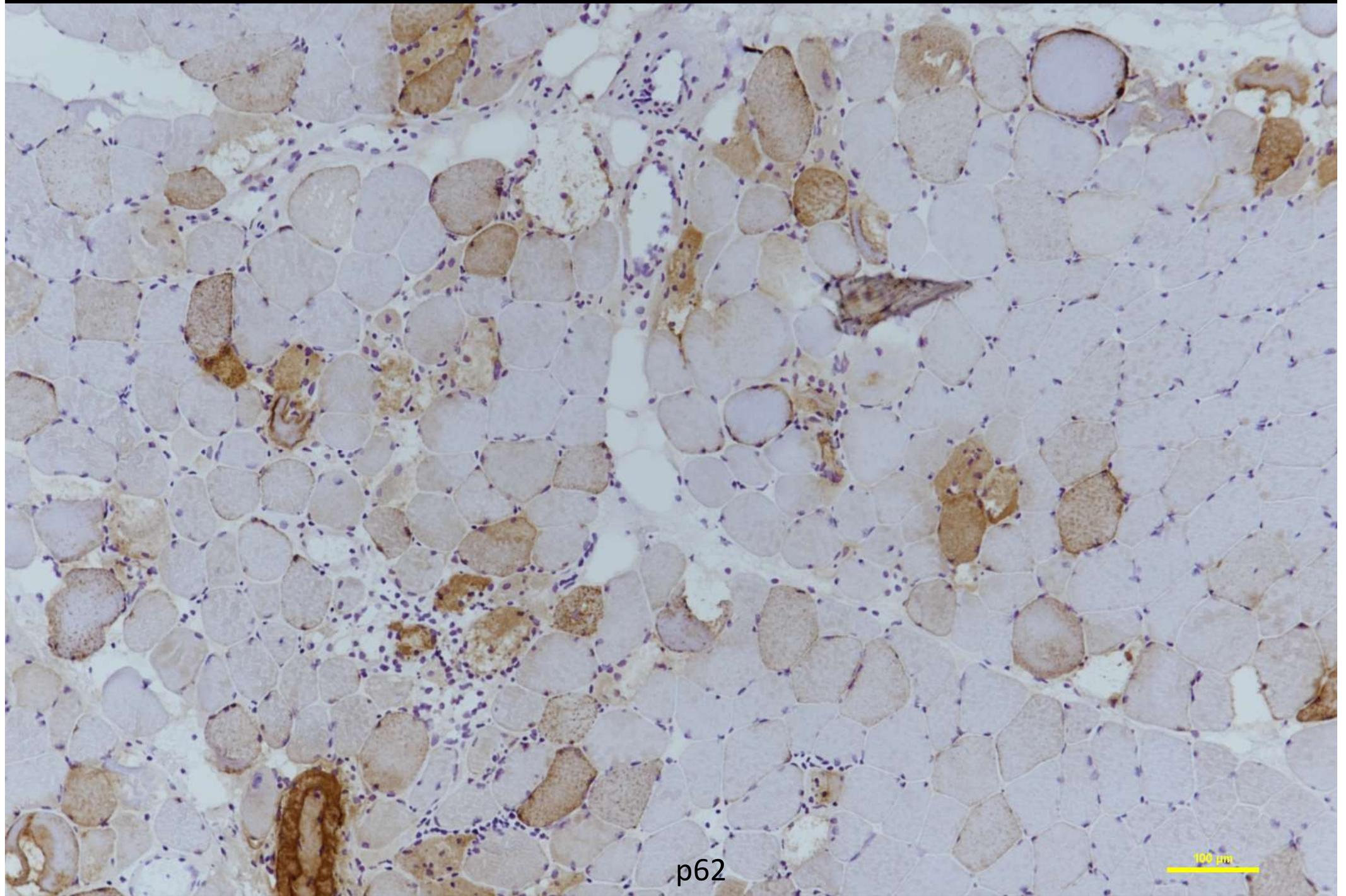
C5b9

100  $\mu$ m



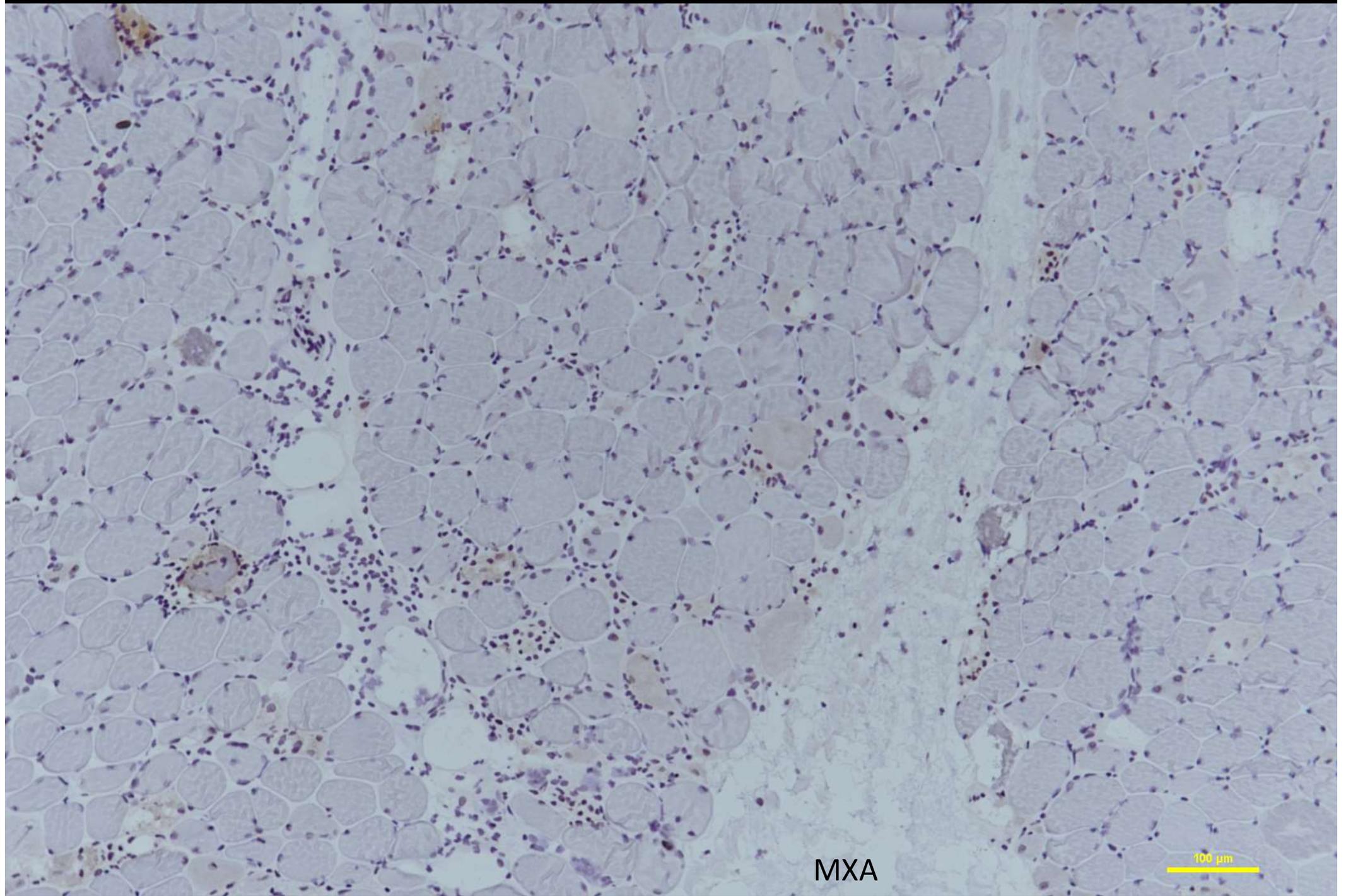
C5b9

50  $\mu$ m



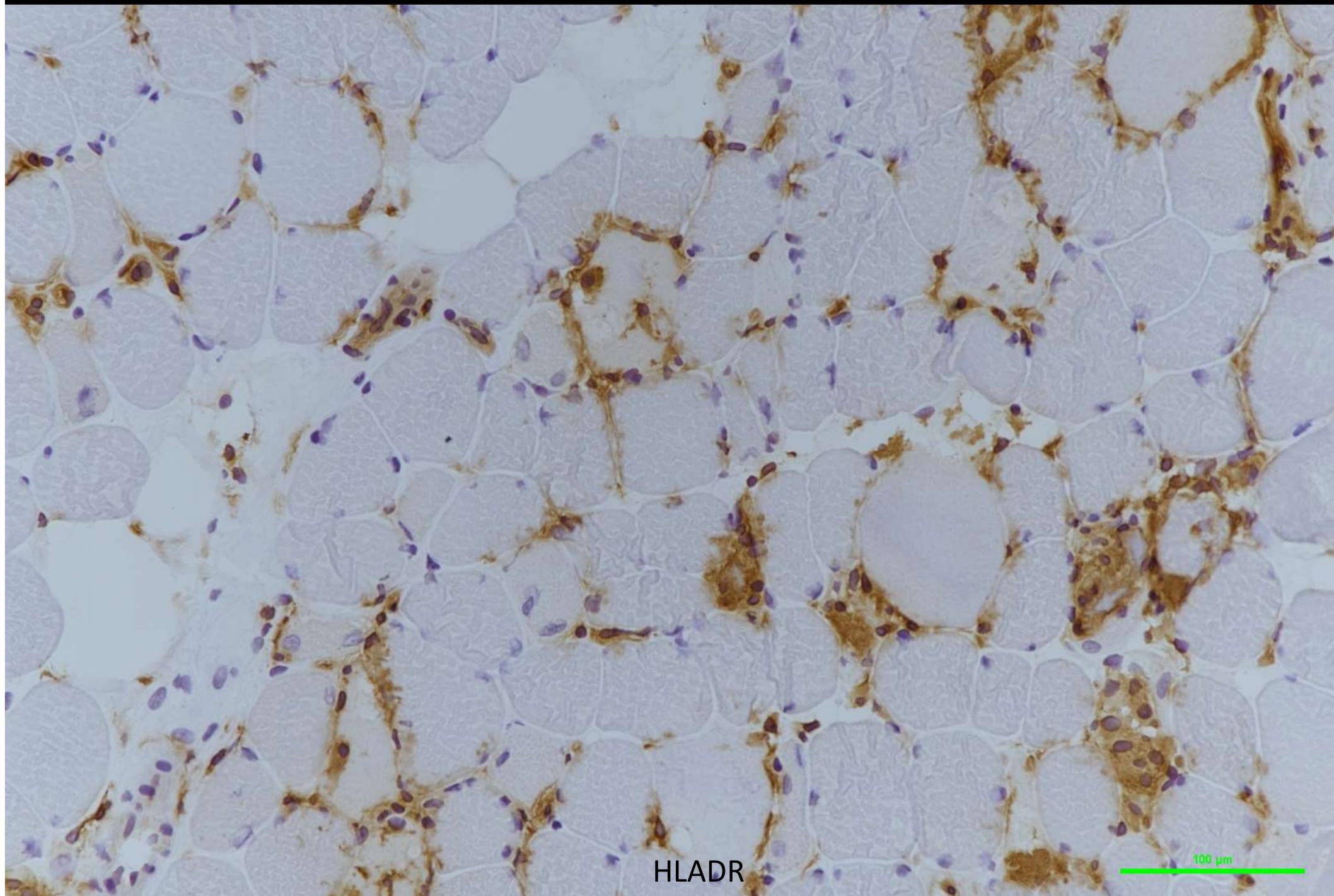
p62

100 μm



MXA

100  $\mu$ m



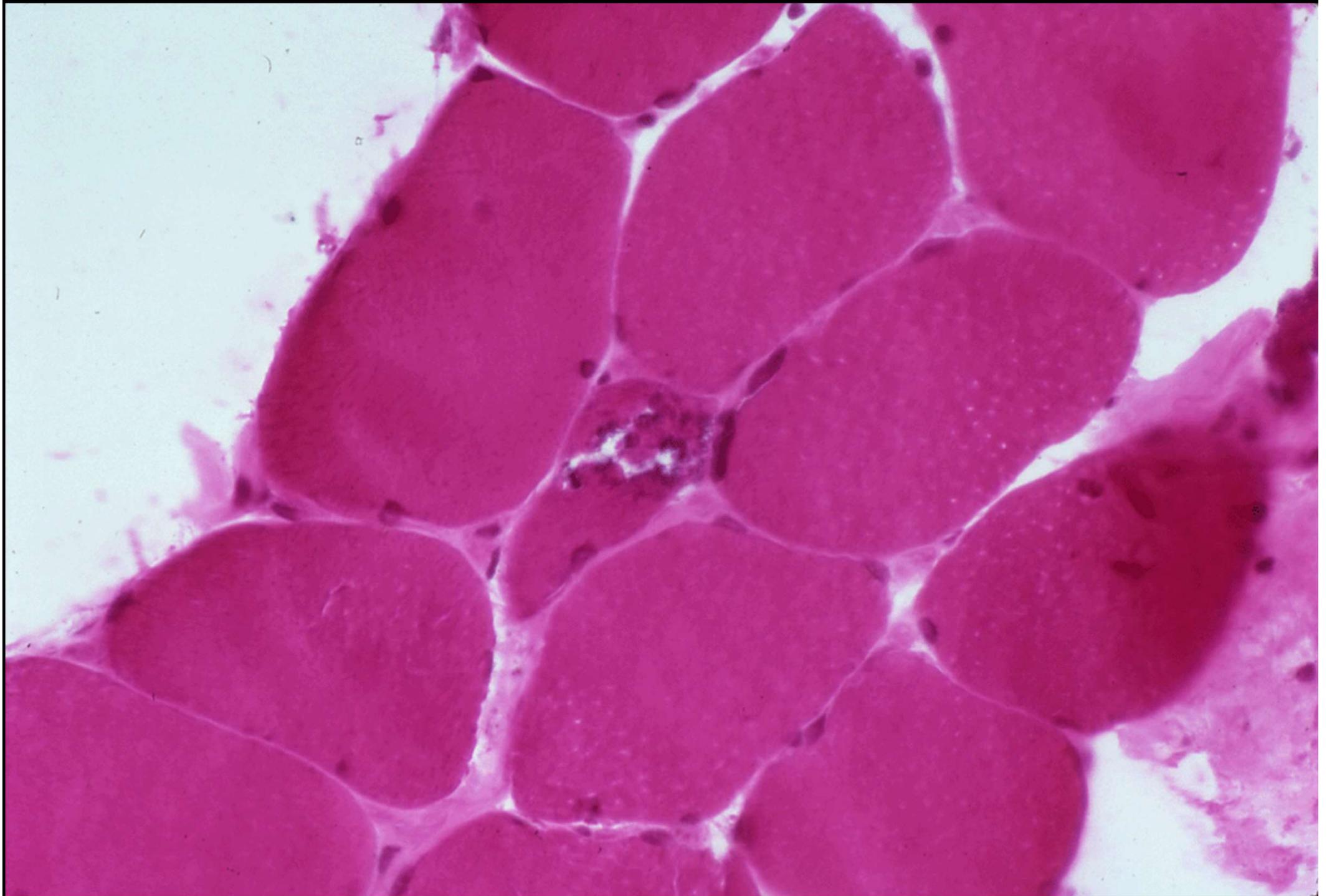
HLADR

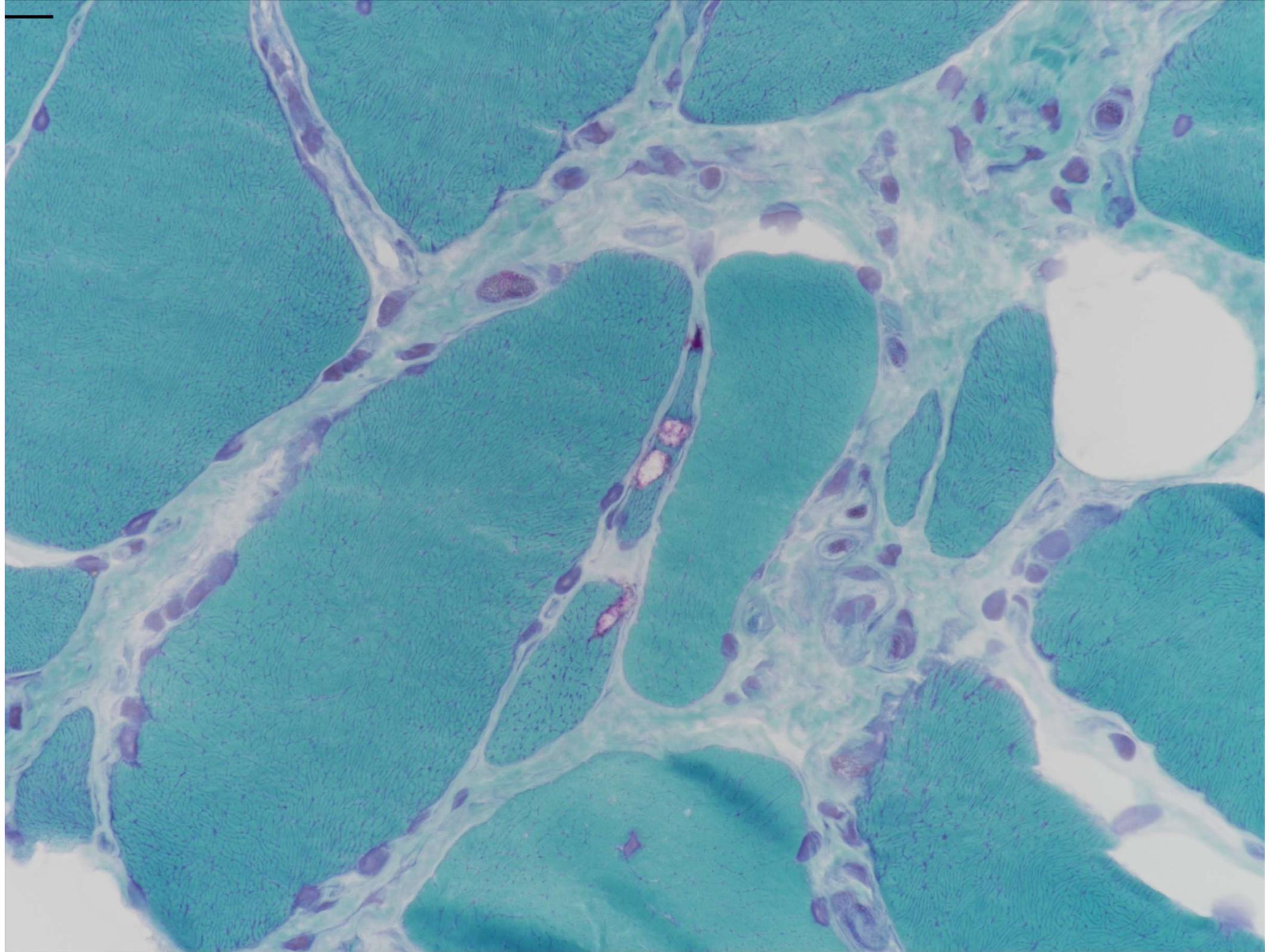
100  $\mu$ m

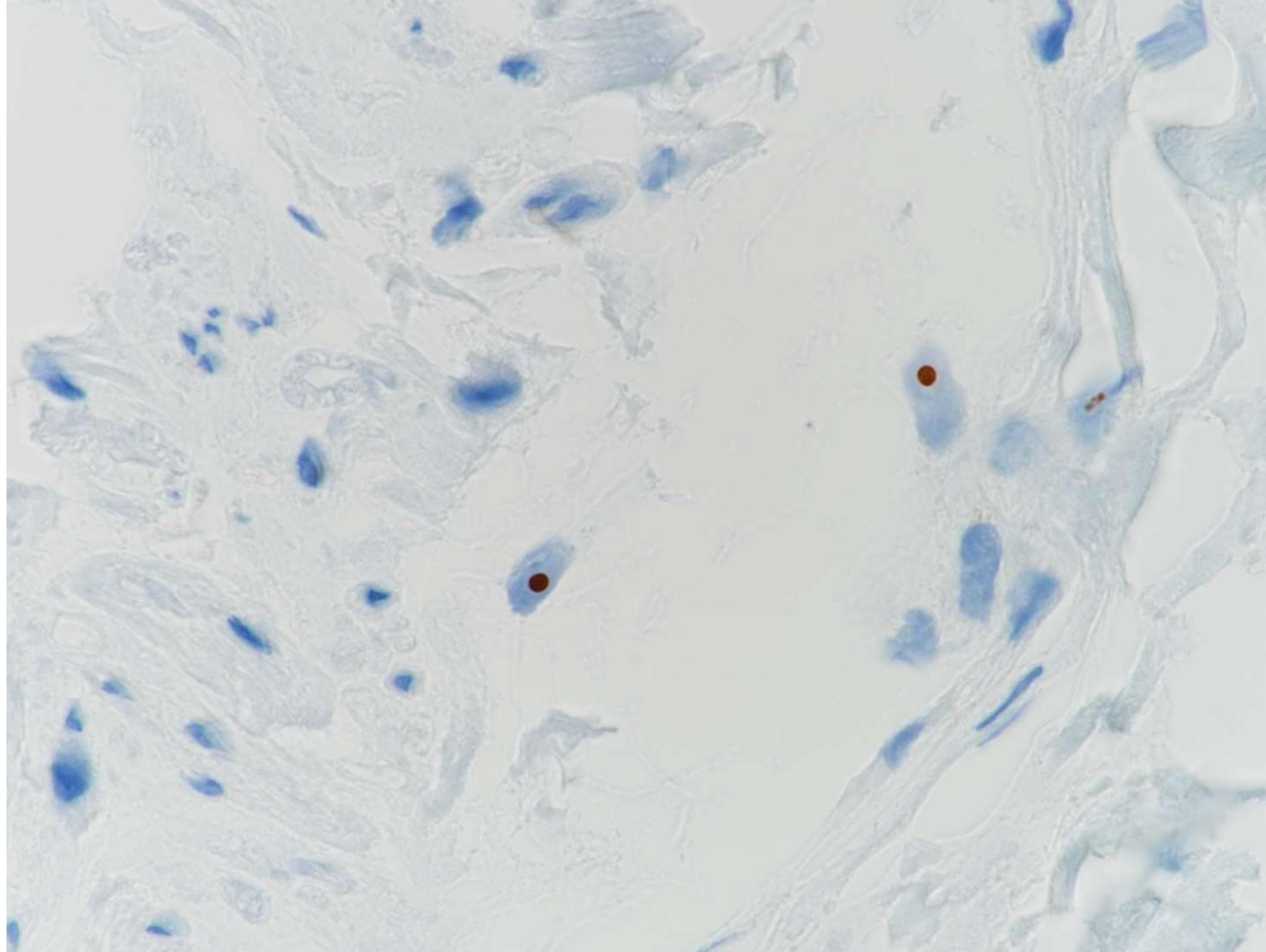
(OPDM)  
Oculopharyngo-  
Distal Myopathy

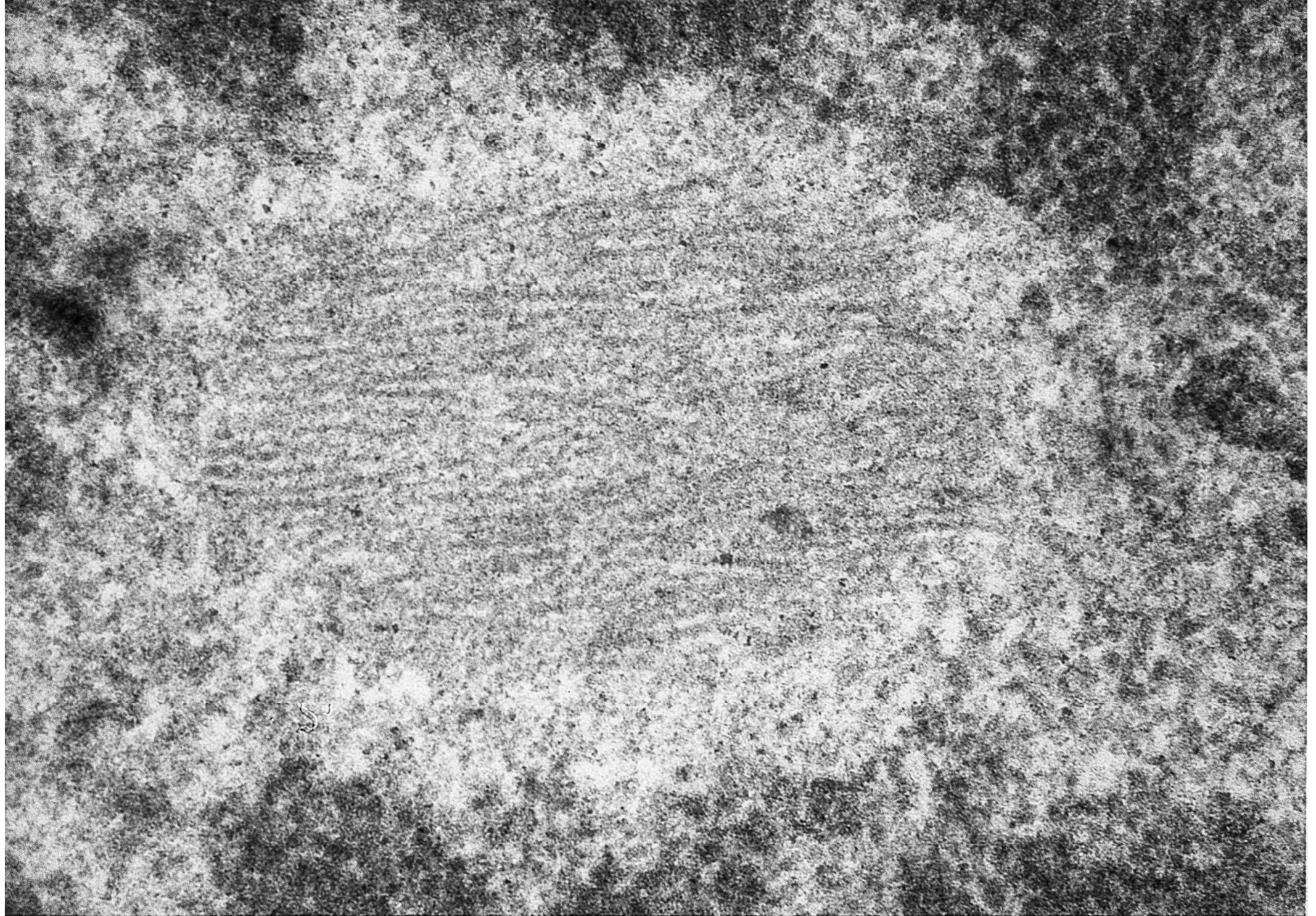


a heterozygous  
trinucleotide  
repeat expansion  
(CGG) in the 5-  
prime untranslated  
region of the  
LRP12 gene on  
chromosome  
8q22.





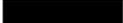




EM08-36-5.tif

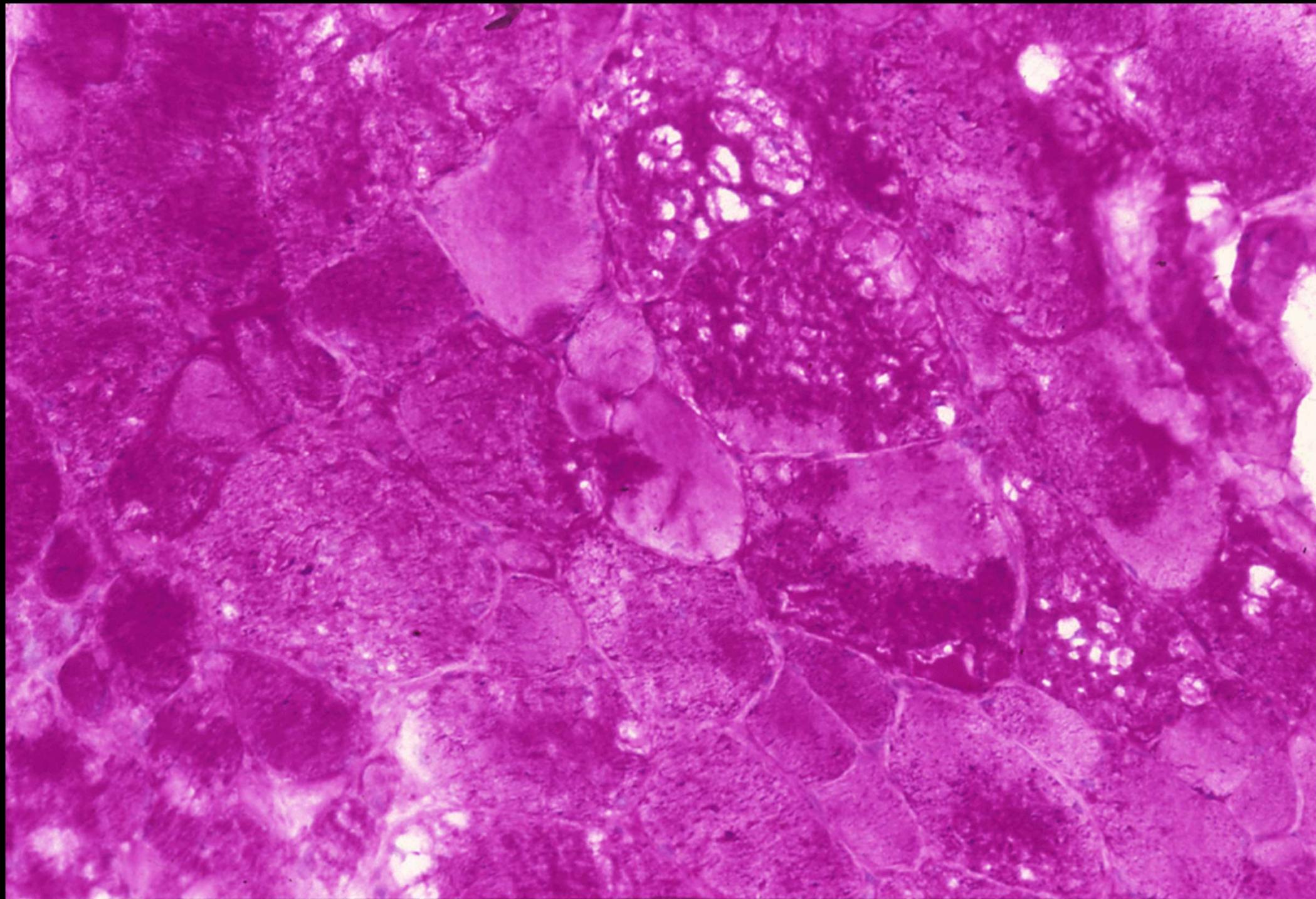
Cal: 0.467508 nm/pix

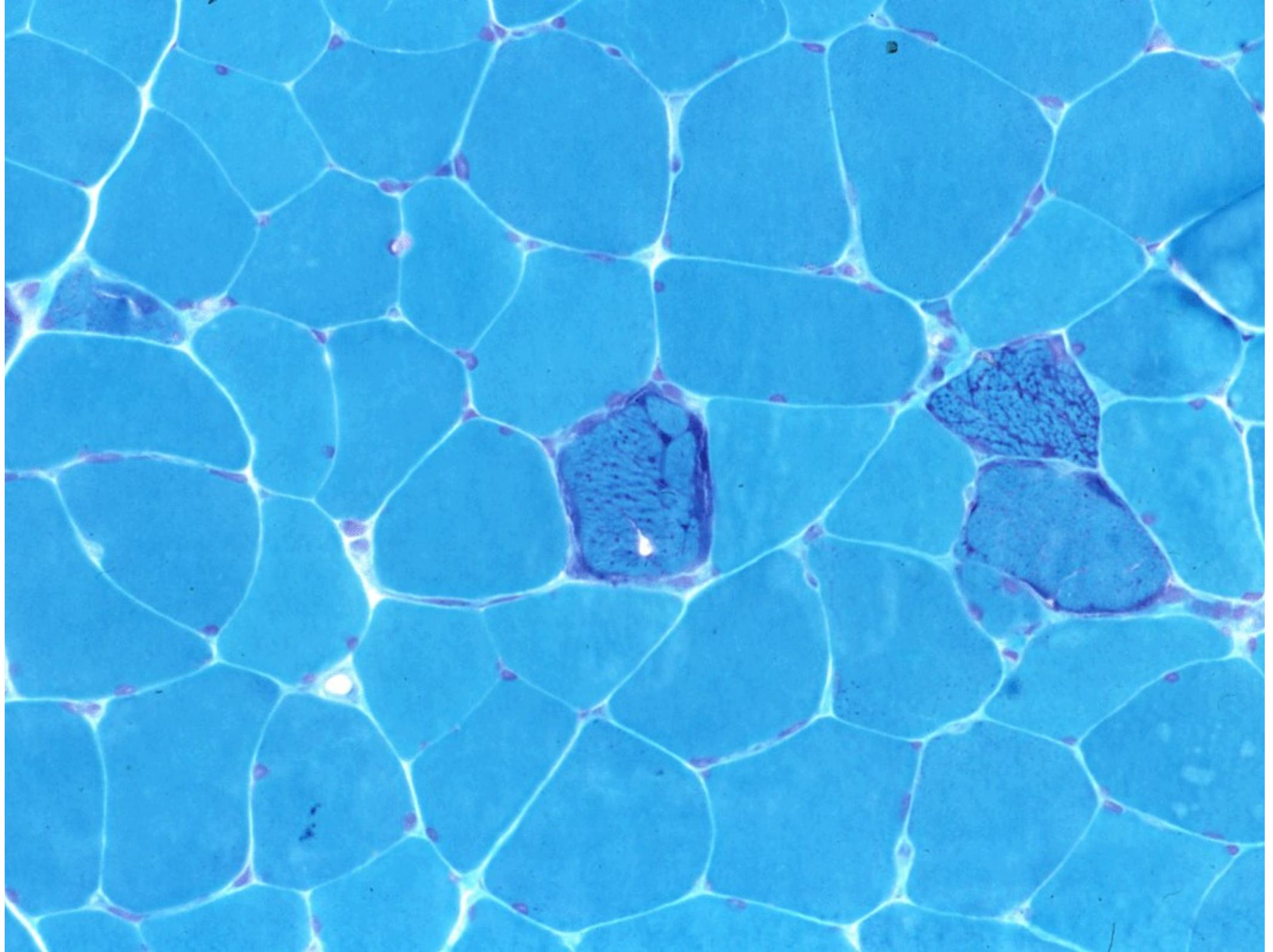
Matsubara et al eNeuroSci

 100 nm

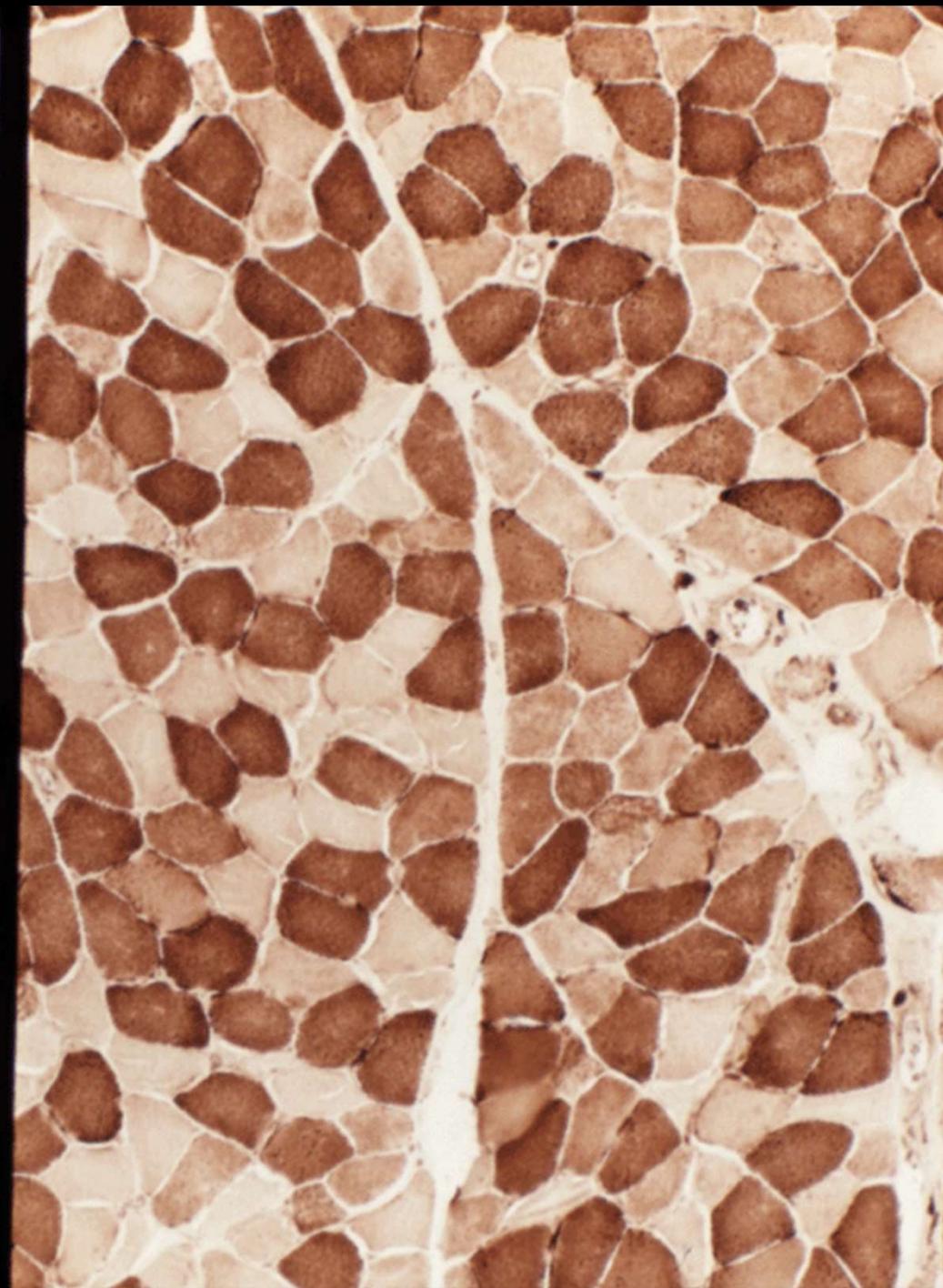
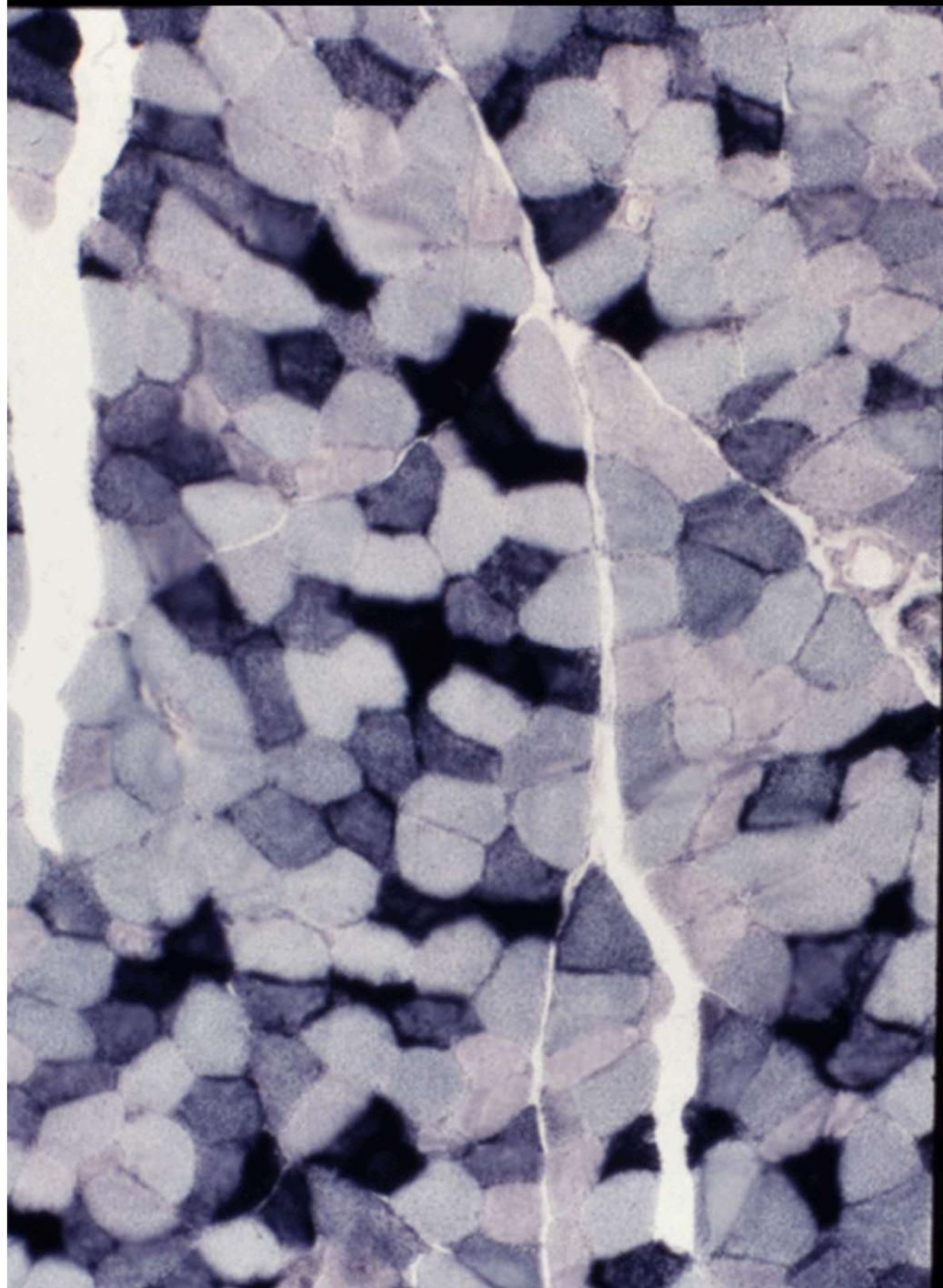
# 代謝性ミオパチー

- ポンペ病
- ミトコンドリア病

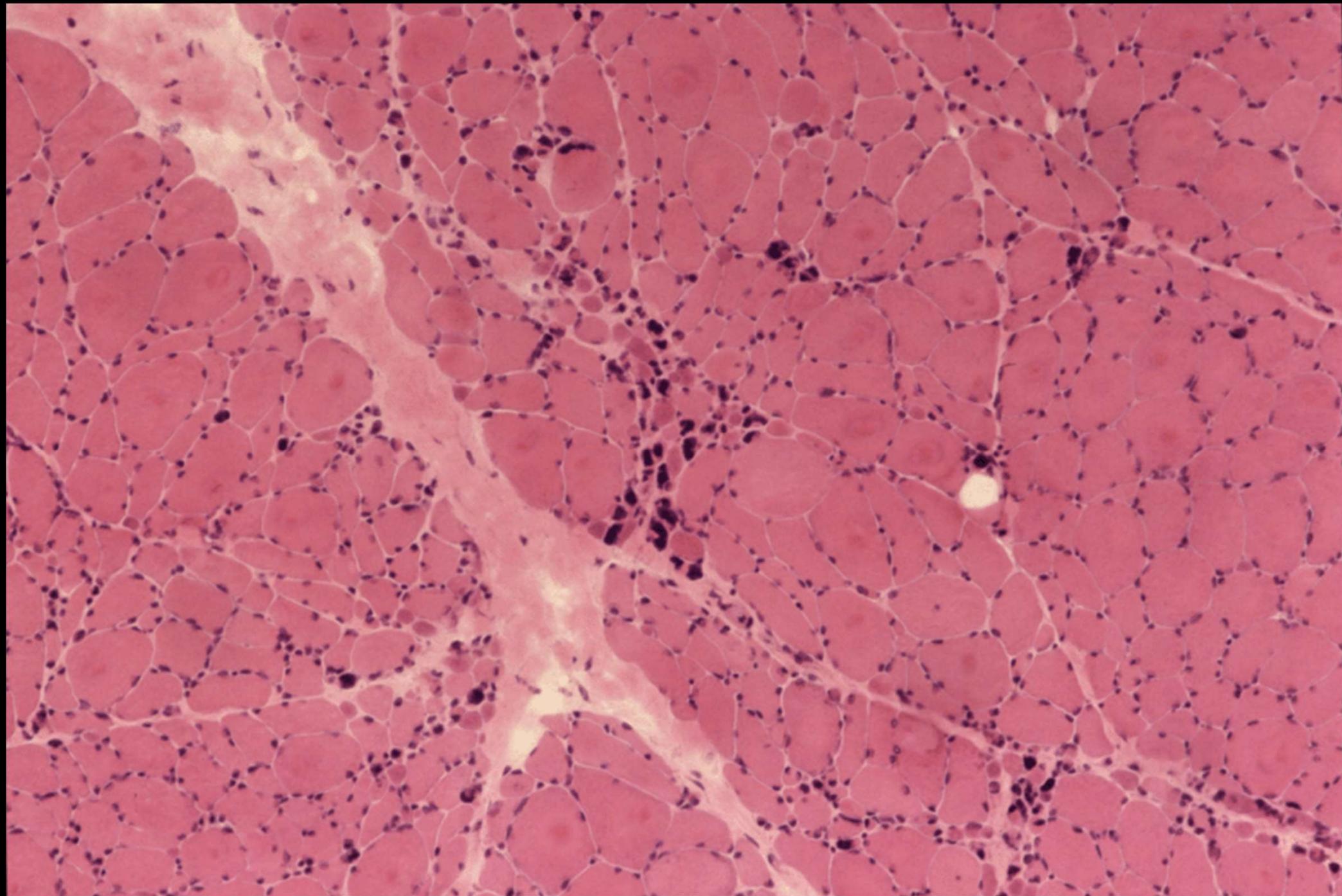


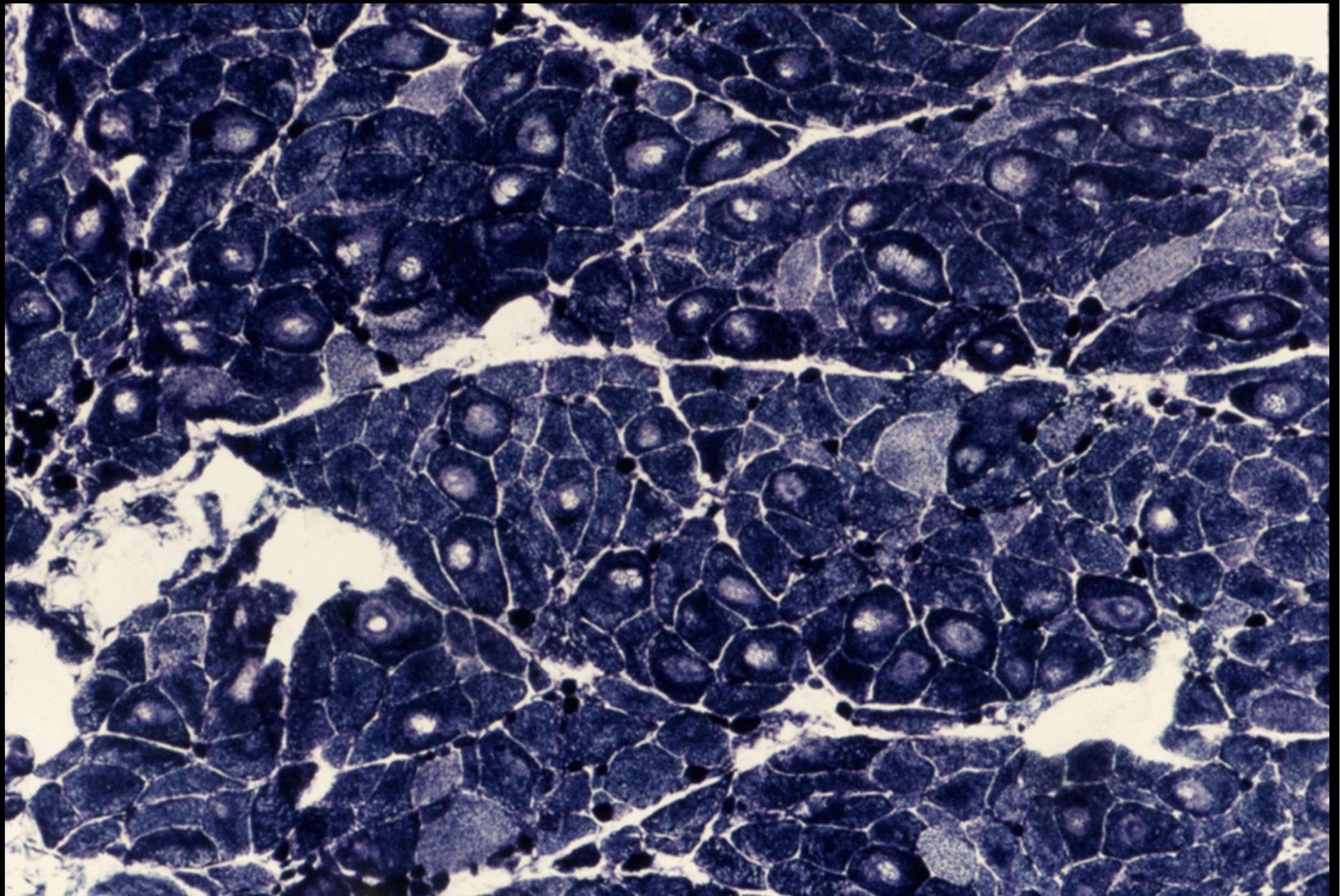




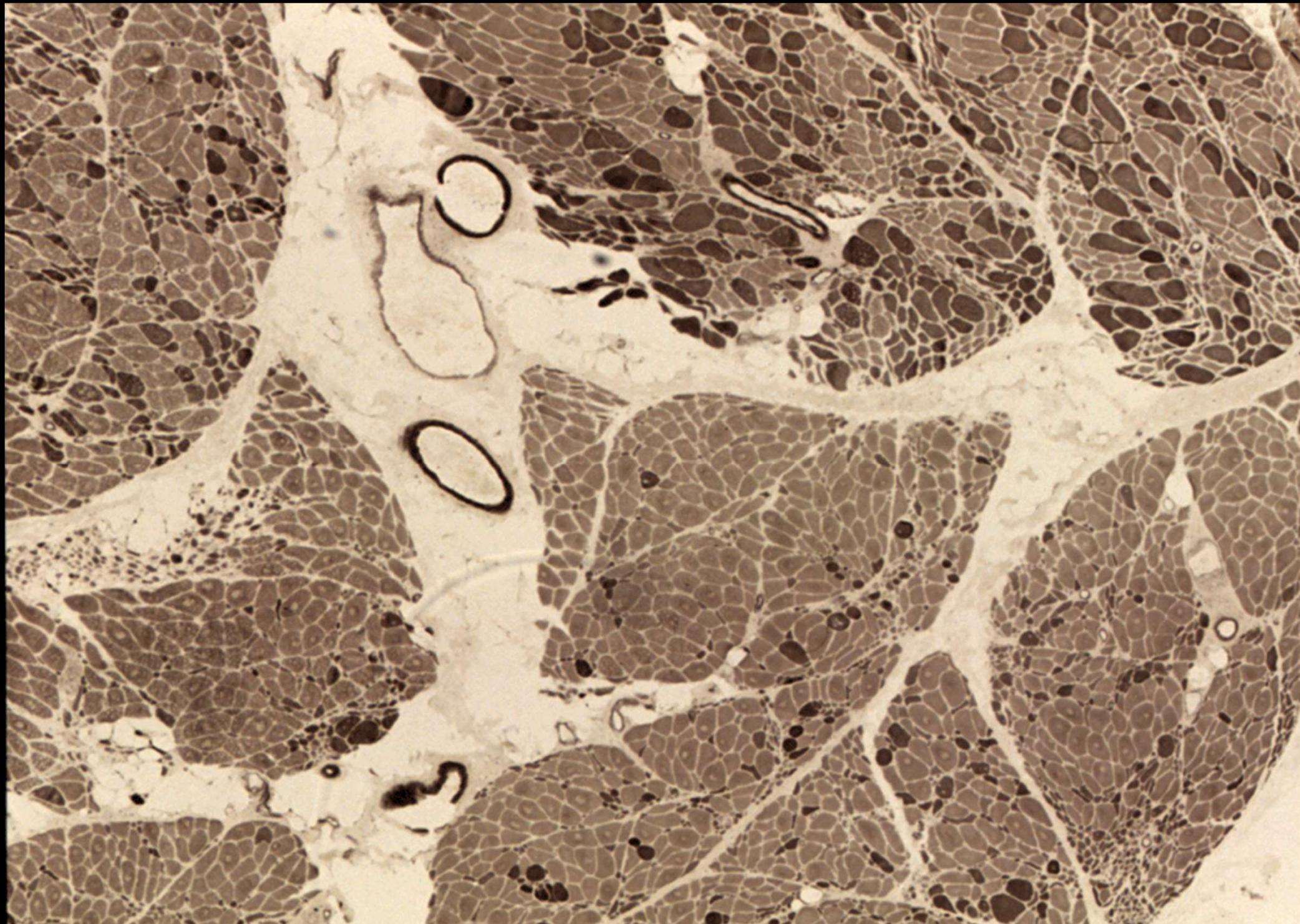


# 神經原性筋萎縮

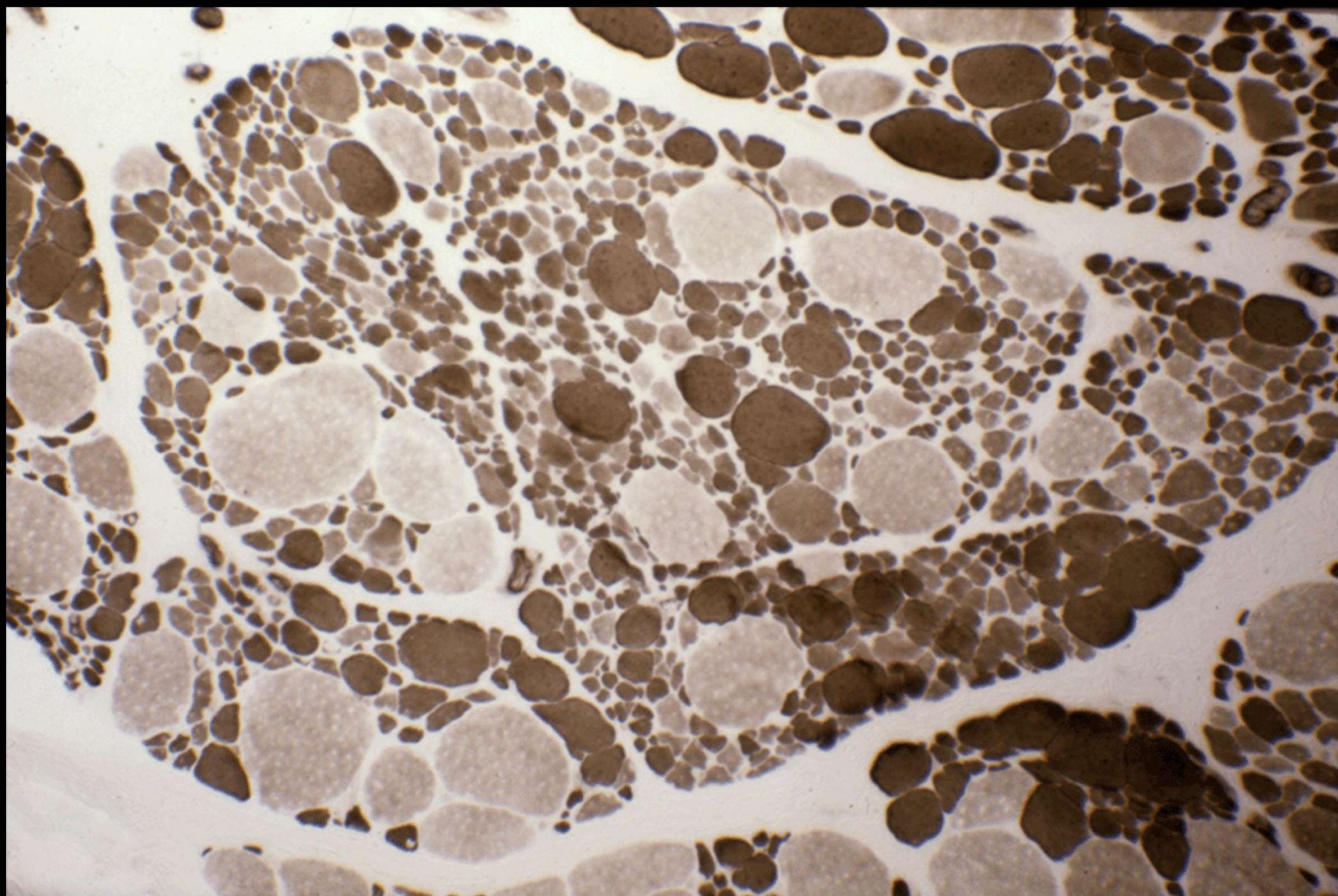




n- hexane neuropathy



BSMA



SMA Type 1: ヌシネルセン 核酸医薬

# 末梢神経病理

1. 腫瘍病理は、構成細胞の腫瘍

シュワン細胞腫、神経周膜腫、神経線維腫

2. 神経の解剖学的特異性に由来

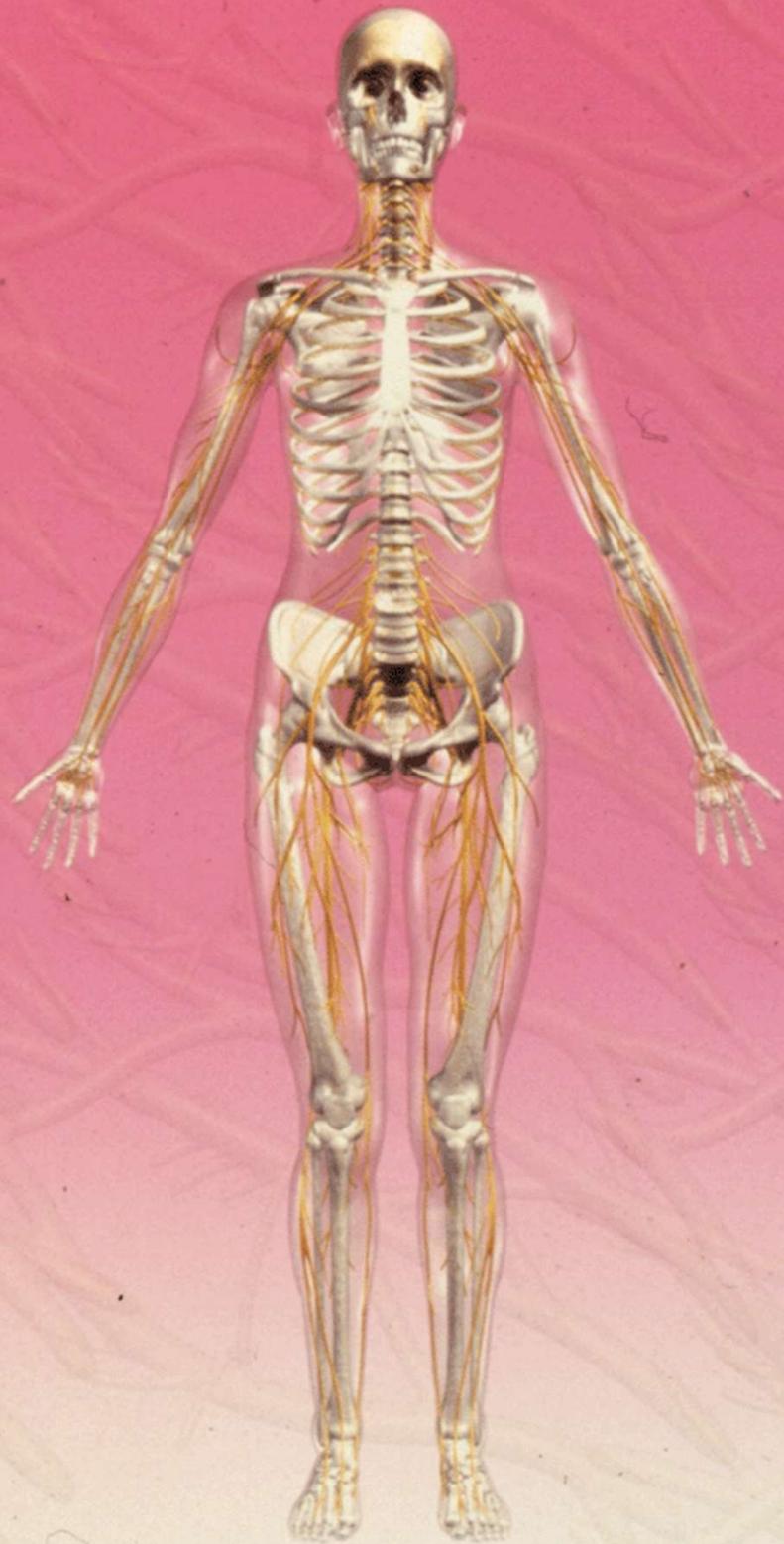
神経細胞体・軸索・髄鞘の全体的把握が必須

– 軸索が極めて長い

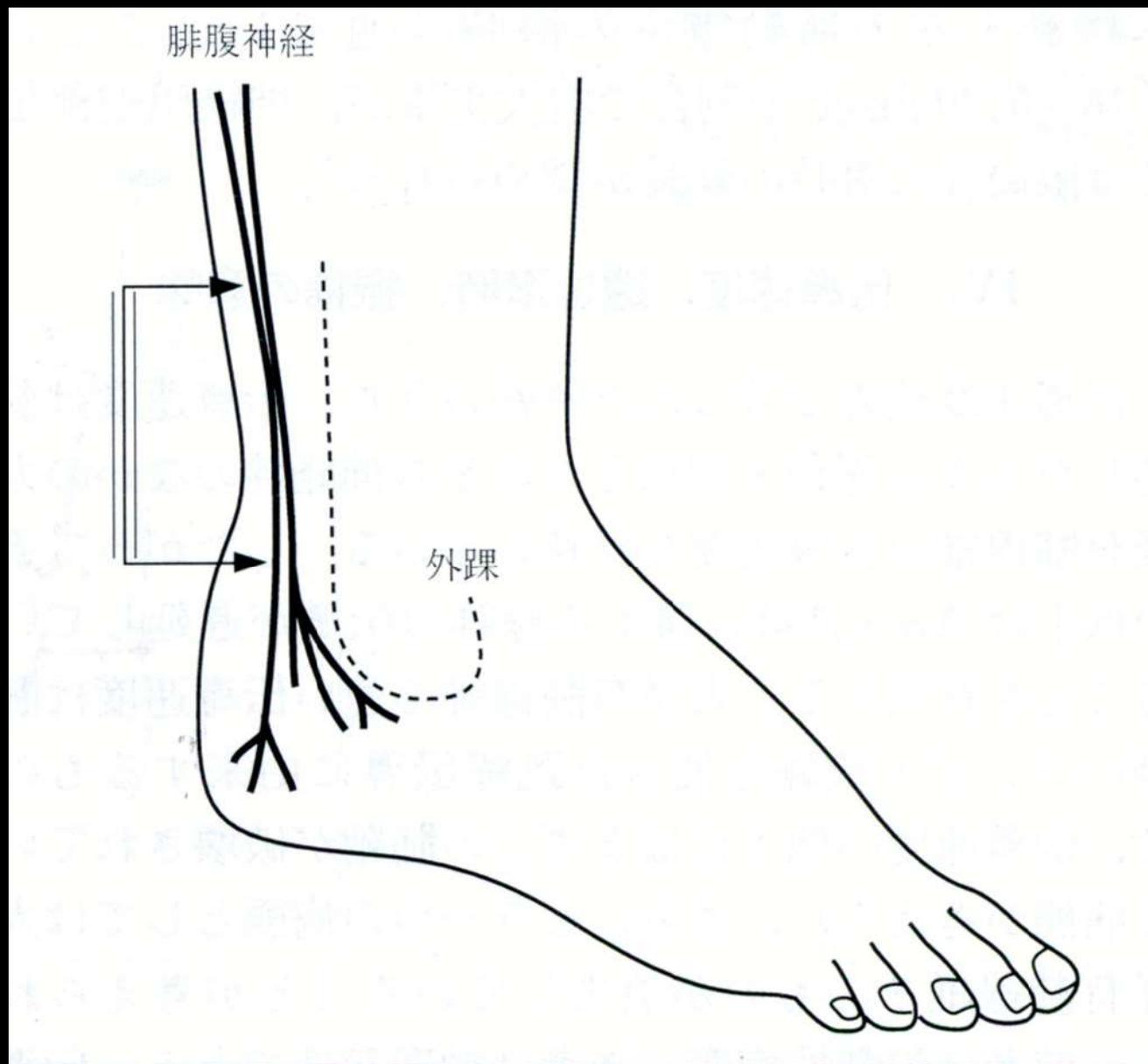
– 情報伝達が生理学的機能

3. 遺伝子疾患の場合、髄鞘構成蛋白の異常が関与することが多い

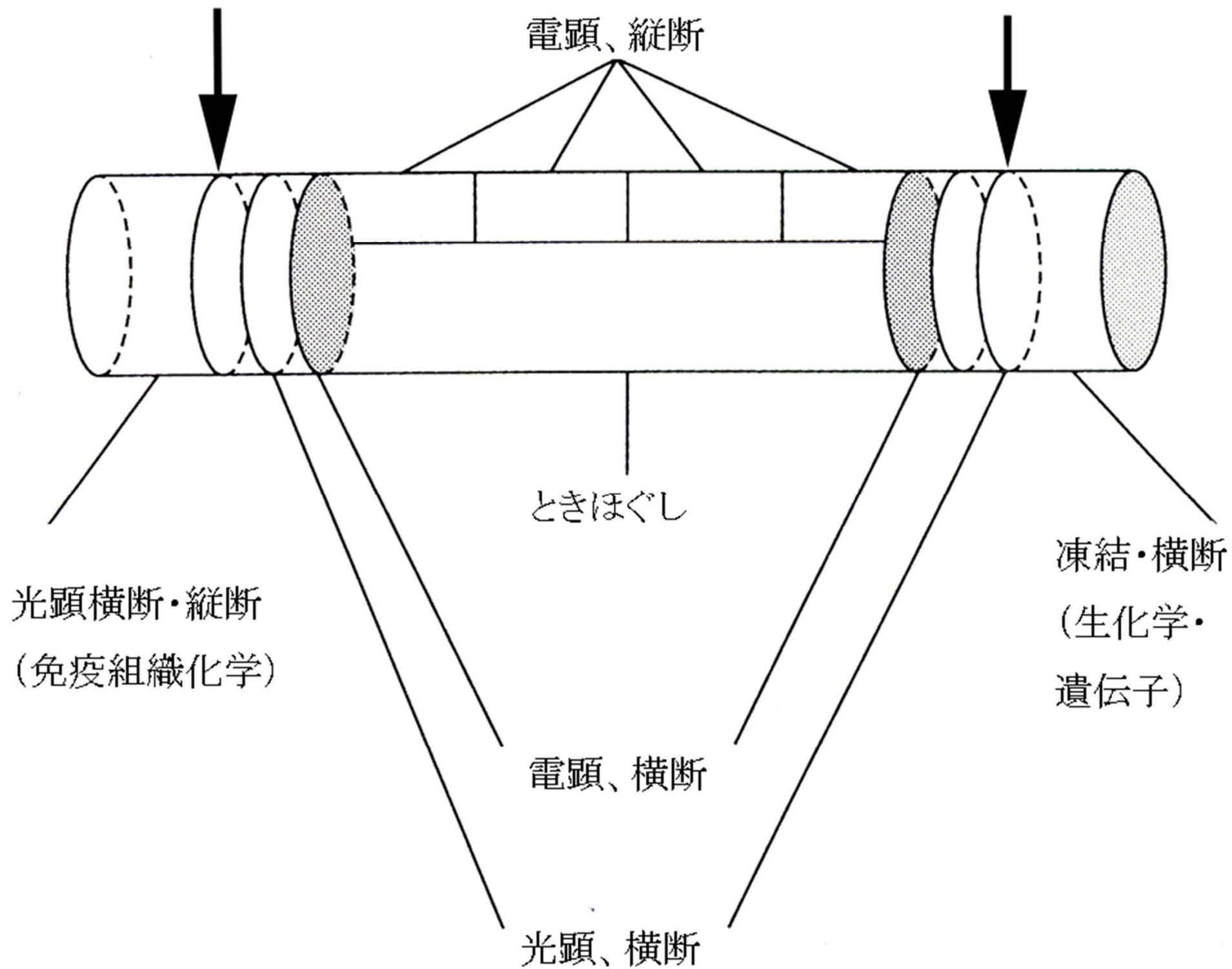
4. 孤発性疾患の場合、代謝・循環障害、自己免疫機序の両方が重要



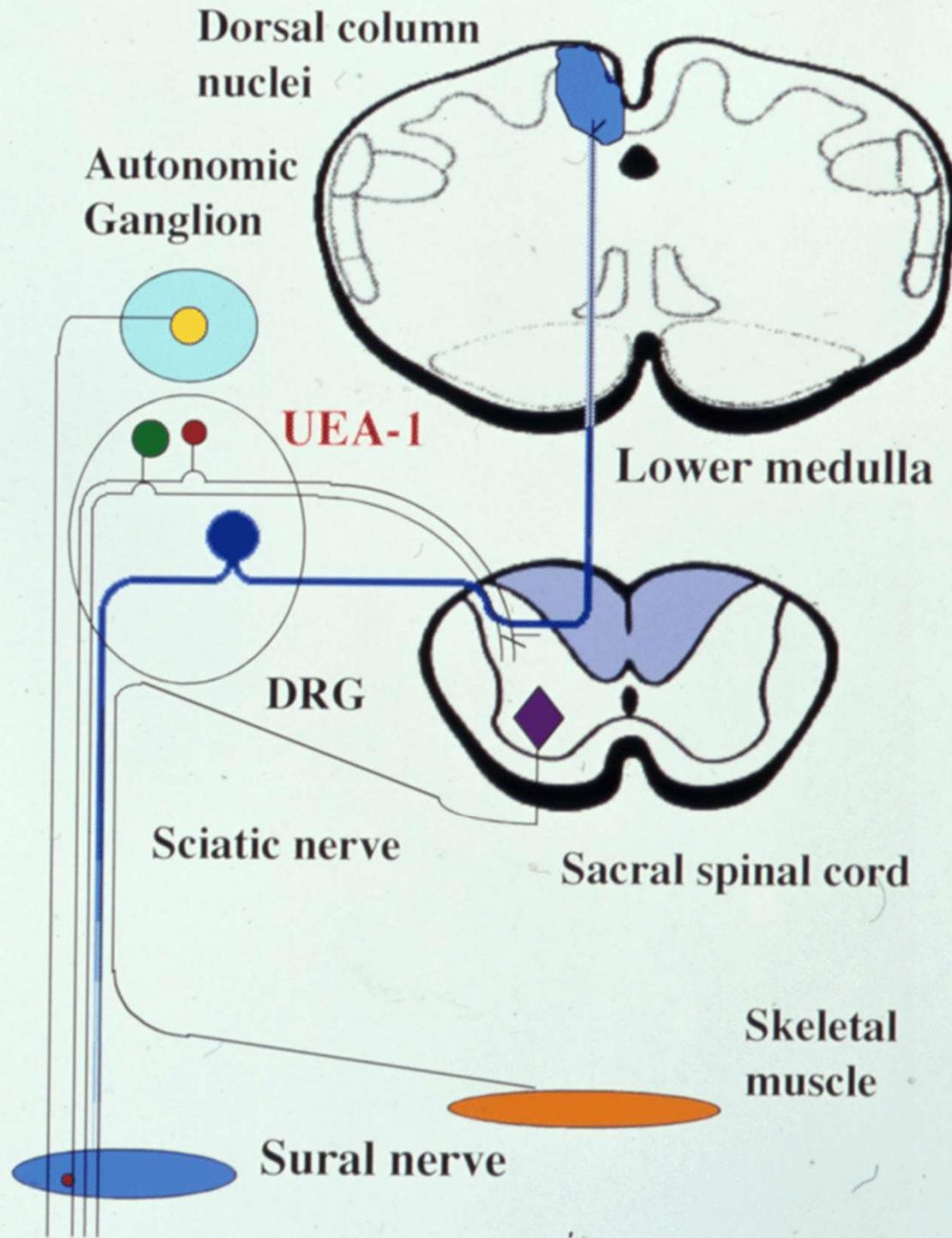
# 腓腹神經 短腓骨筋 (同時生檢)







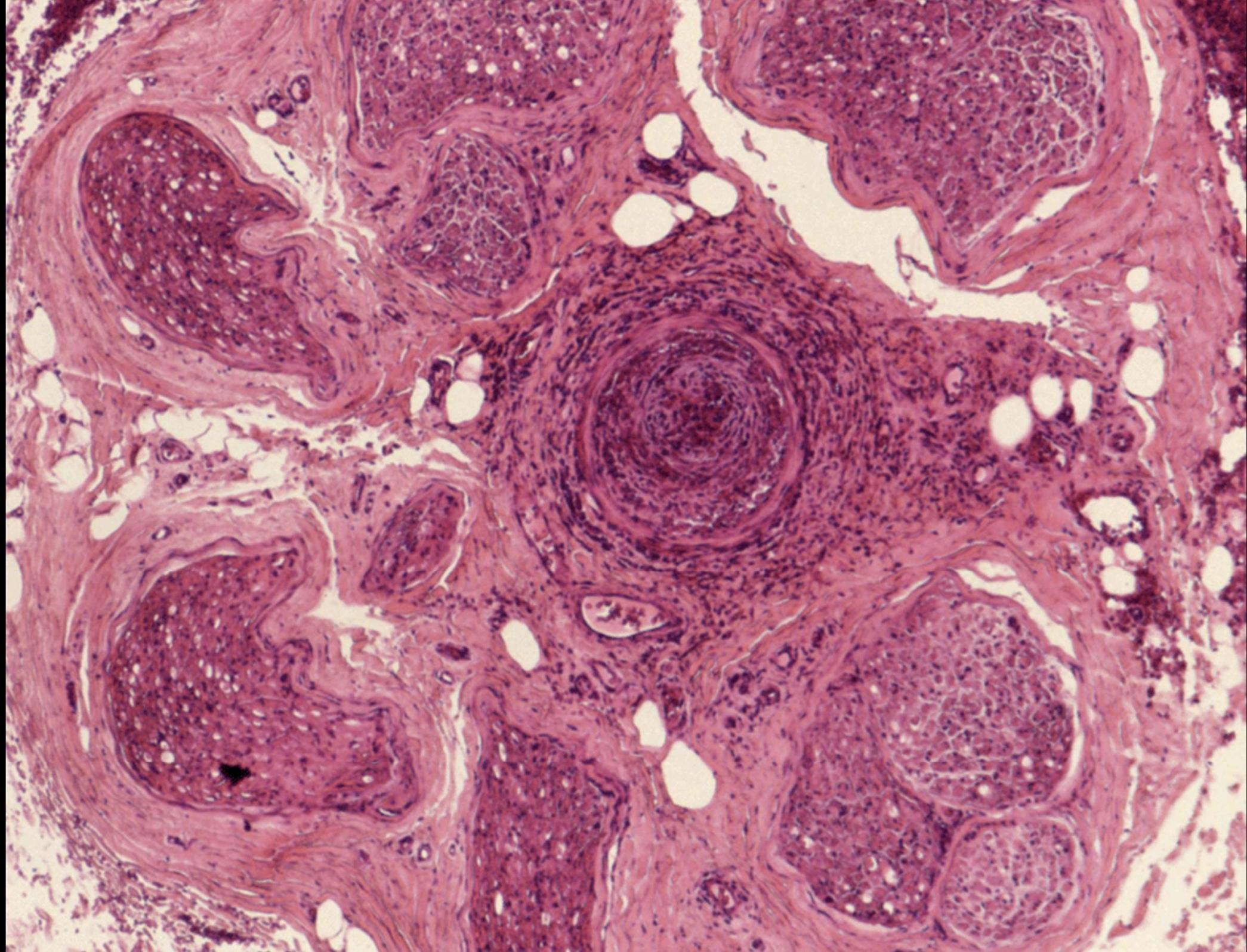
# Pathology of the Sural Nerve

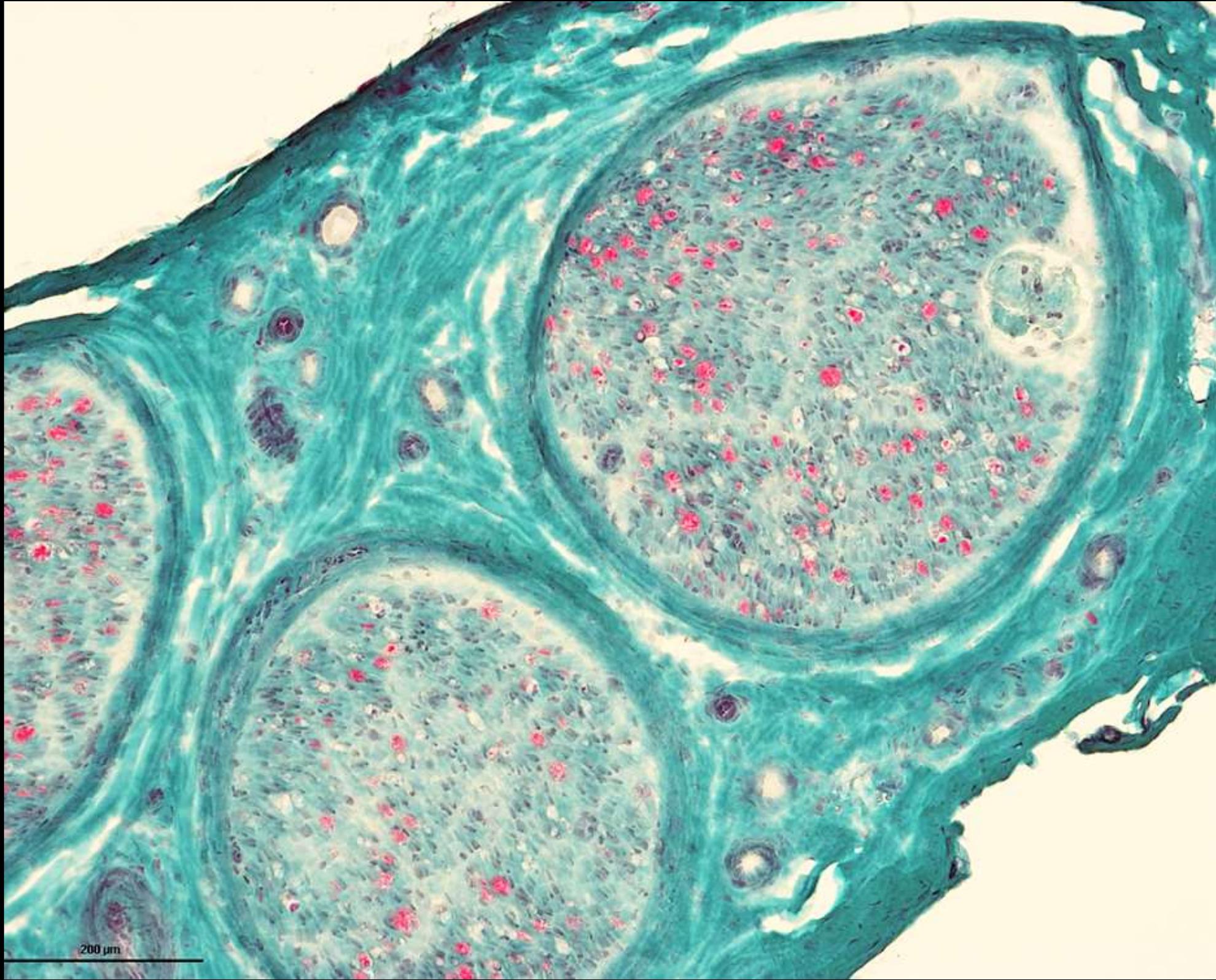


# 通常標本で診断可能な疾患

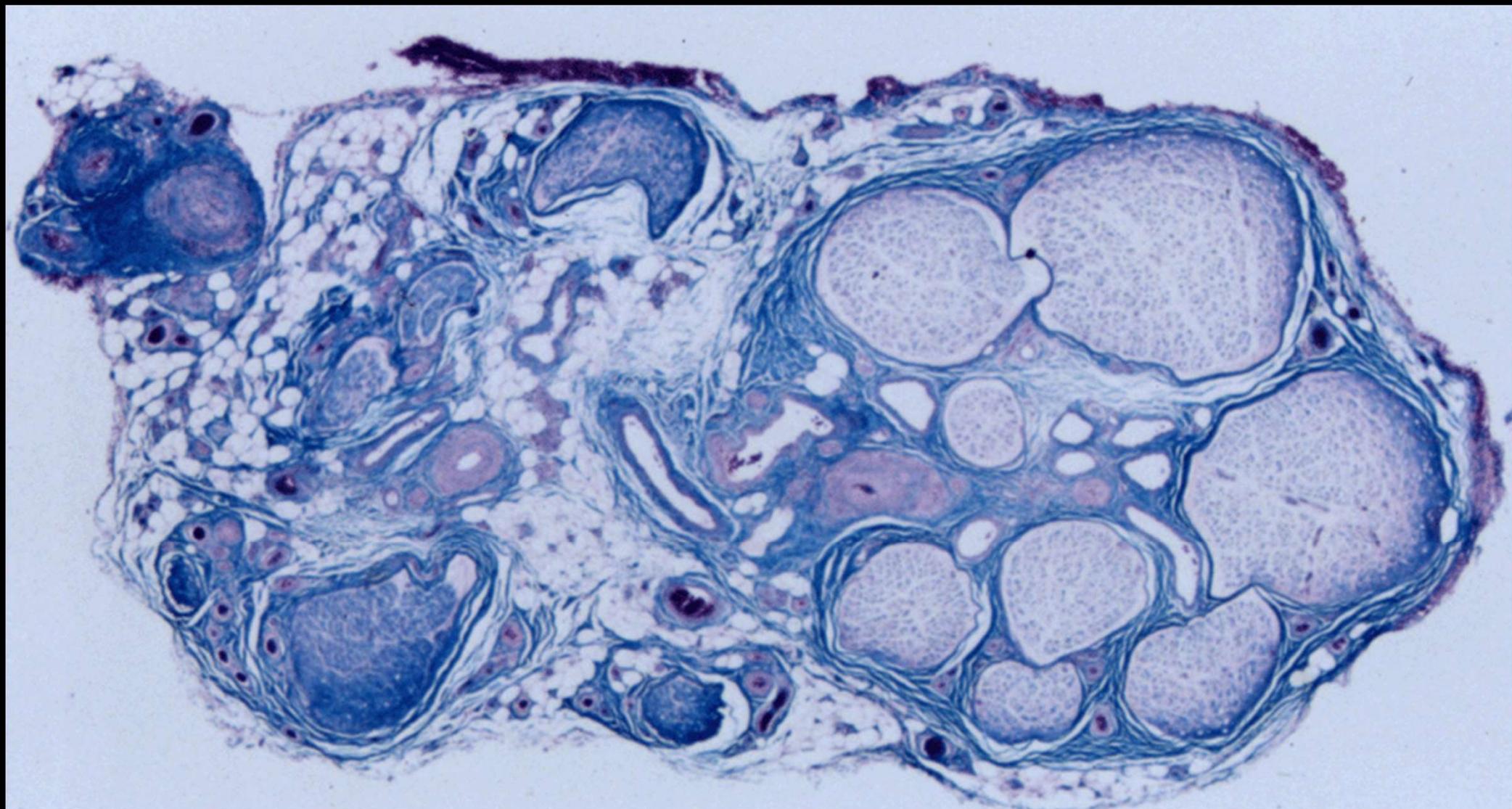
- 血管炎
- サルコイドーシス
- アミロイドーシス

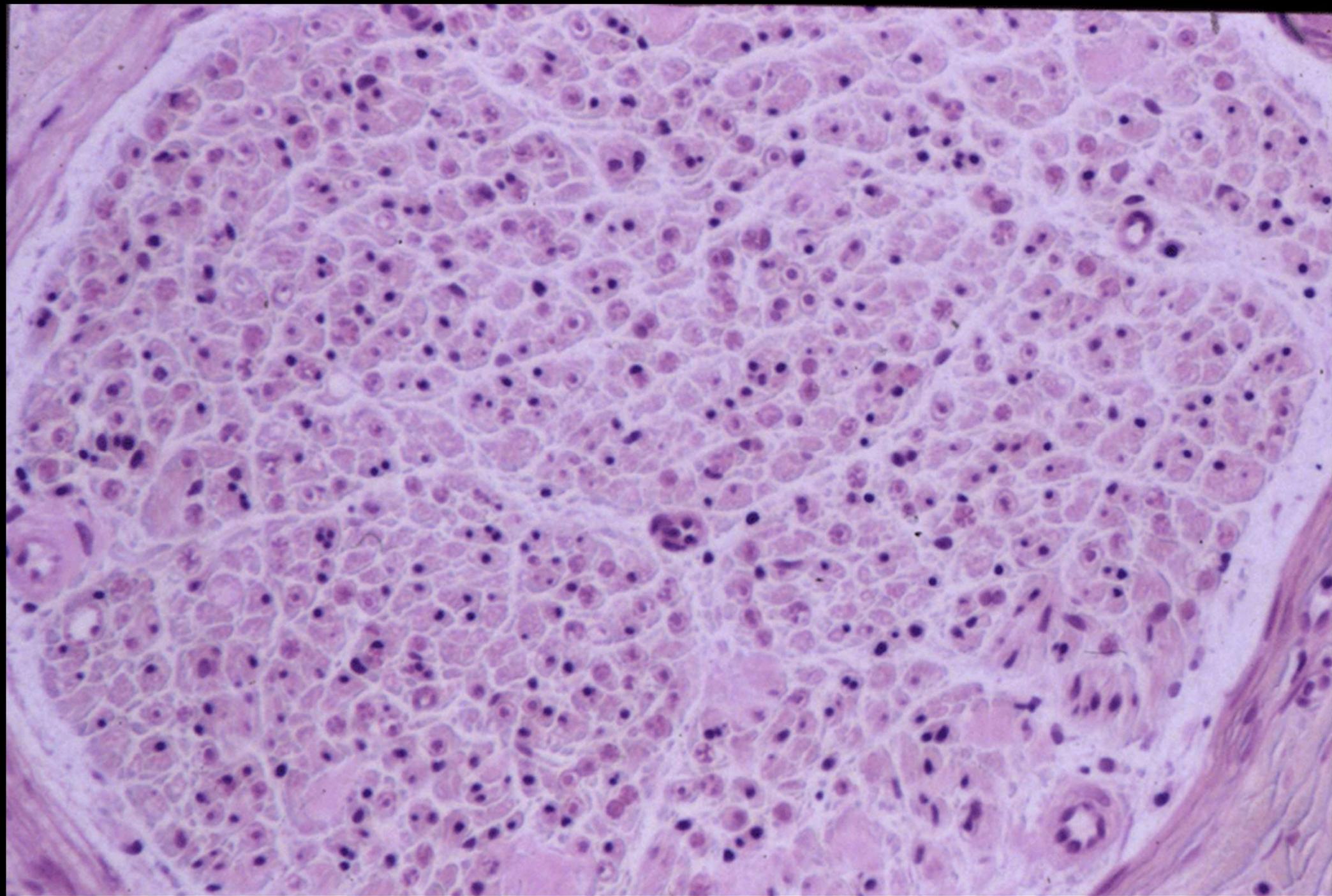


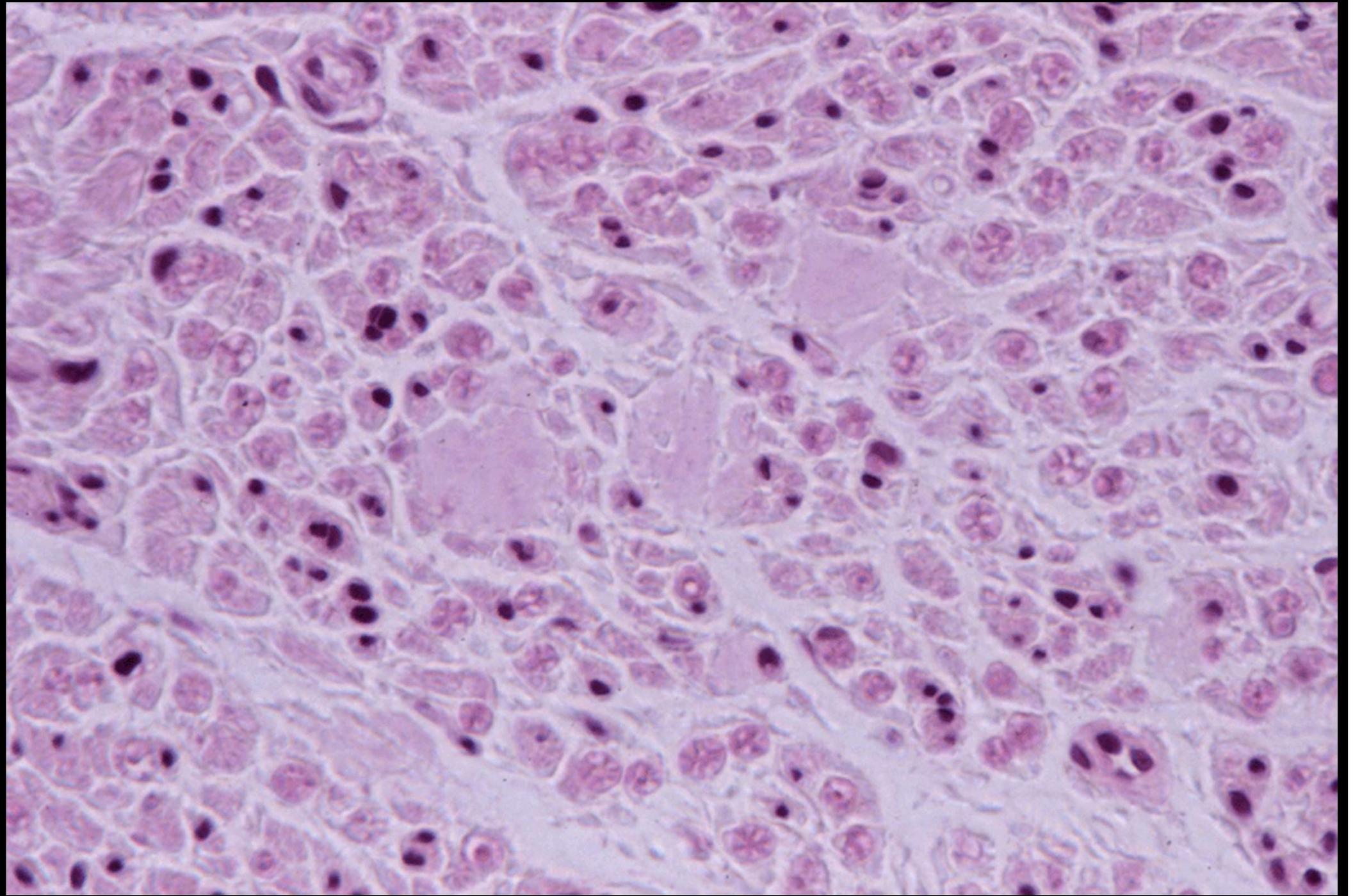


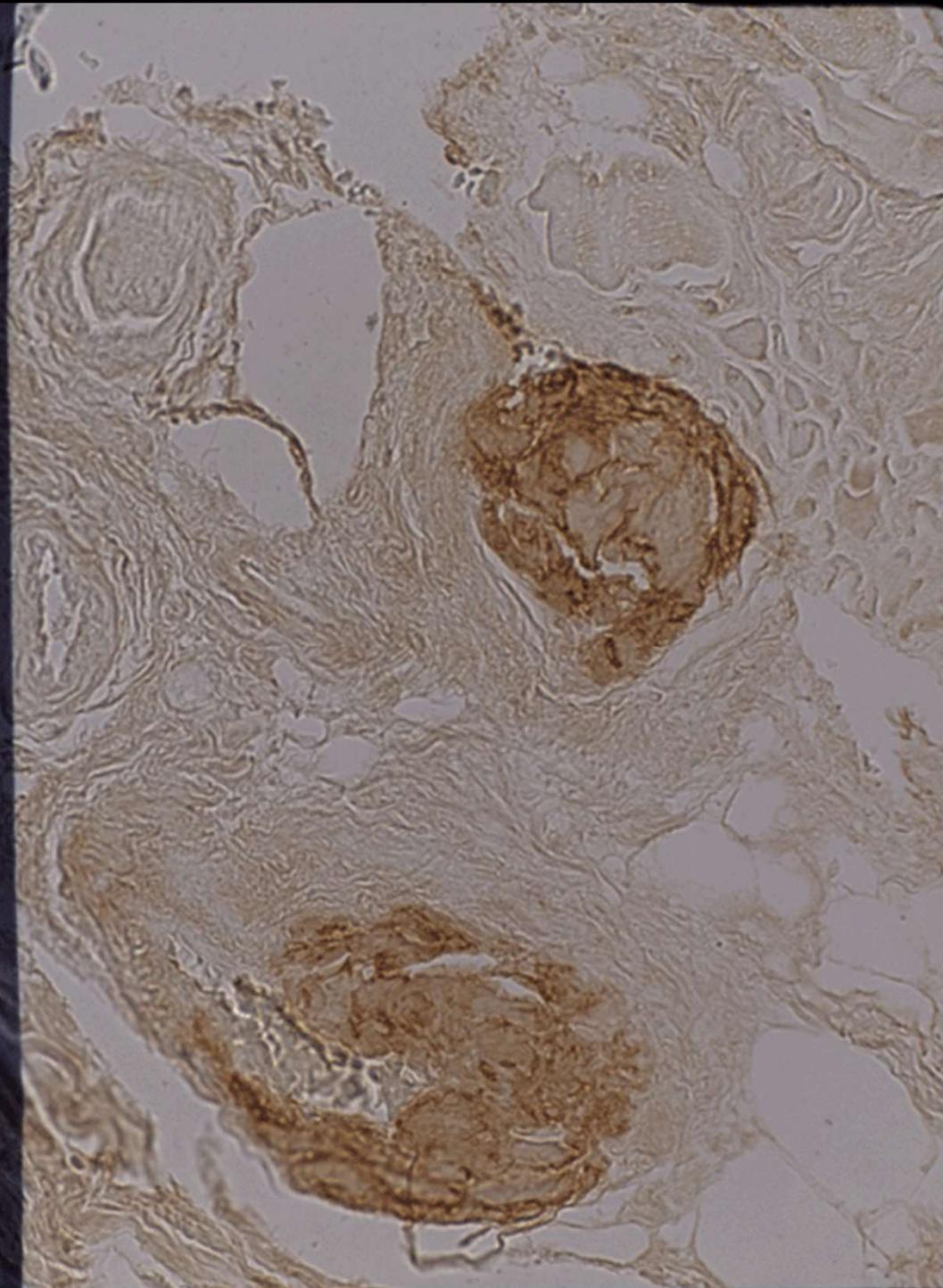
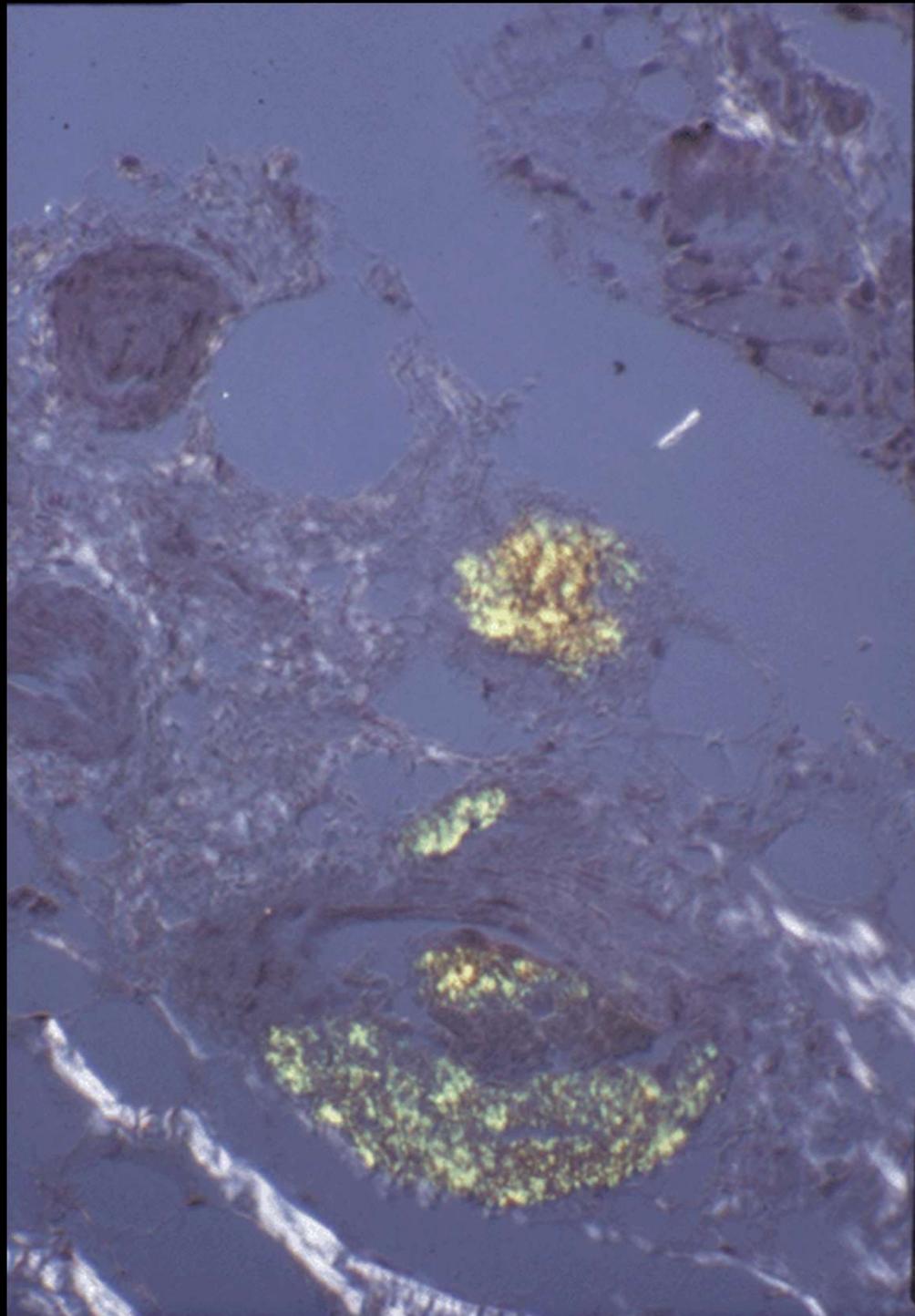


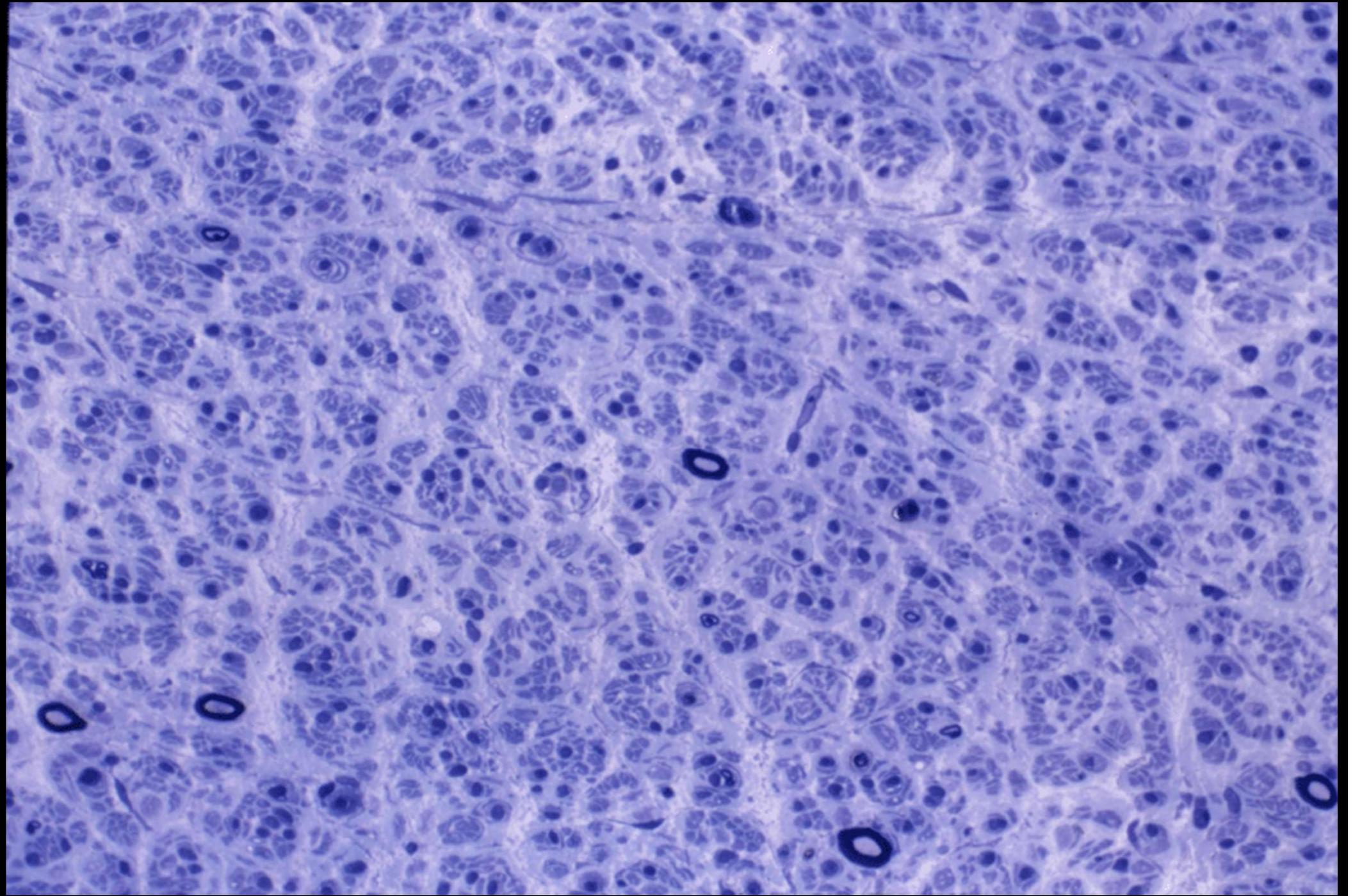
200  $\mu$ m

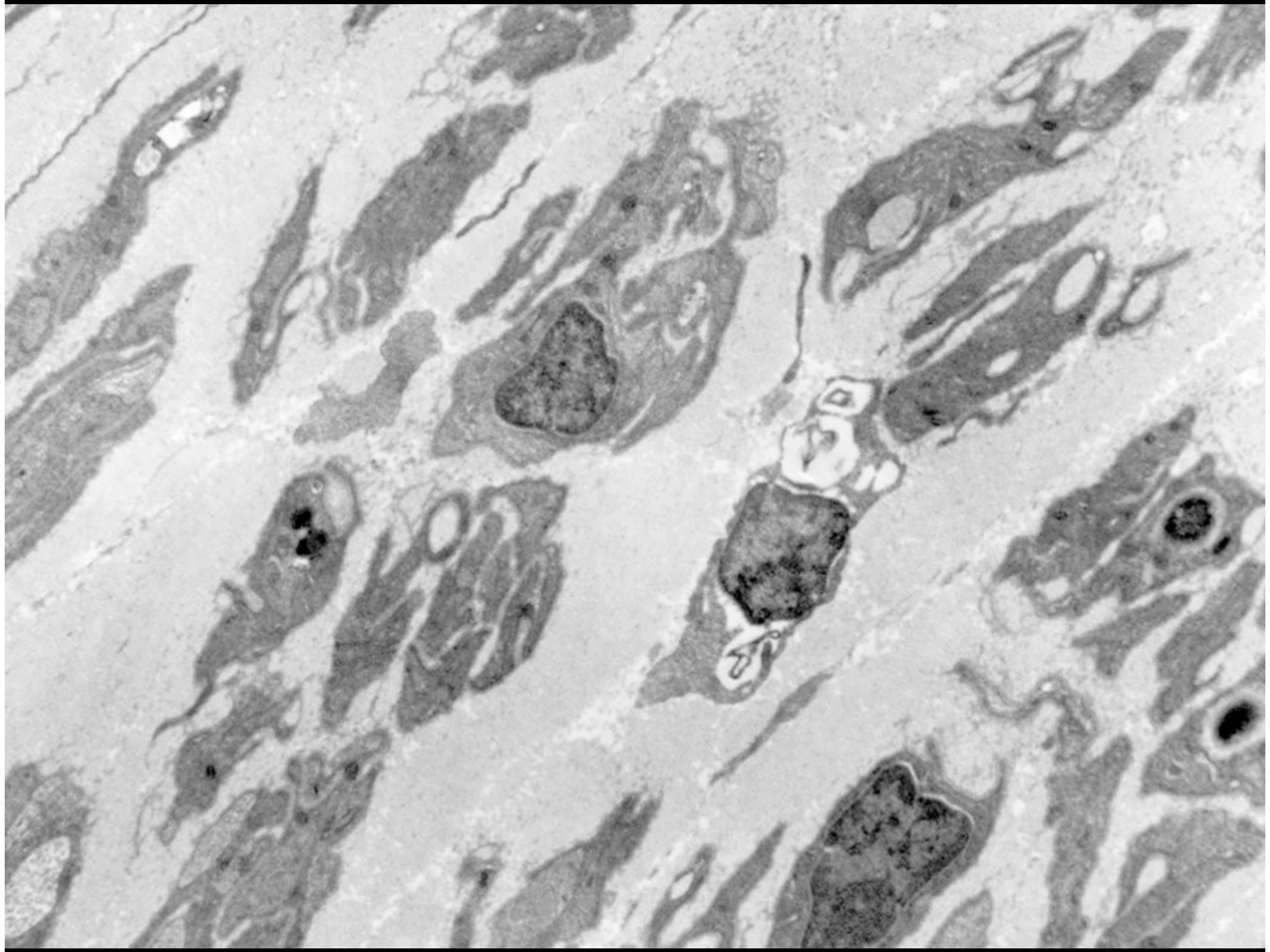






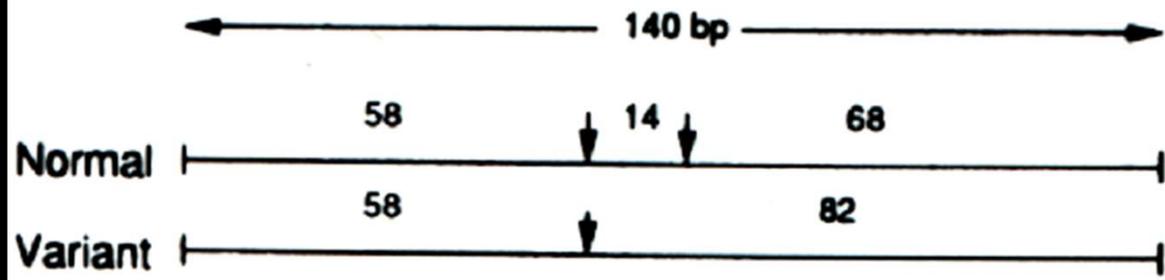
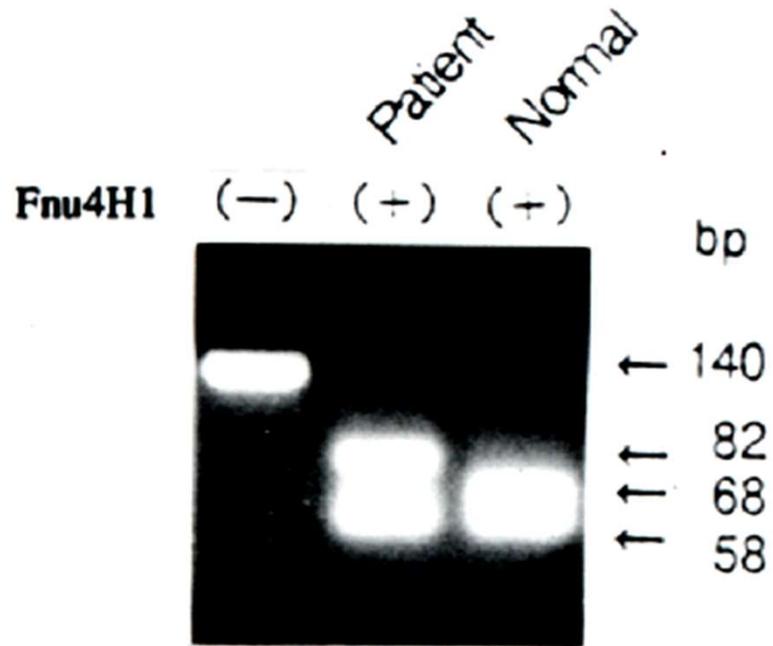








# Transthyretin 109 Ala → Ser のDNA診断



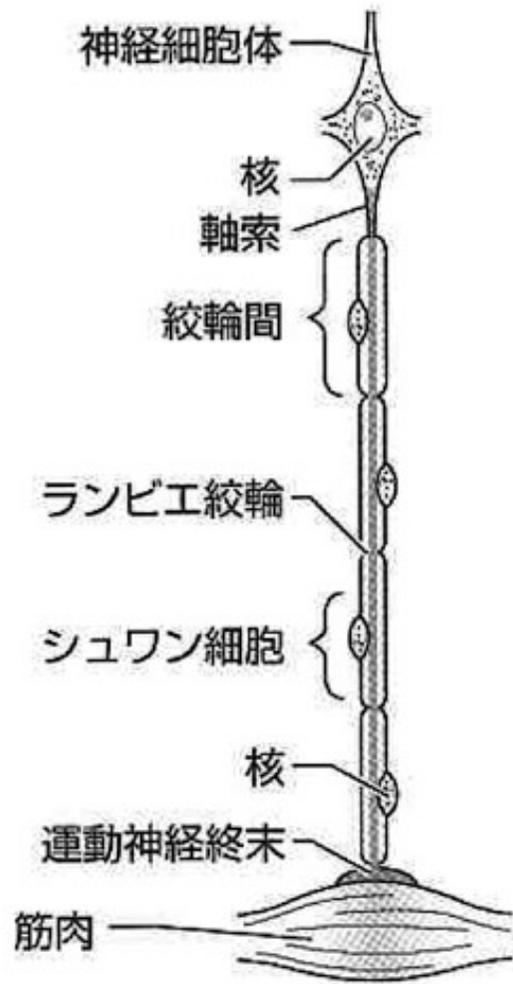
**Fnu4H1**

Normal	· · ·	ATT	GCC	GCC	CTG	· · ·
		Ile	Ala	Ala	Leu	
				↓		
Variant	· · ·	ATT	GCC	TCC	CTG	· · ·
		Ile	Ala	Ser	Leu	

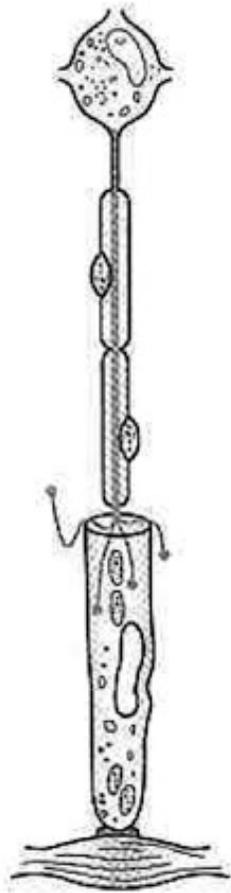


# エポン包埋切片が必要な疾患

- 末梢神経固有疾患は全て



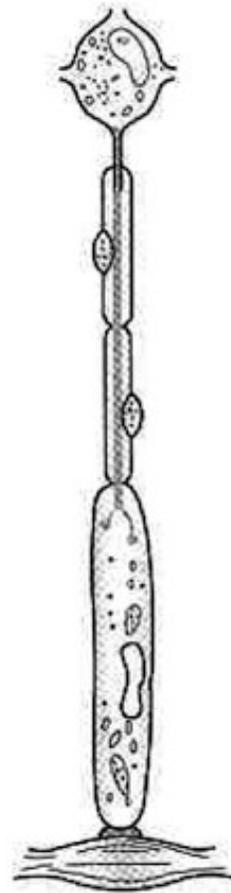
正常



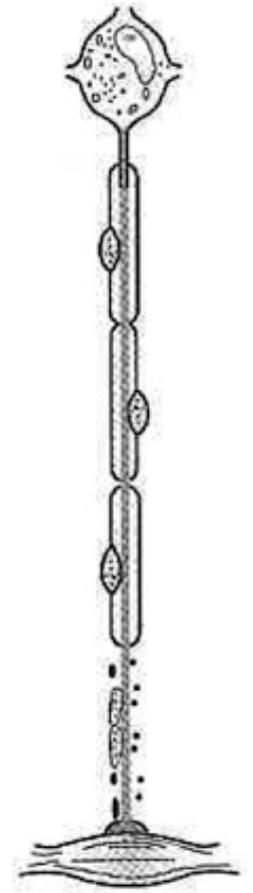
ワラー変性



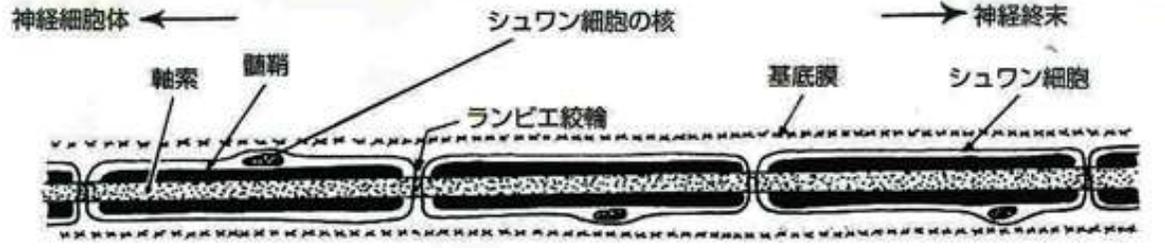
節性脱髄



軸索変性



dying-back  
ニューロパチー



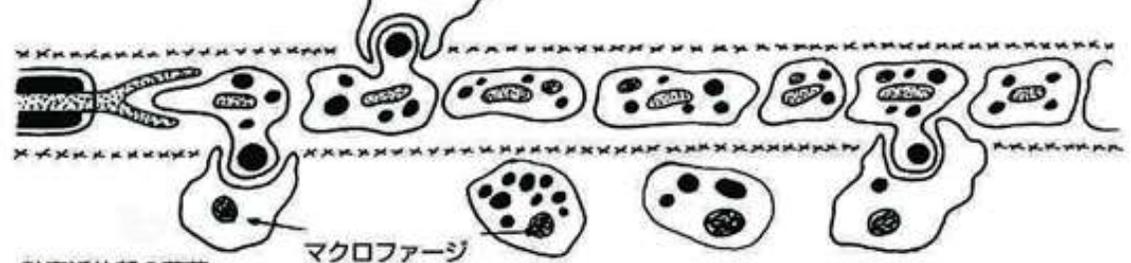
軸索離断



遠位の髄鞘および軸索成分の変性

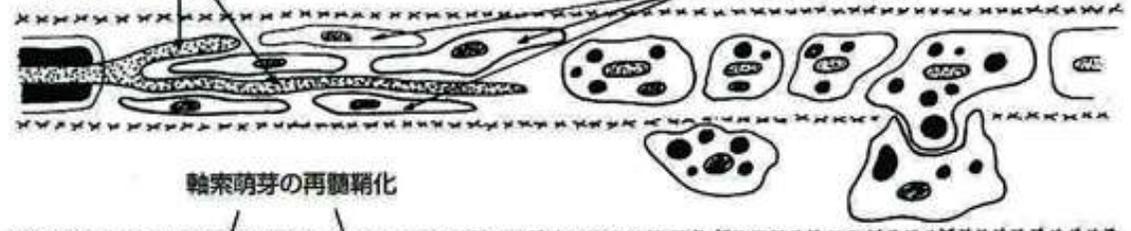


マクロファージによる髄鞘と軸索の残骸の除去

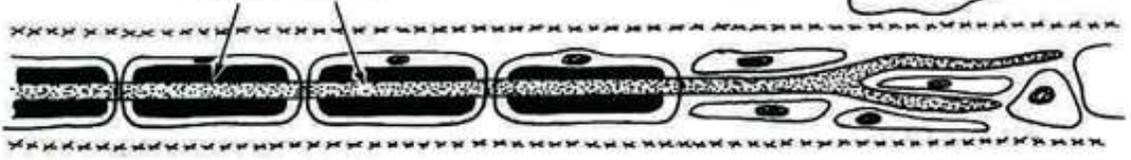


軸索近位部の萌芽

シュワン細胞の増殖

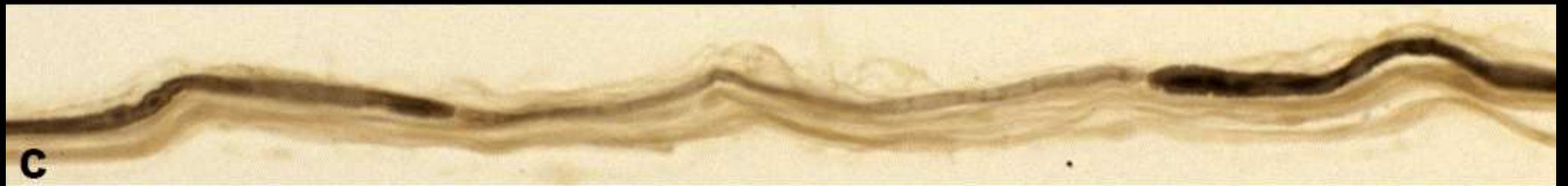
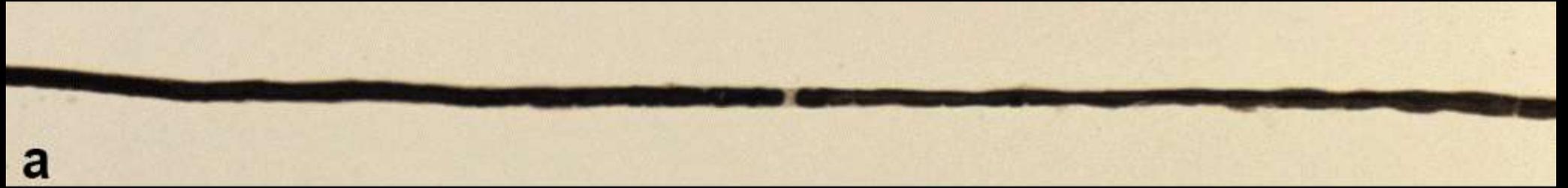


軸索萌芽の再髄鞘化

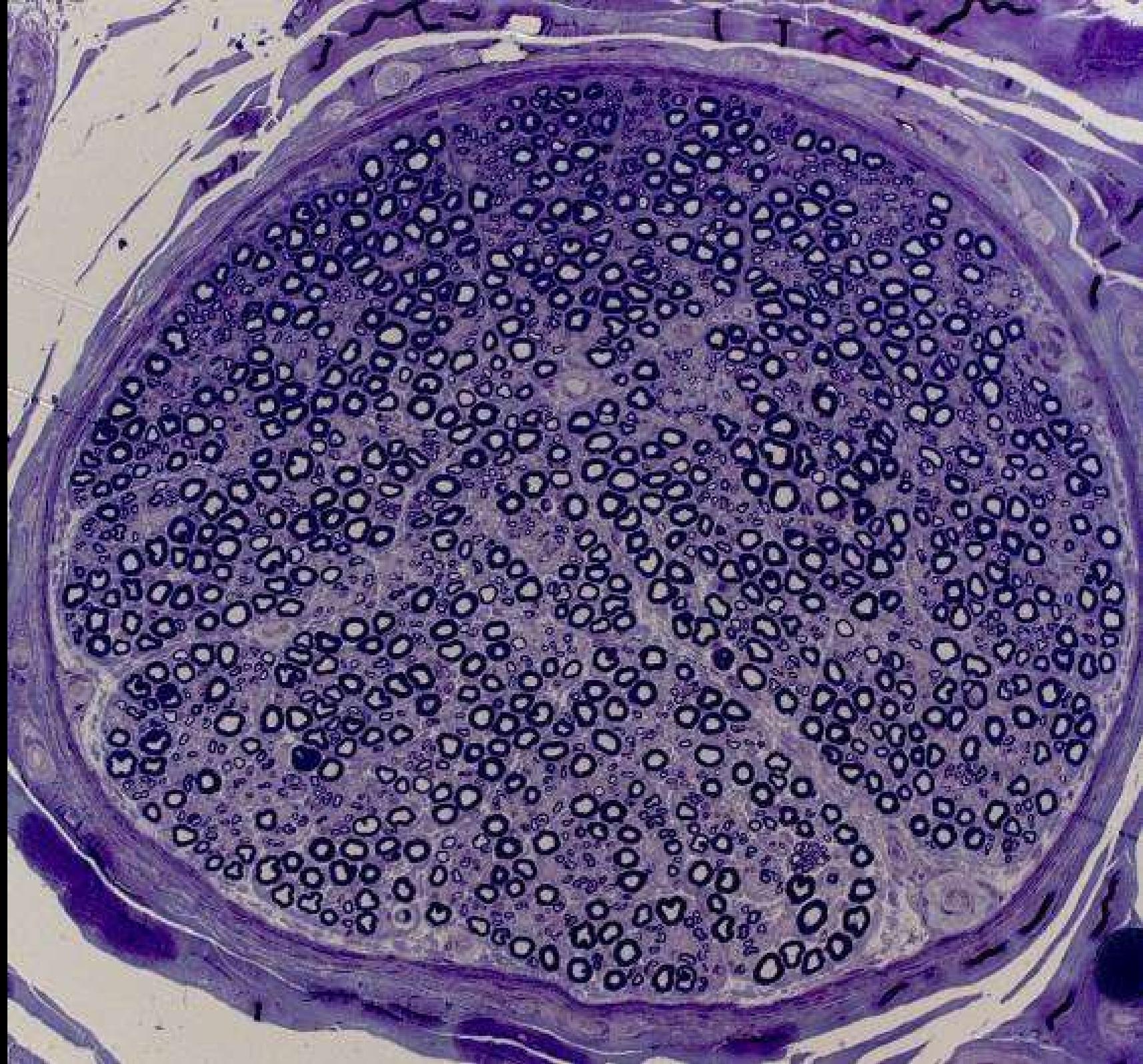


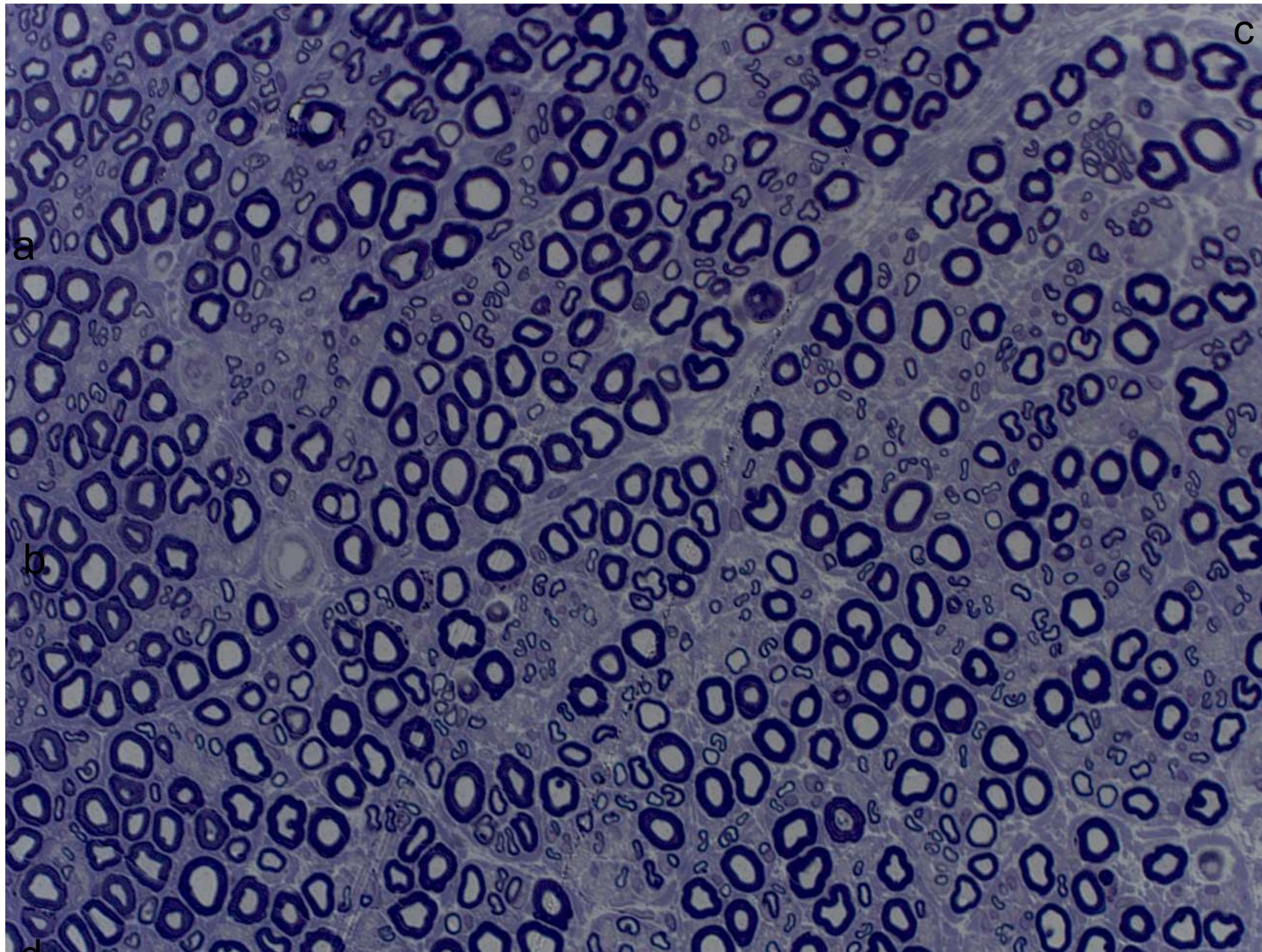
神経線維の完全な再生











a

b

d

c

Control

80M

無髓線維

小血管

髓鞘 (ミエリン)

大径有髓線維

神経周膜

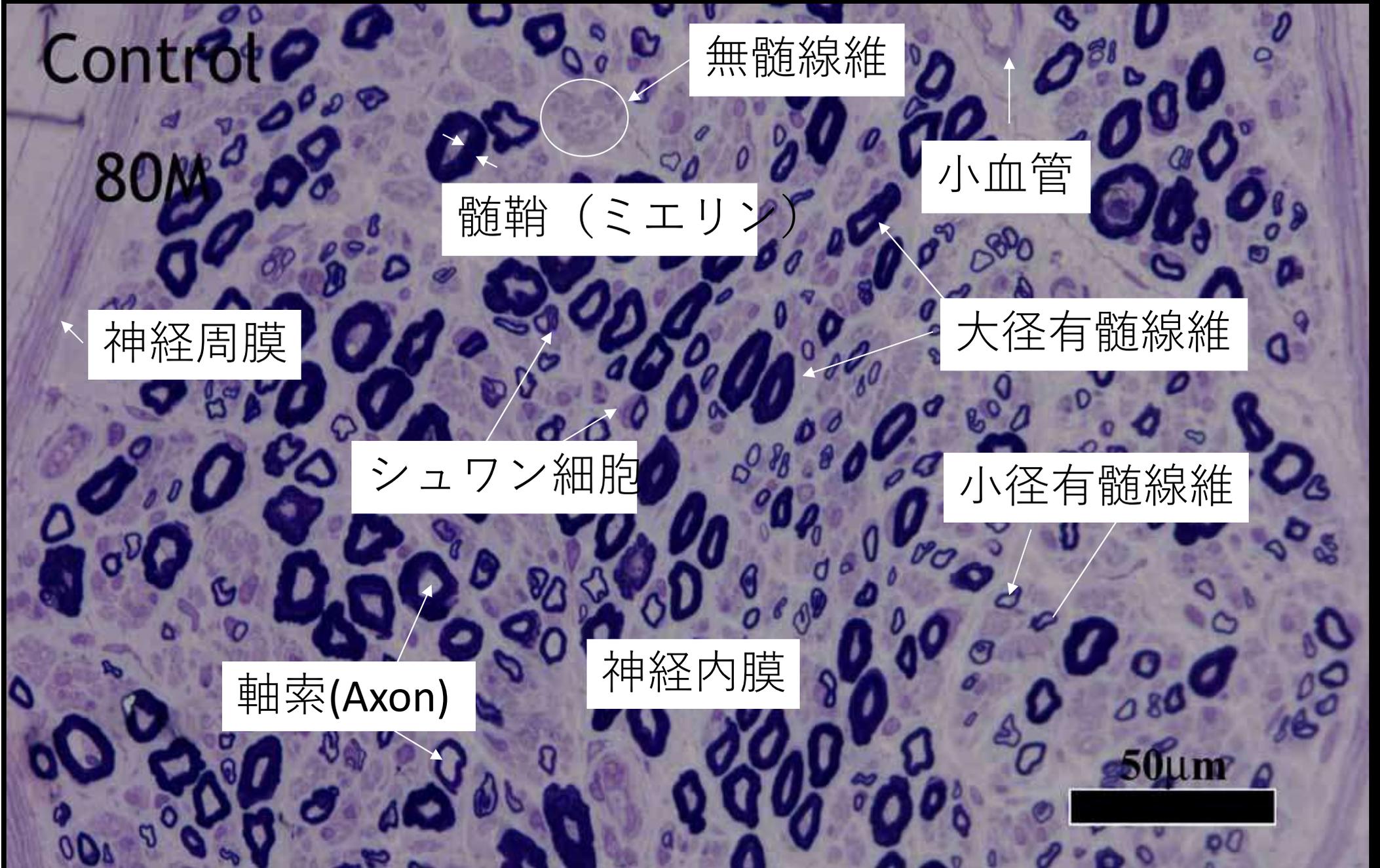
シュワン細胞

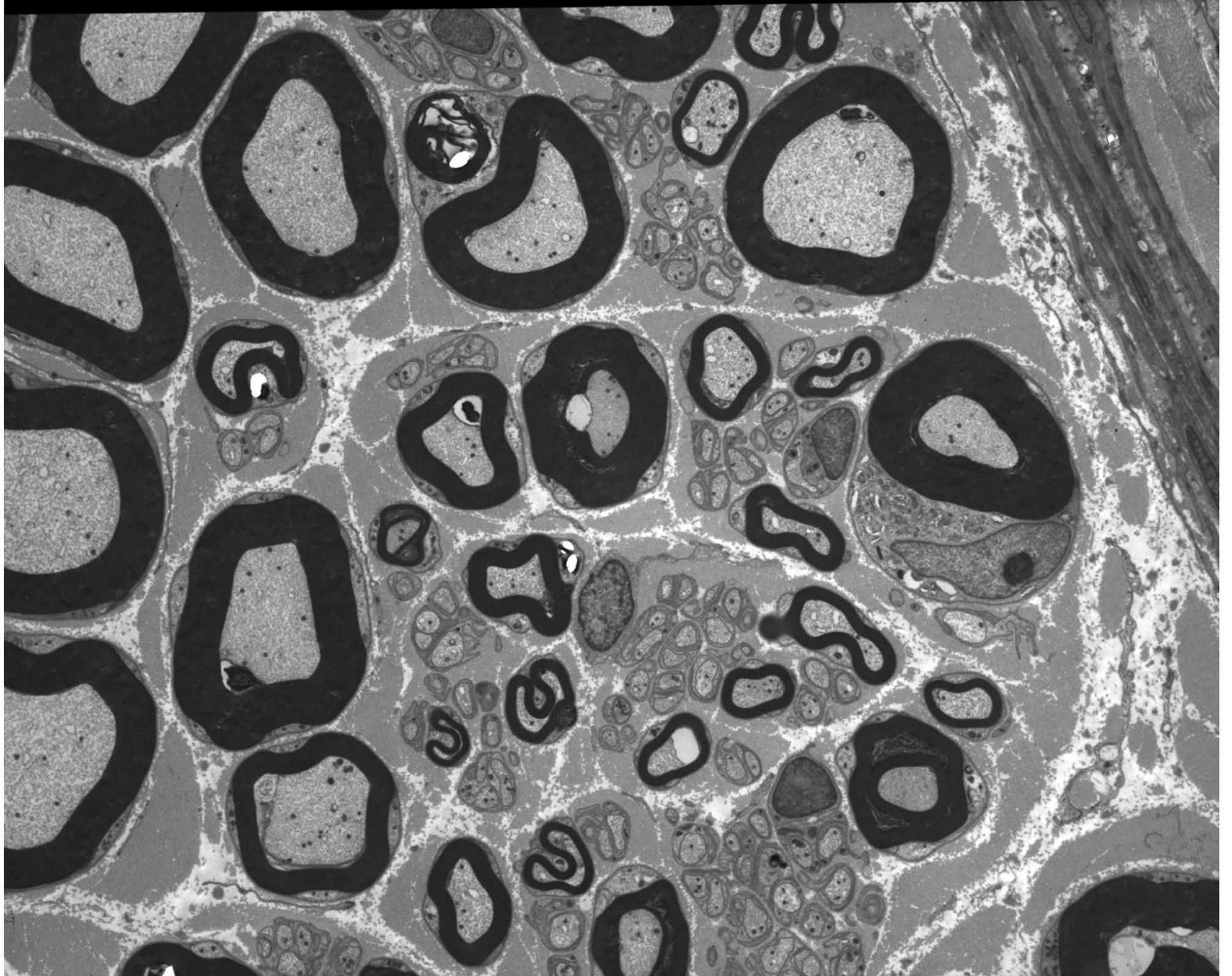
小径有髓線維

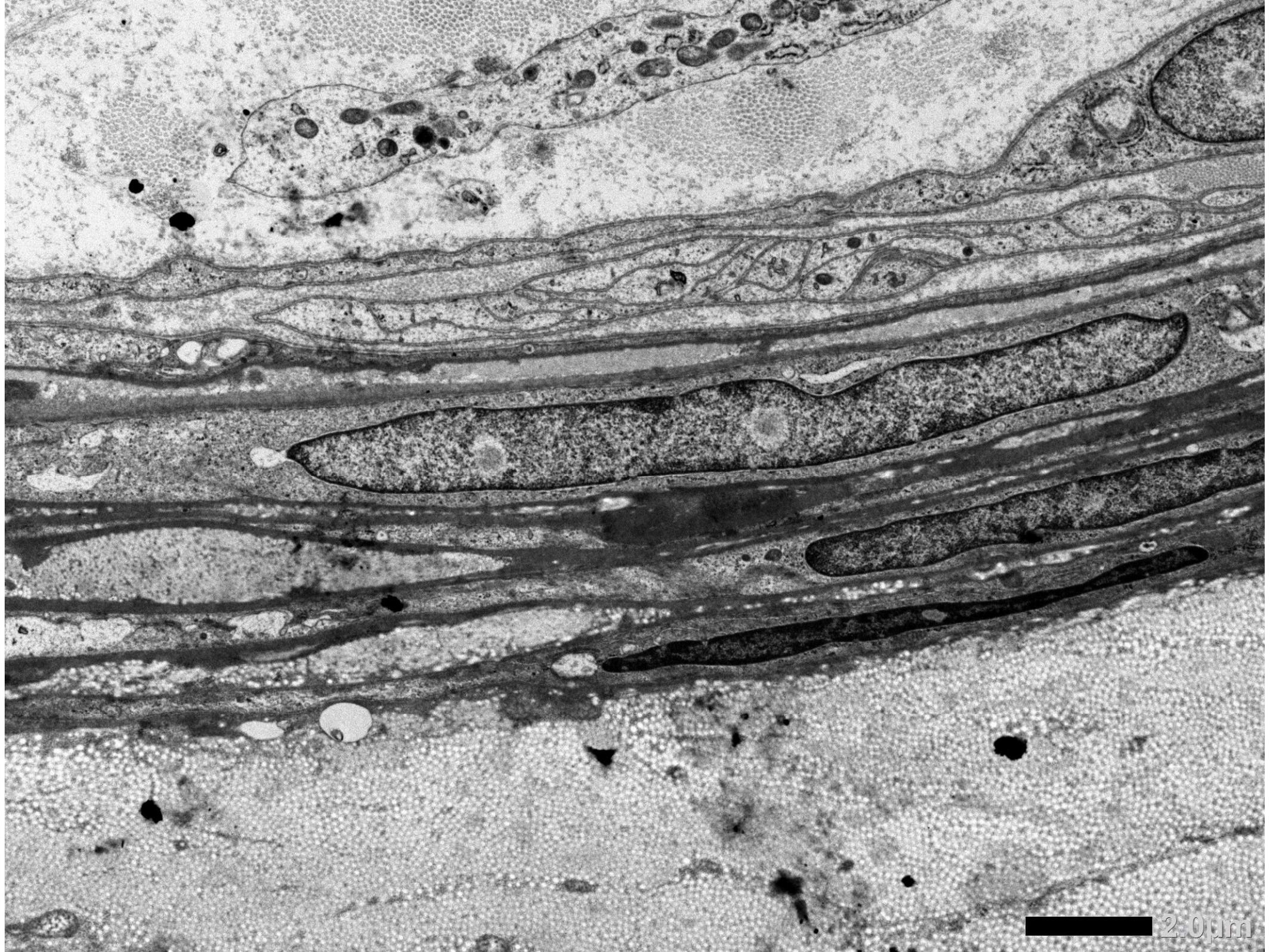
軸索 (Axon)

神経内膜

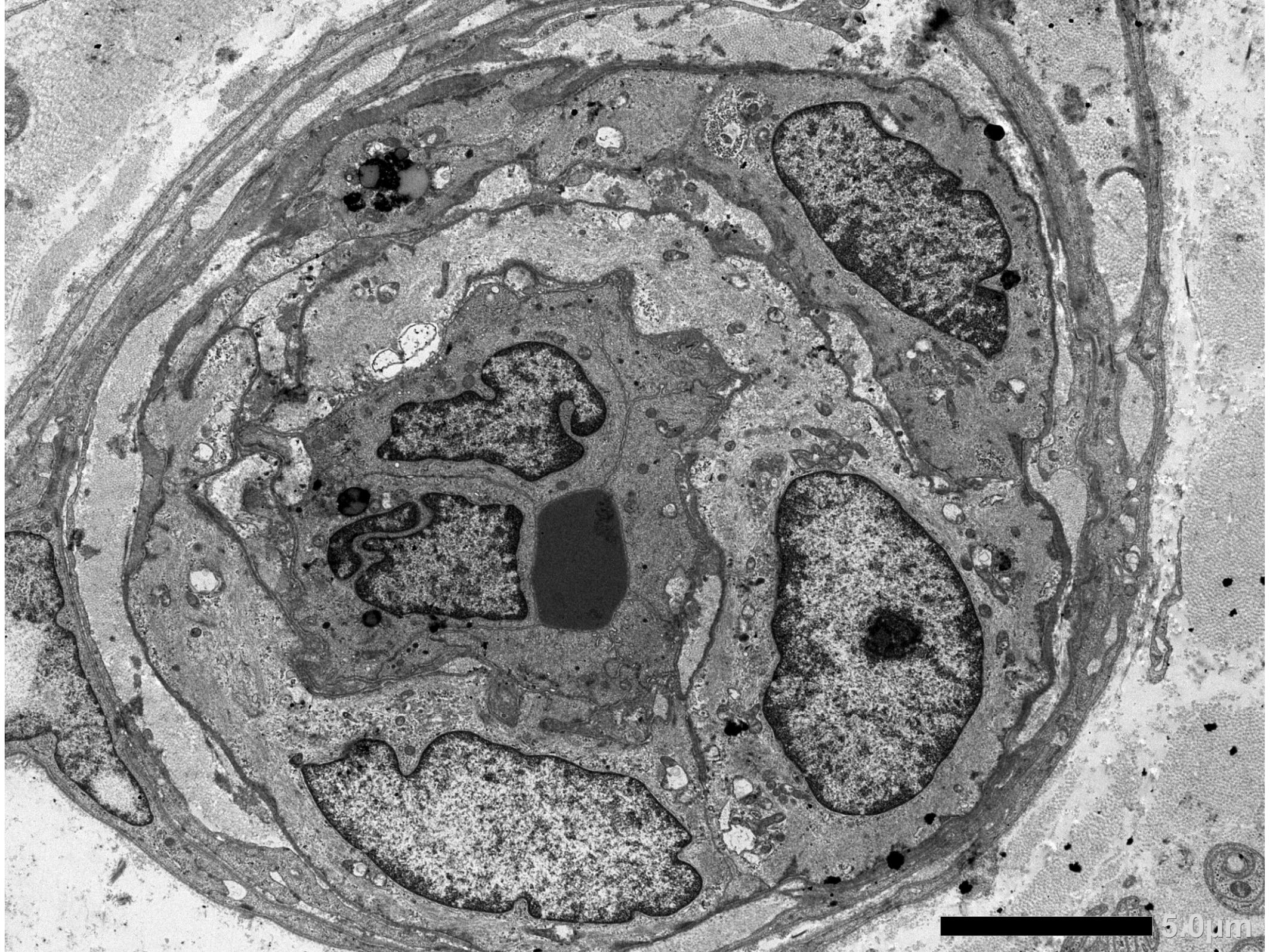
50μm



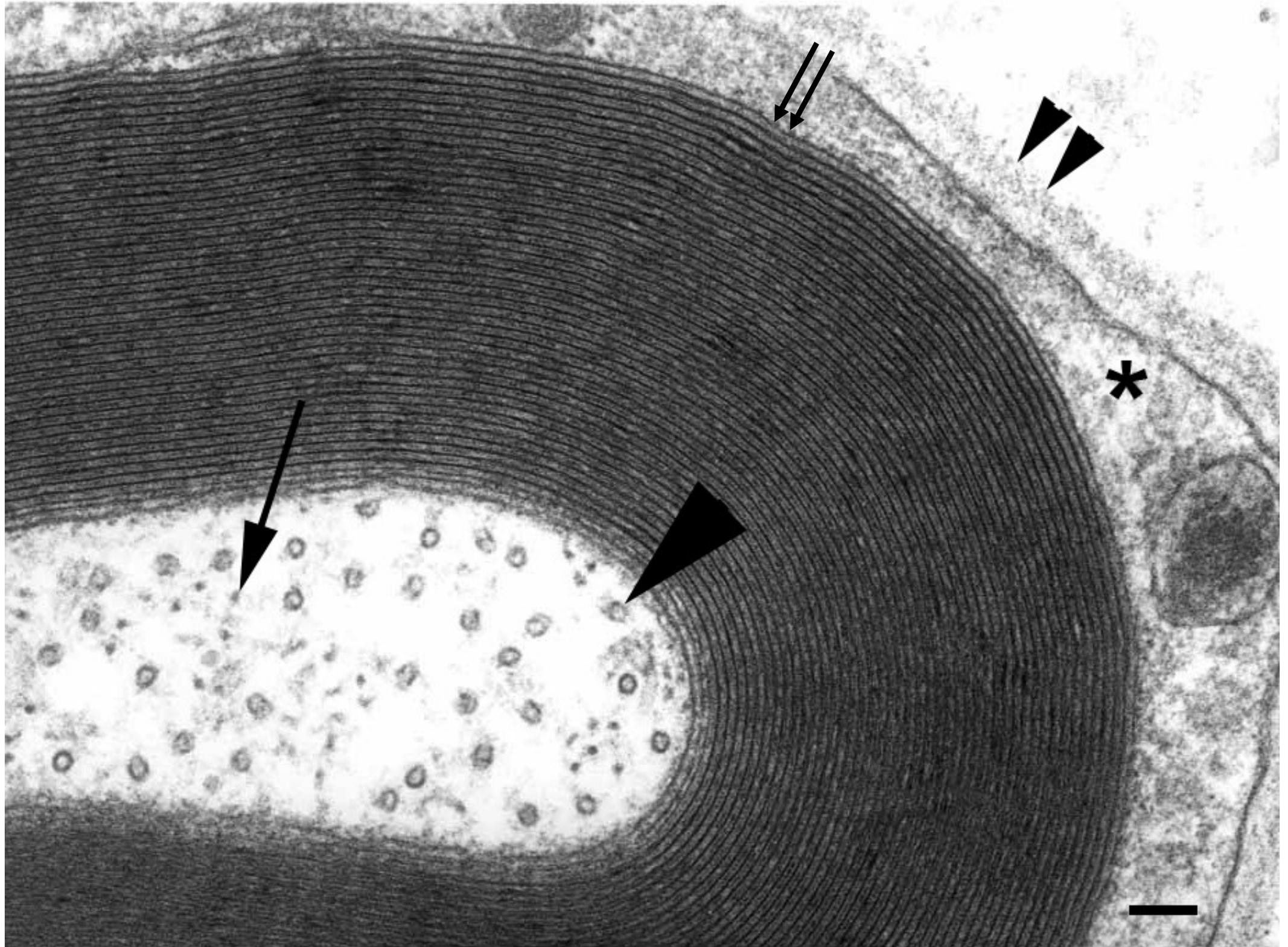


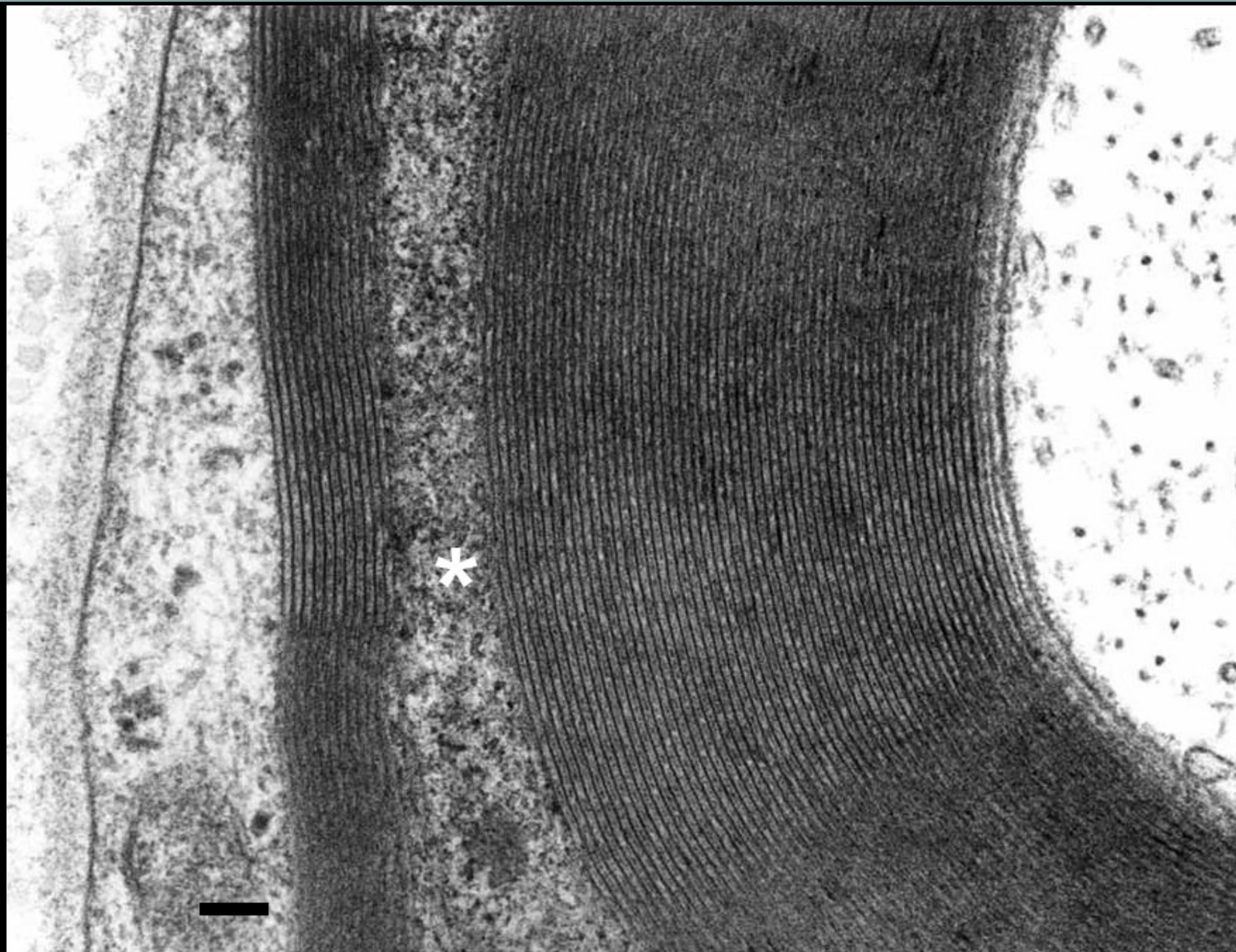


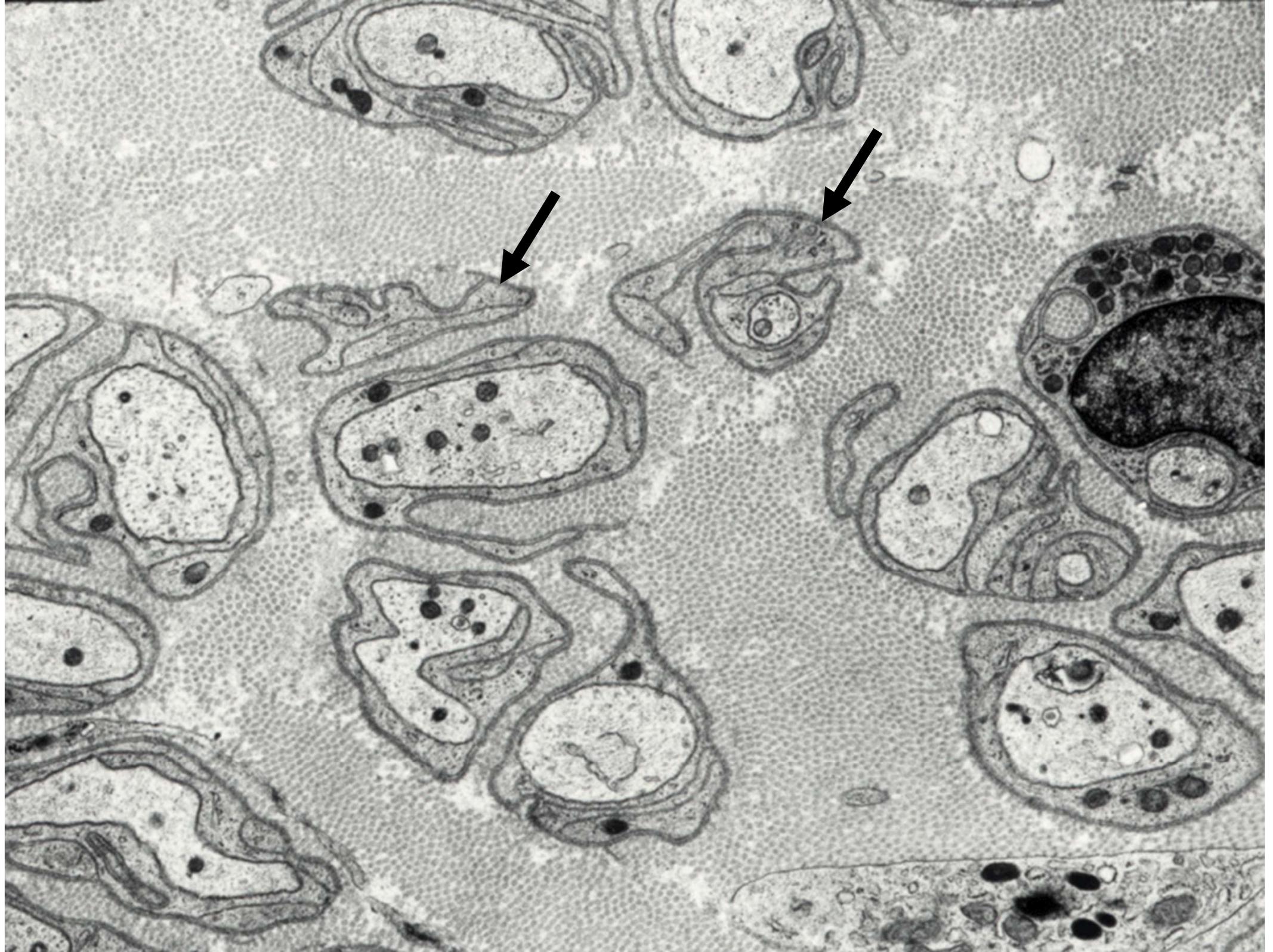
2.0µm

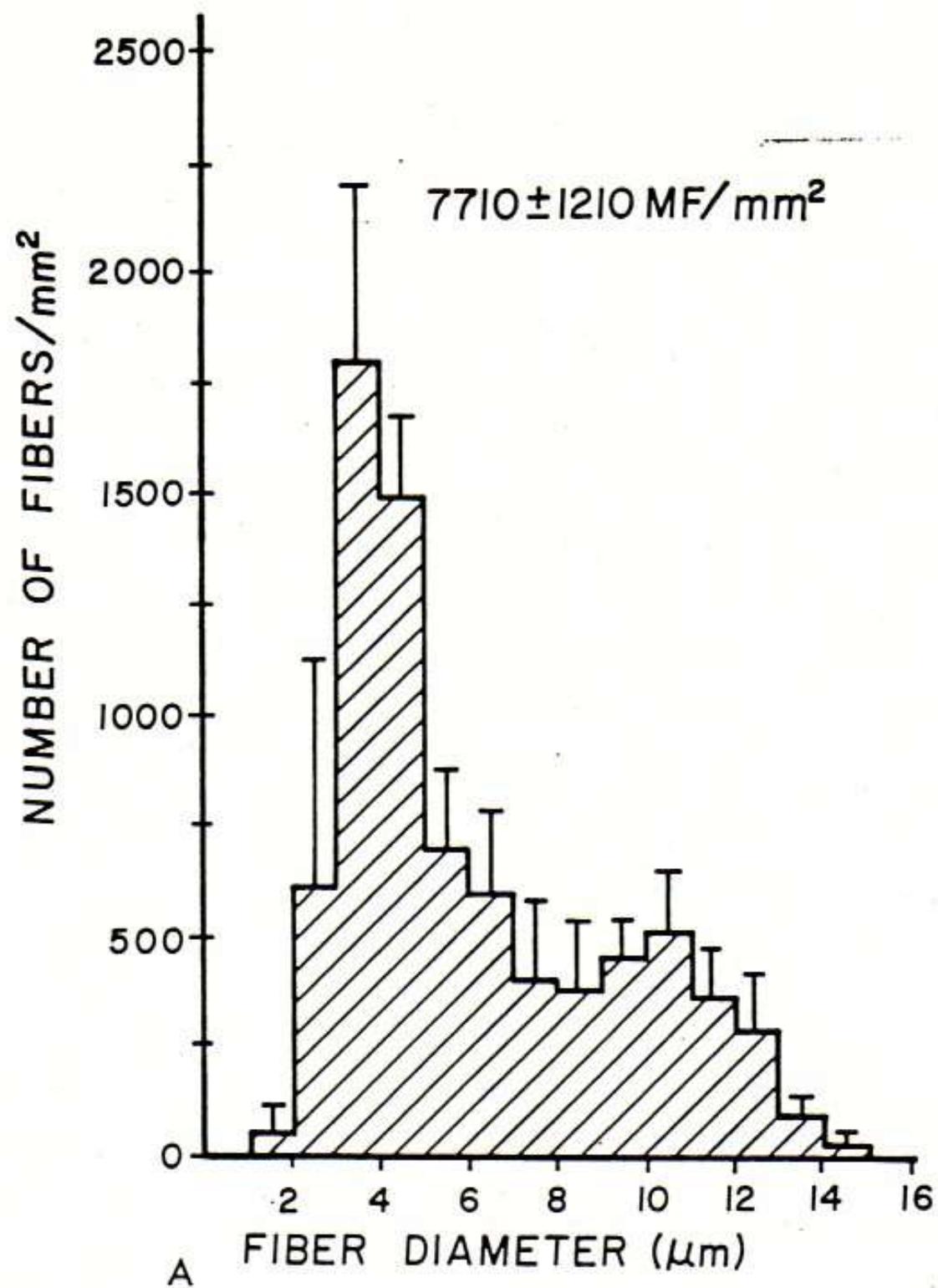


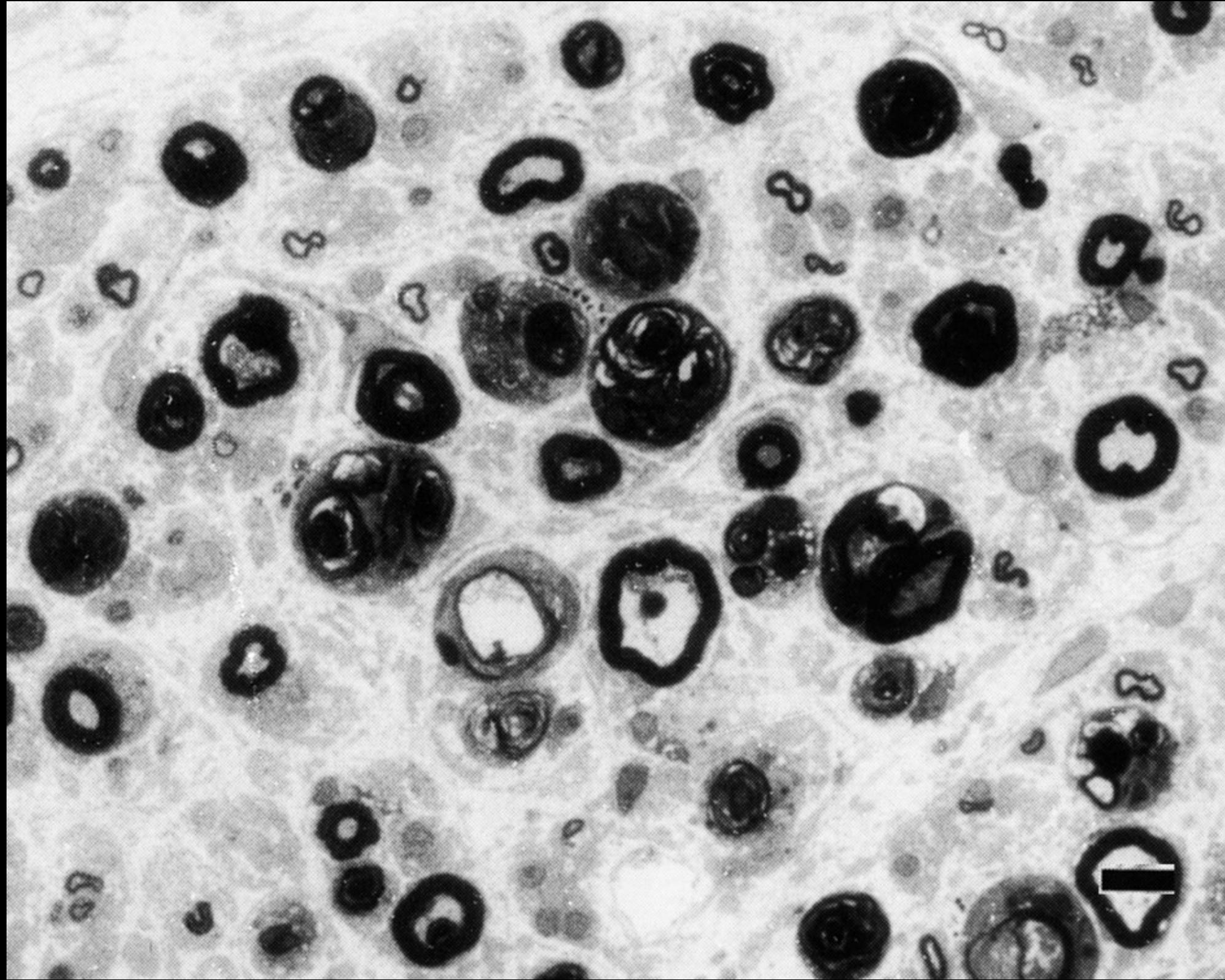
5.0 μm

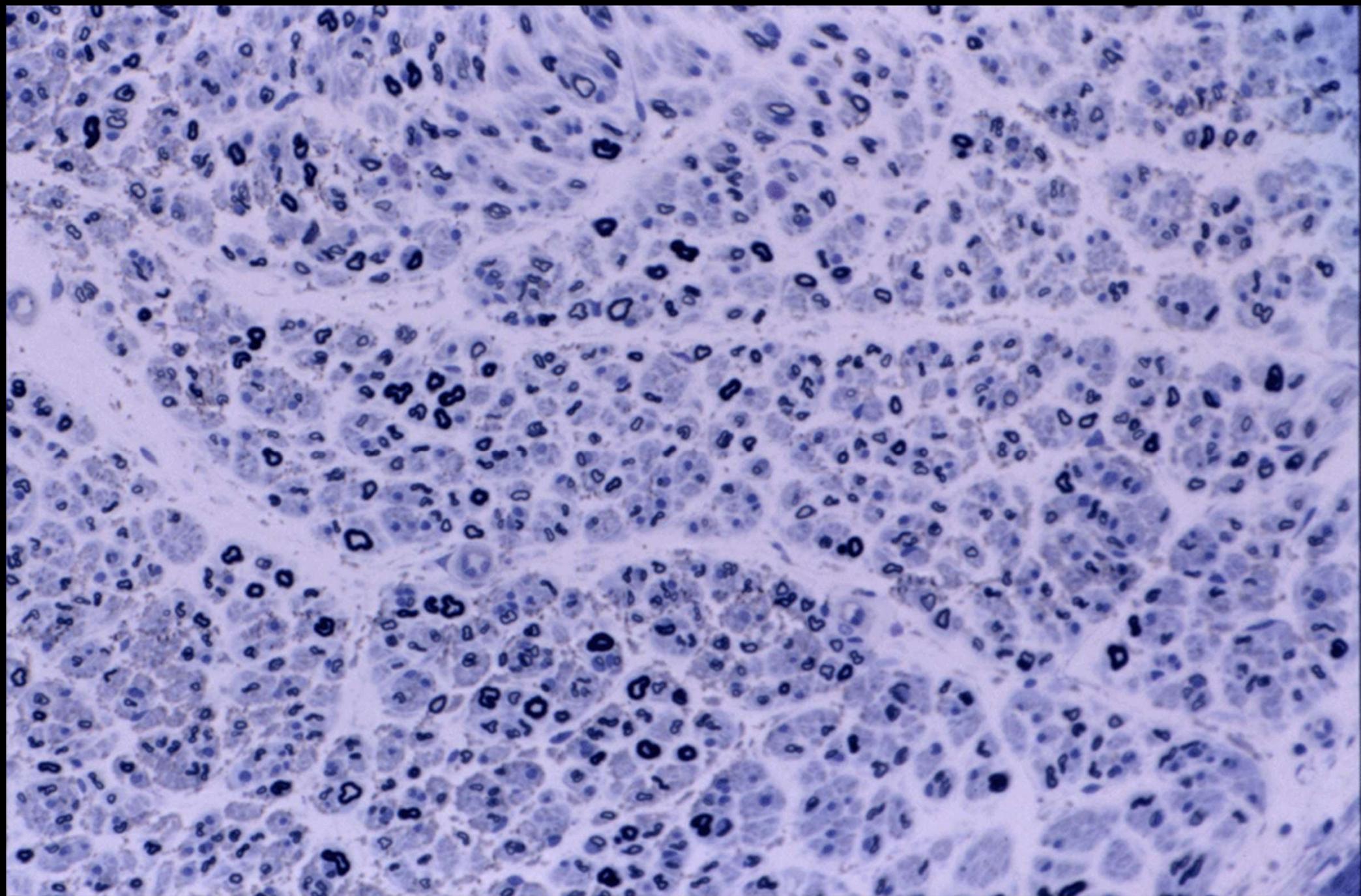




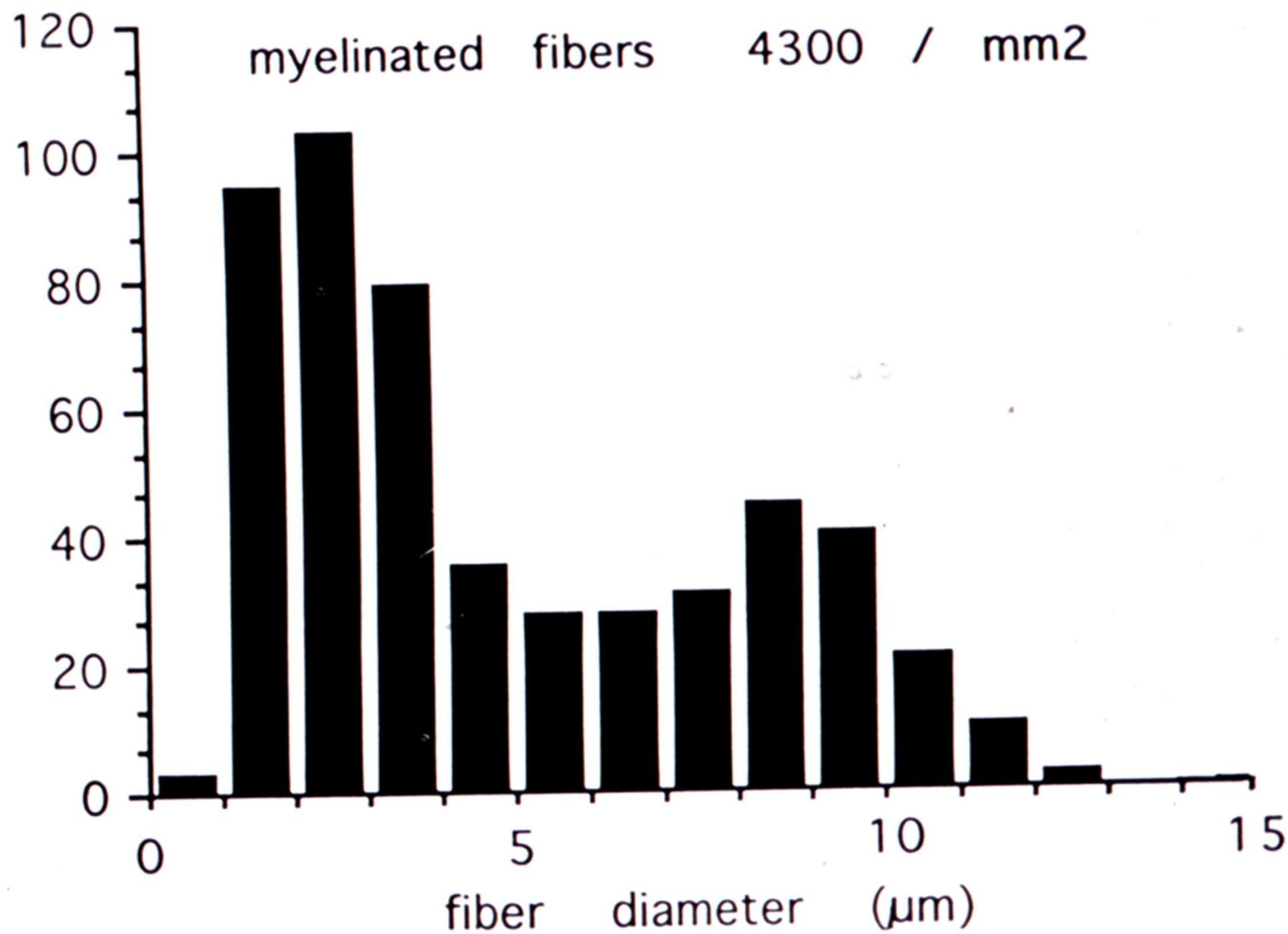


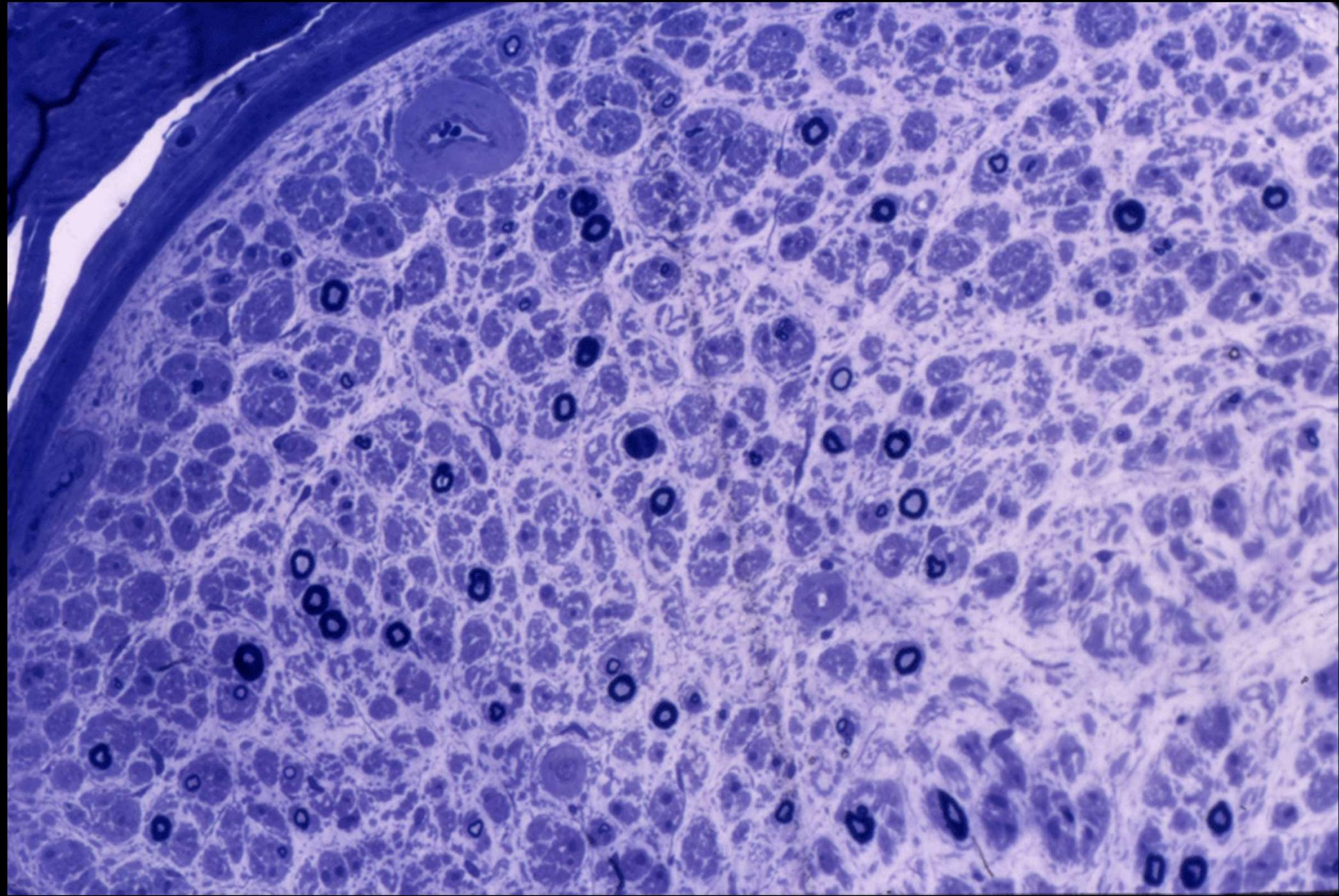




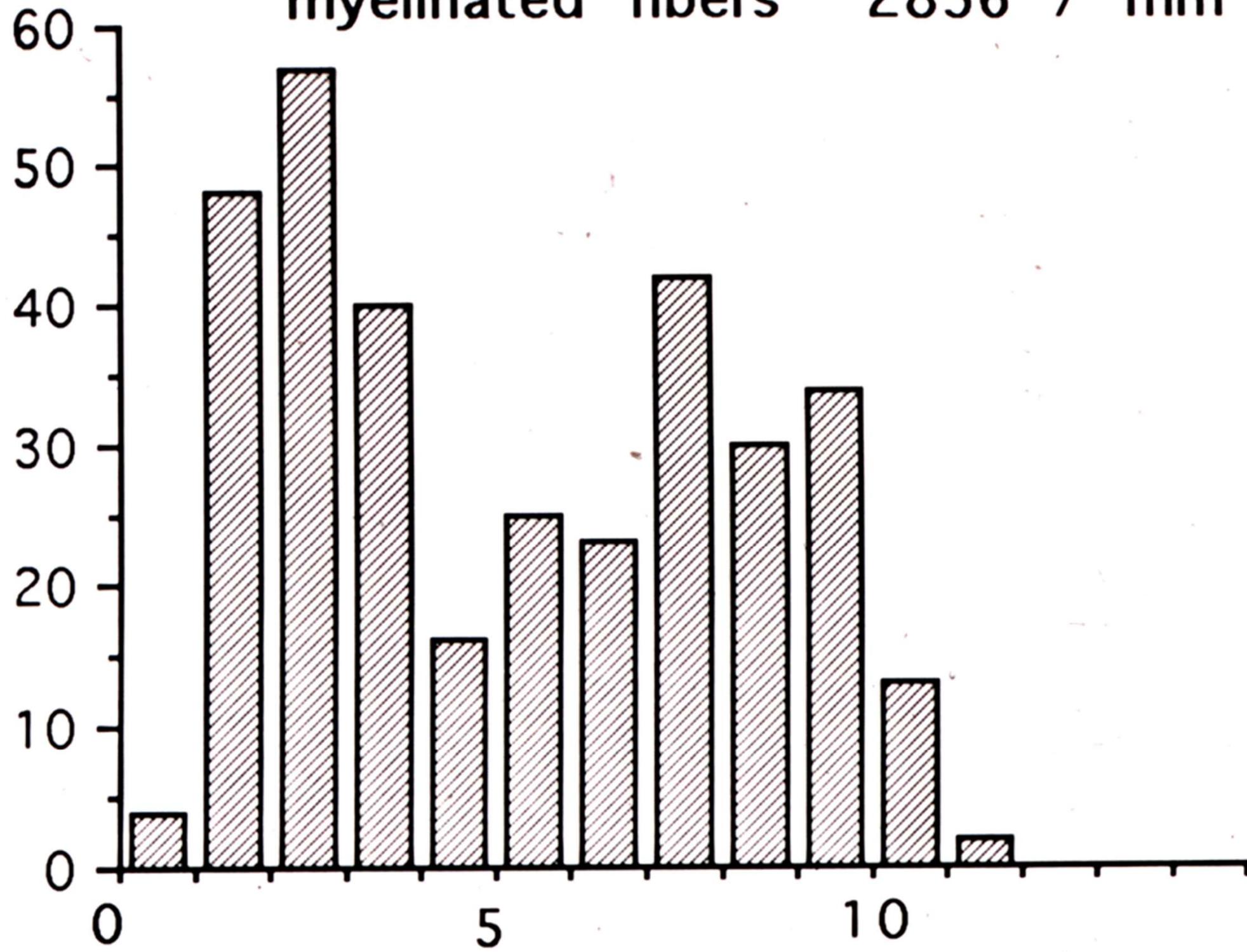


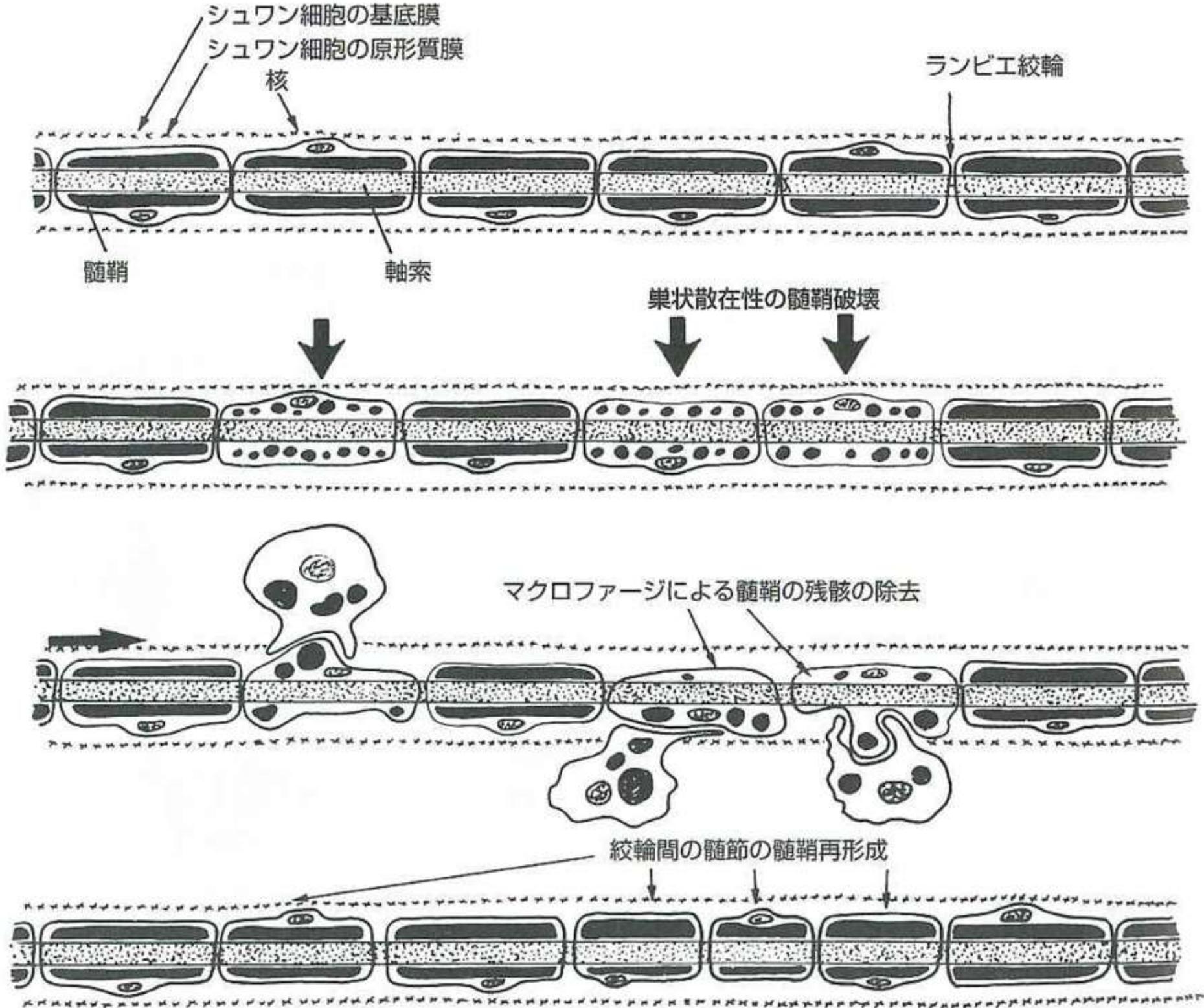
B2351 H.K. 69F Lt sural nerve biopsy





myelinated fibers 2856 / mm<sup>2</sup>



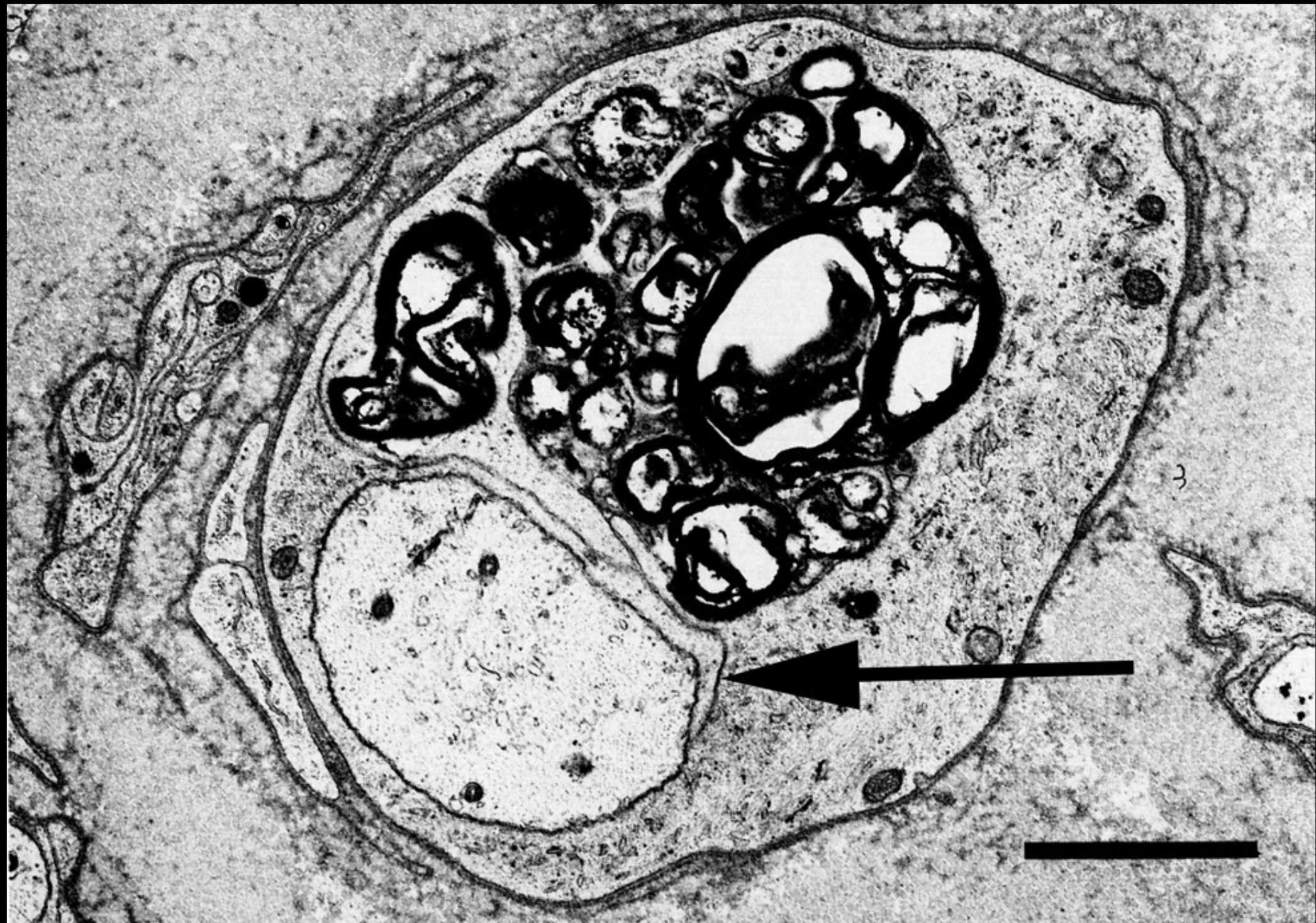


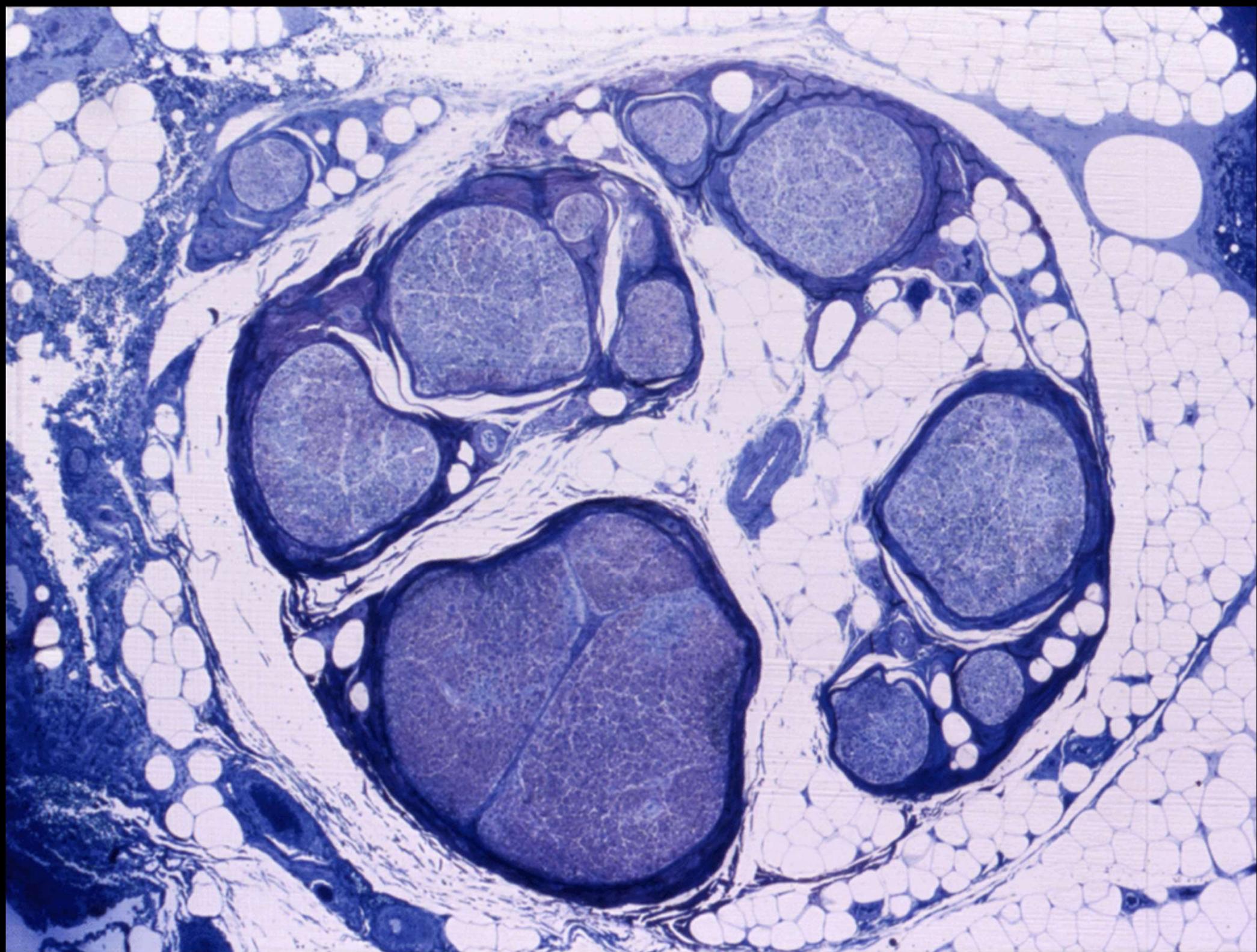
シュワン細胞の基底膜  
 シュワン細胞の原形質膜  
 核  
 ランビエ絞輪  
 髄鞘  
 軸索

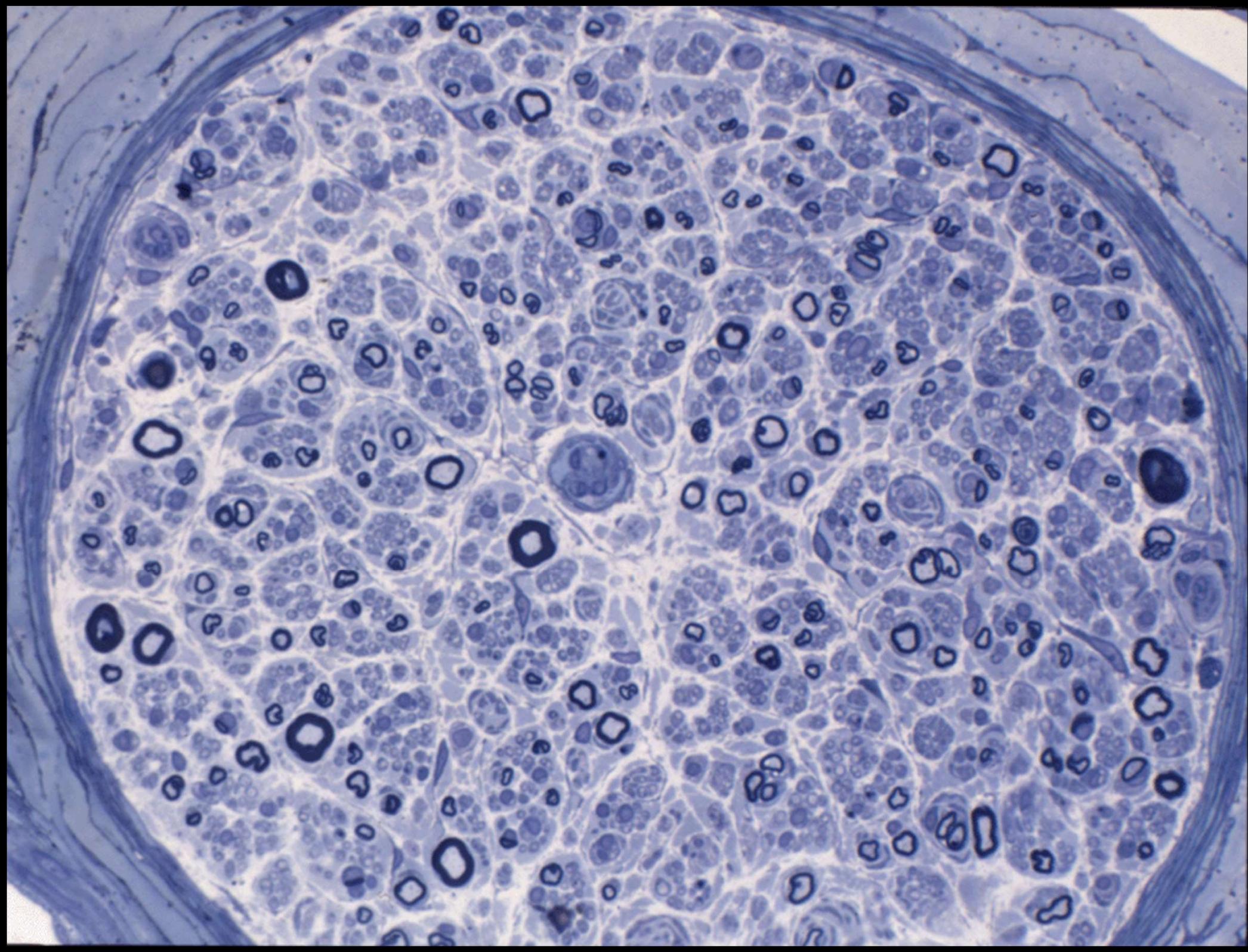
巣状散在性の髄鞘破壊

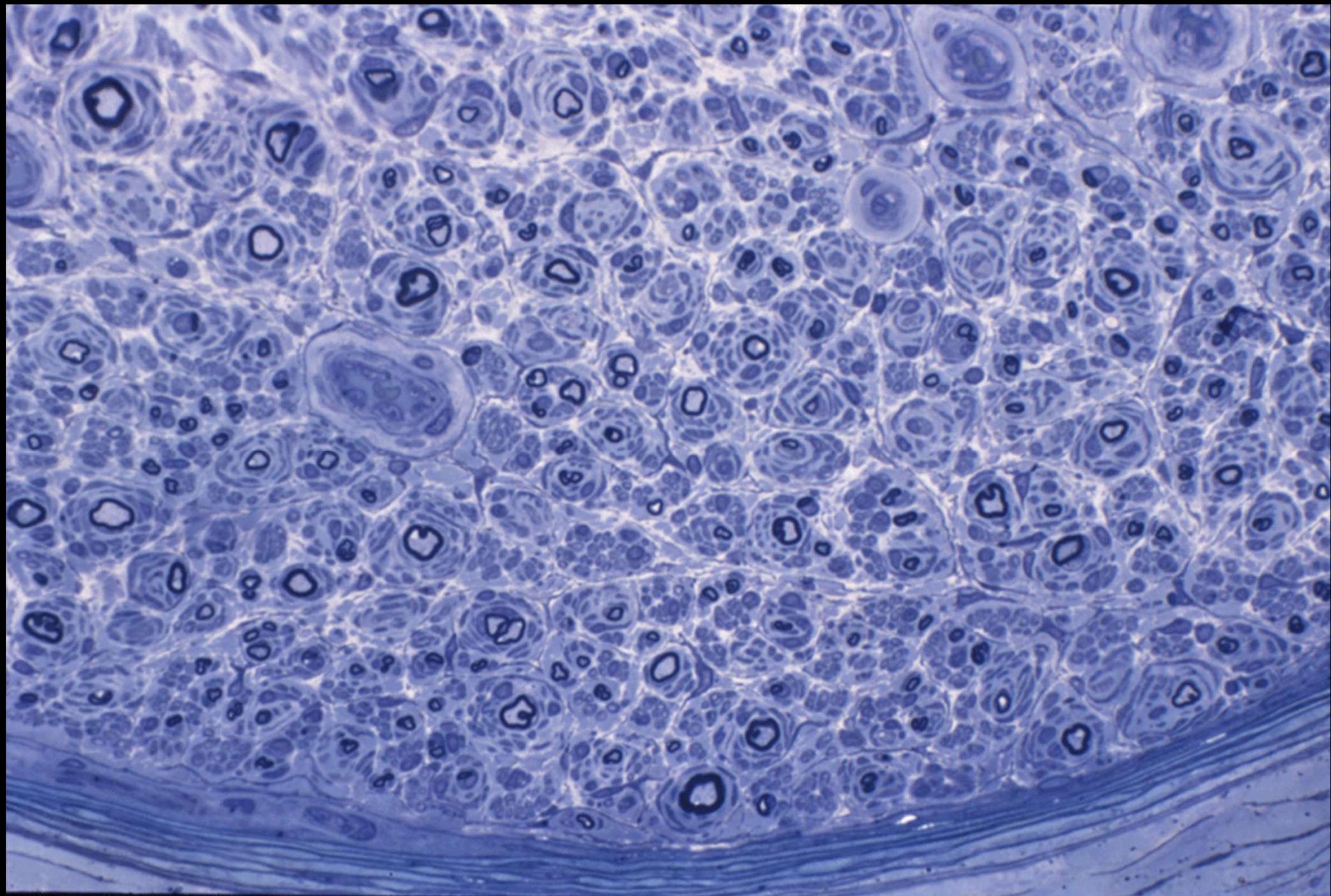
マクロファージによる髄鞘の残骸の除去

絞輪間の髄節の髄鞘再形成









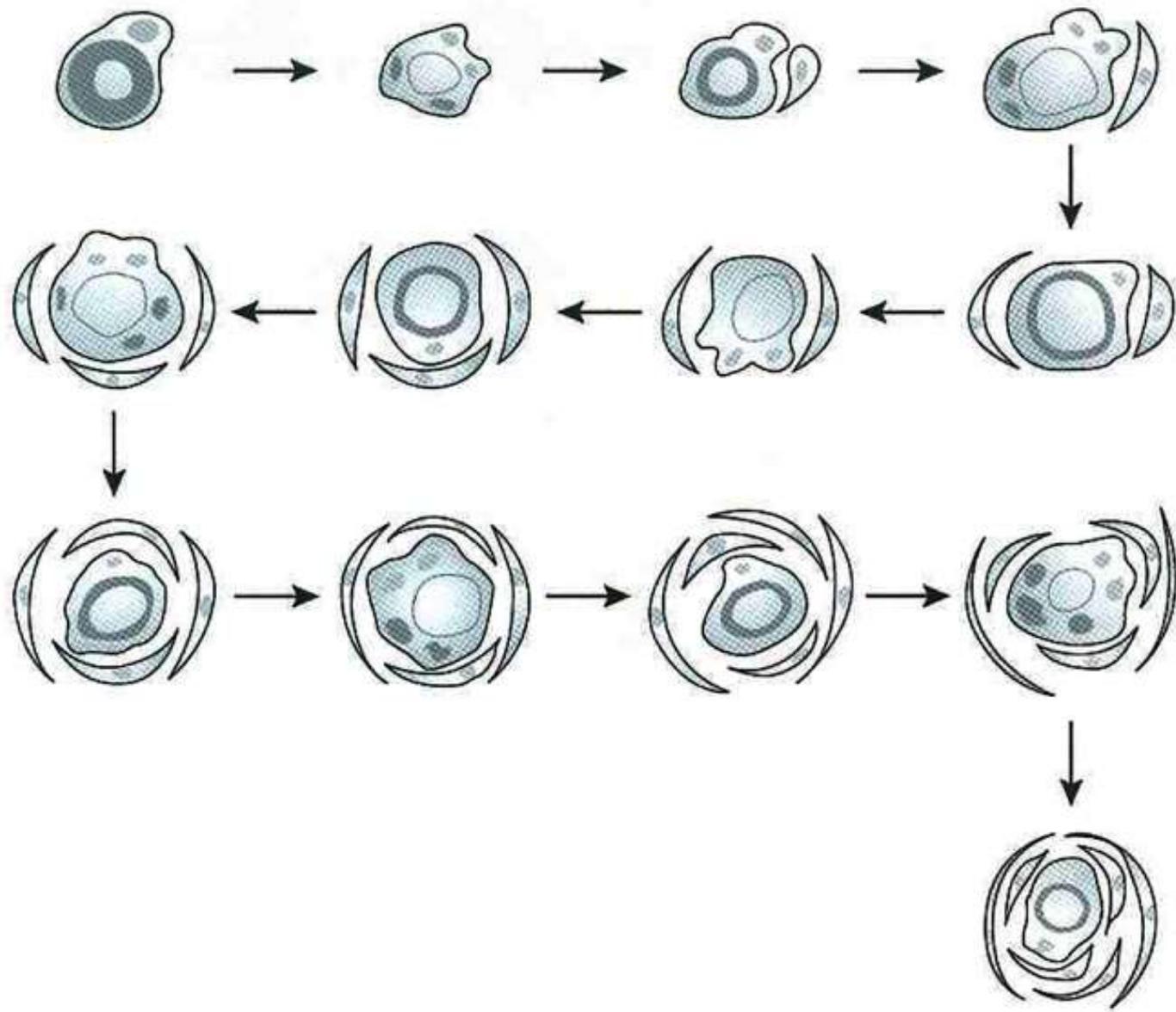
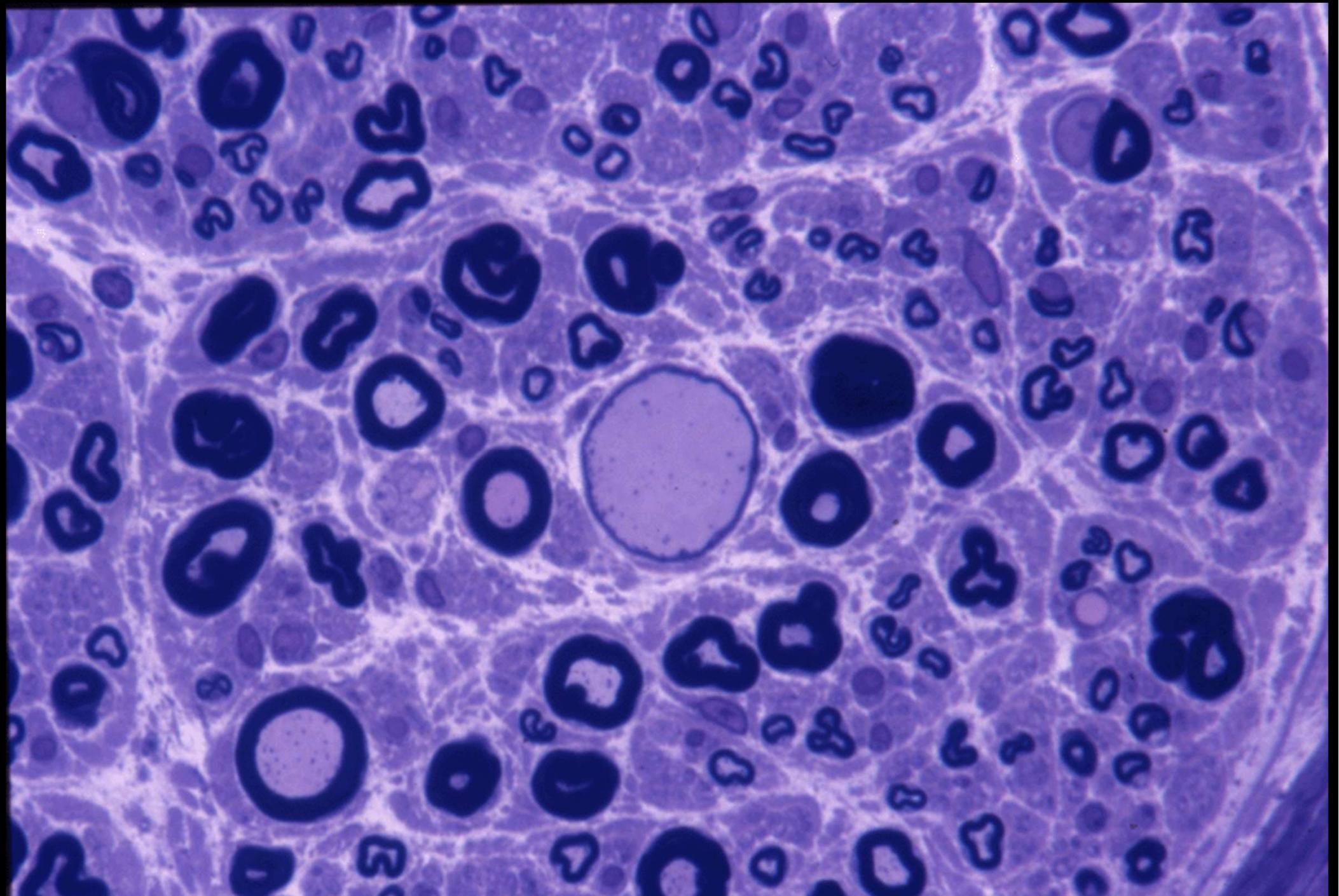
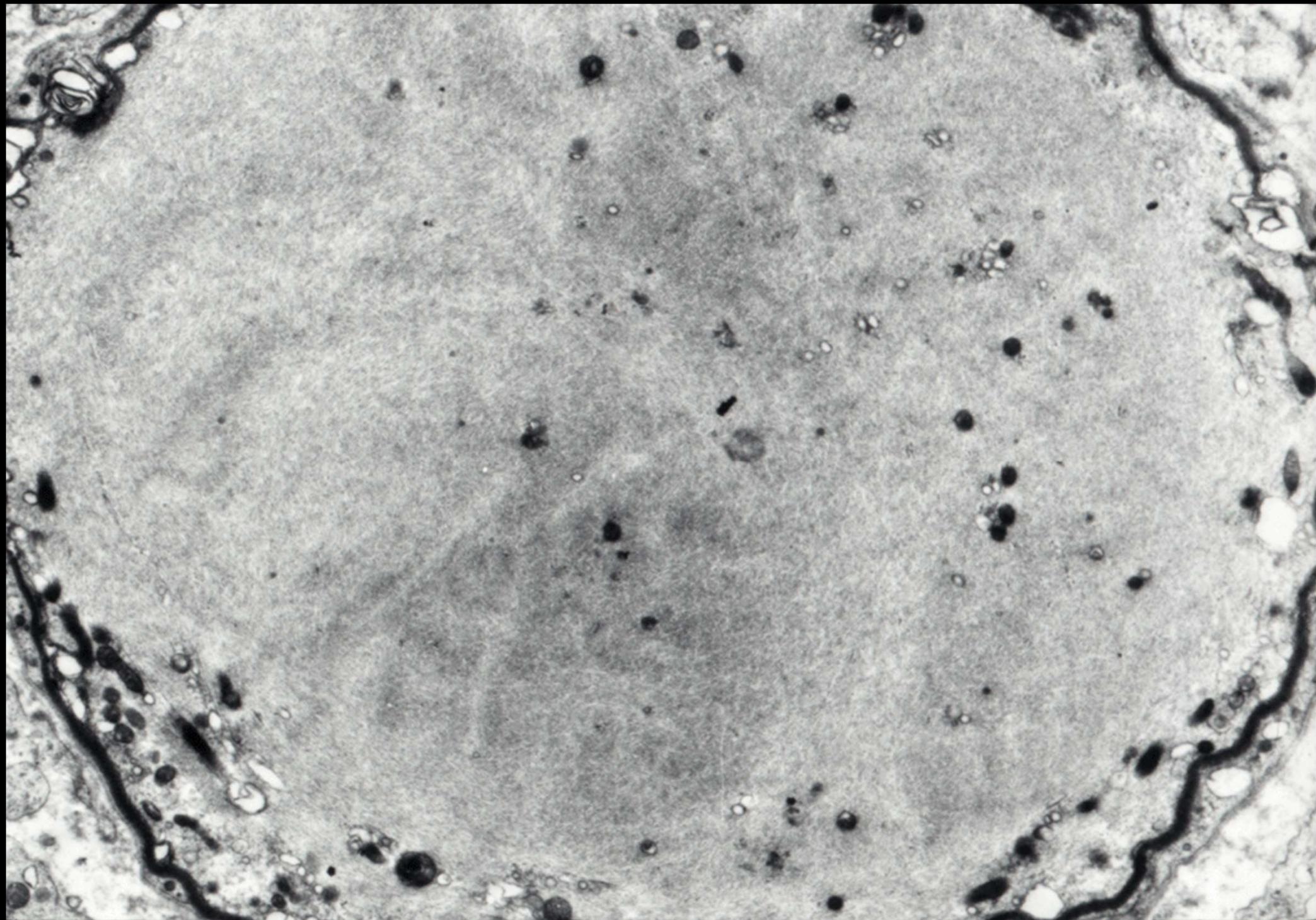


図 14-10

オニオンバルブの形成過程

(Bradley WG.: *Disorders of peripheral nerves*. Oxford, Blackwell, 1974, p. 144 より改変して引用)

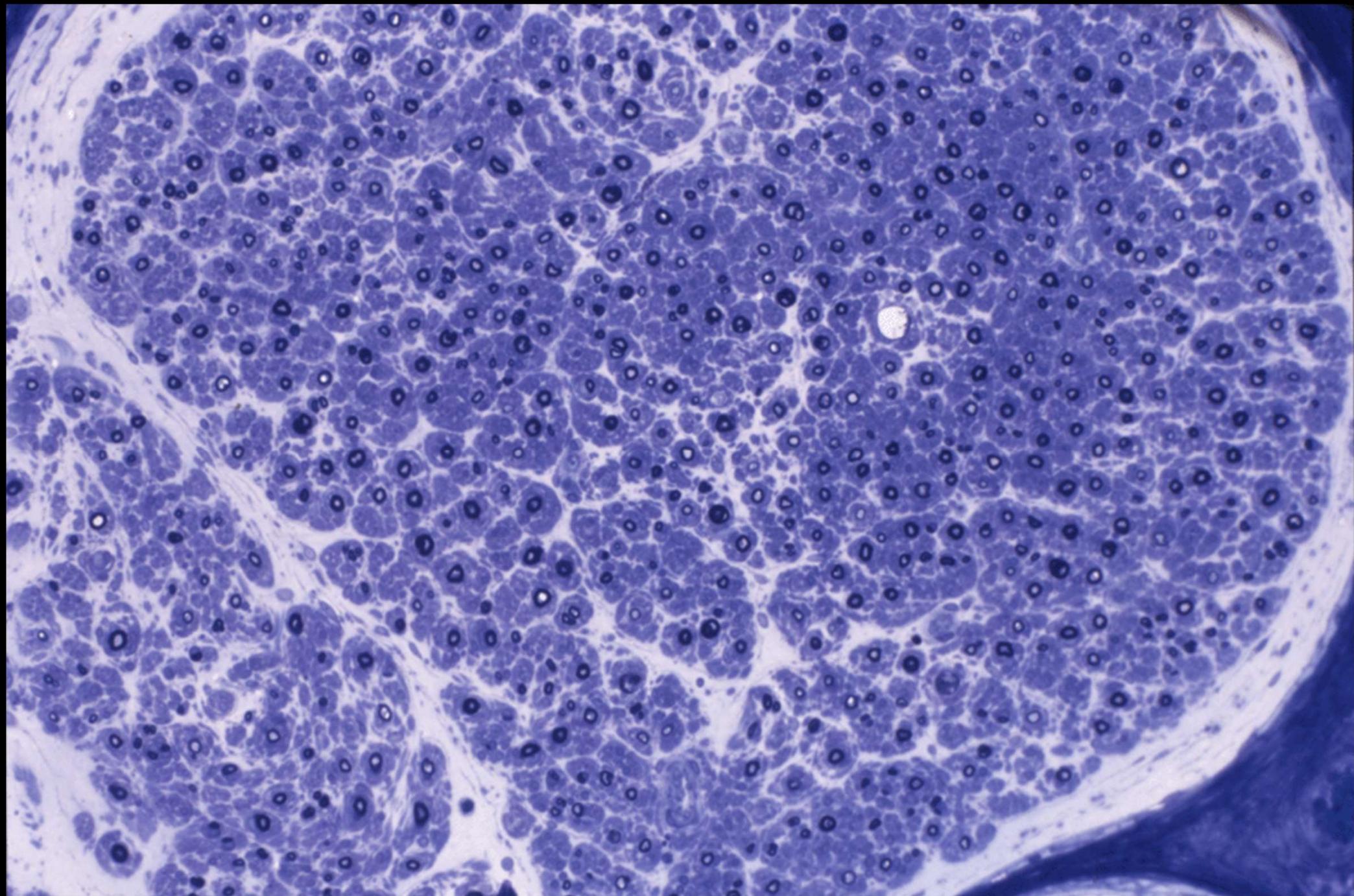




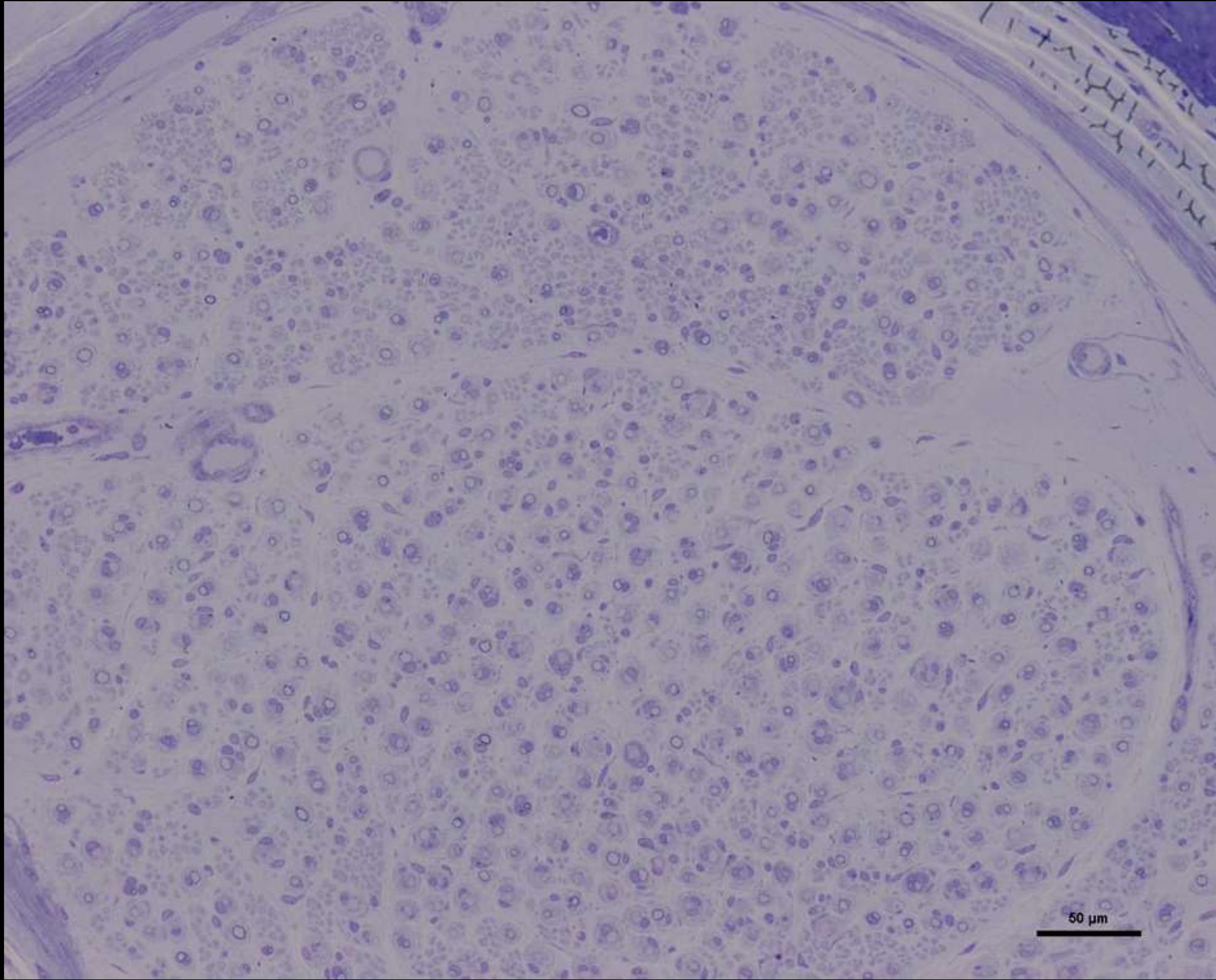


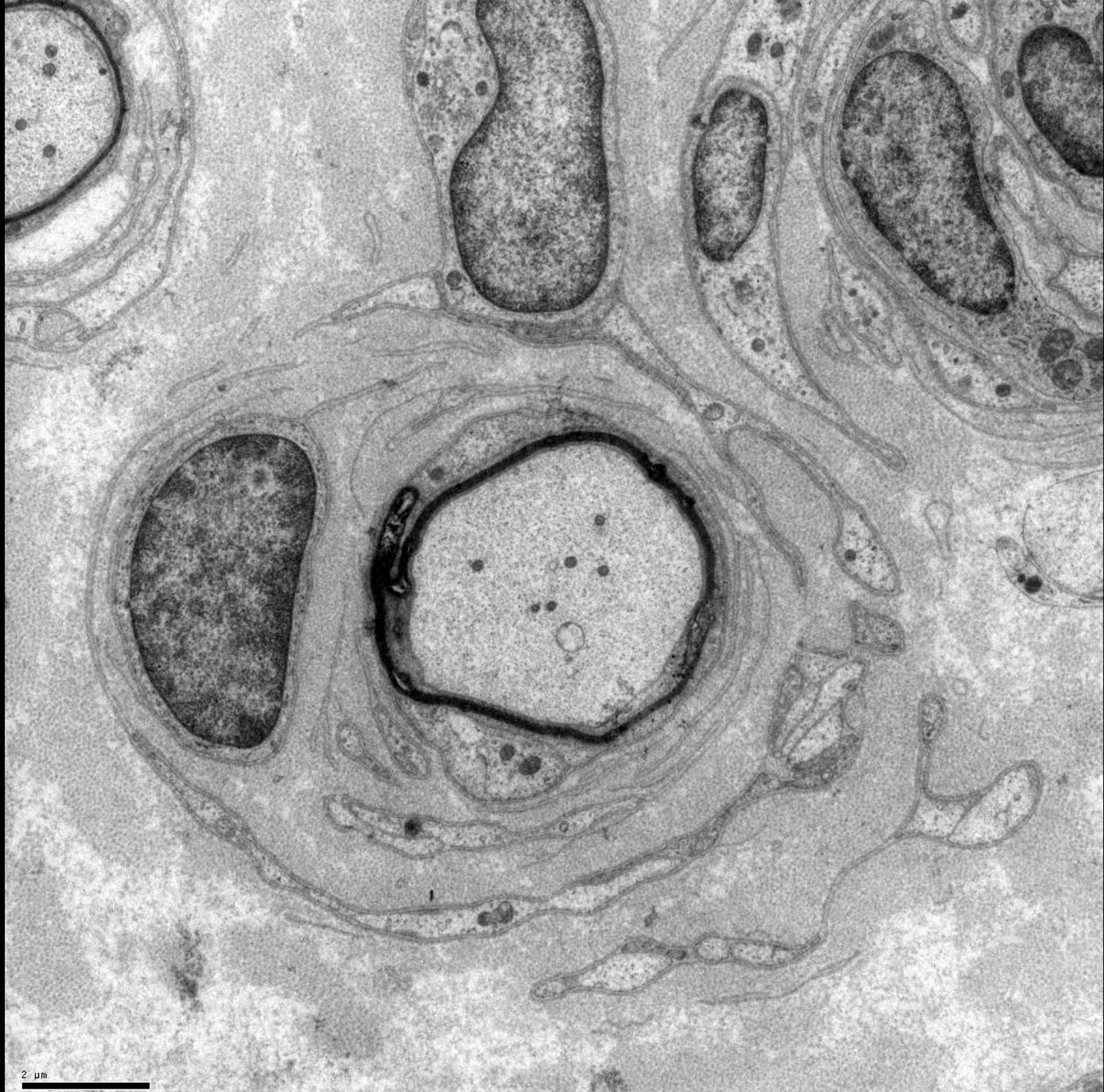
CMT	HMSN	遺伝形式	遺伝子 (座)	臨床症状
1=常染色体優性脱髄性ニューロパチー=末梢神経伝導速度がすべて 38m/s 以下				
1A	I	AD	<i>PMP22</i> dup	古典的 CMT 病 より重症 古典的 CMT 病
1A	I	AD	<i>PMP22</i> mut	
1B	I	AD	<i>P0</i> mut	
1C	I	AD	<i>lipopolysaccharide-induced tumor necrosis factor-alpha</i> mut	
1D	I	AD	<i>EGR2</i> mut	古典型 CMT 病?
1E	I	AD		
1F	I	AD	<i>neurofilament protein light chain</i> del	
2=常染色体優性あるいは劣性軸索変性型ニューロパチー=末梢神経伝導速度がすべて 38m/s 以上				
2A	II	AD	1p35-p36	小児期初発, 進行性下肢筋萎縮 感覚優位ニューロパチー
2B	II	AD	3q21	
2B1	II	AR	<i>lamin A/C</i>	声帯・呼吸筋麻痺 上肢優位の筋萎縮と筋力低下 左右対称性下腿萎縮と筋力低下 錐体路障害 難聴・瞳孔異常 重症型
2B2	II	AR	19q13.3	
2C	II	AD	12q23-q24	
2D	II	AD	7p14	
2E	II	AD	<i>neurofilament protein light chain</i> mut	
2F	II	AD	<i>heat-shock 27-kDa protein-1</i>	
2G	II	AD	12q12-q13.3	
2H	II	AR	<i>GDAP1</i>	
2I	II	AD	<i>P0</i> mut	
2J	II	AD	<i>P0</i> mut	
2K	II	AR	<i>GDAP1</i> mut	
2L	II	AD	12q24	
X=性染色体優性・劣性ニューロパチー				
X1	II	XD	<i>CX32</i> mut	男性が重症, ときに難聴 精神発達遅滞 痙性対麻痺を伴う
X2		XR	Xp22.2	
X3		XR	Xq26	
4=常染色体劣性脱髄型ニューロパチー				
4A	I	AR	<i>GDAP1</i>	若年発症・髄鞘低形成
4B1	I	AR	<i>myotubularin-related protein-2</i>	
4B2	I	AR	<i>set binding factor 2</i>	若年性緑内障 薄い髄鞘の onion bulb
4C	I	AR	<i>KIAA1985</i>	
4D	I	AR	<i>N-myc downstream-regulated gene-1</i>	
4E	CHN	AR	<i>P0, EGR2</i> mut	
4F	DSS	AR	<i>P0, PMP22, PMPX, EGR2, periaxin</i>	乳児期発症, 最重症 幼児期発症, 重症 ブルガリアジブシー, 難聴
4Lom	I	AR	8q24	
中間型 (intermediate form)=末梢神経伝導速度が I と II の中間				
DIA	Int	AD	10q24.1-25.1	
DIB	Int	AD	19p13.2-p12	
DIC	Int	AD	1p35	
DID	Int	AD	<i>P0</i> muta	
RIA	Int	AR	<i>GDAP1</i> mut	
遺伝性圧縮弱性ニューロパチー				
HNPP		AD	<i>PMP22</i> del, fra. shi	圧迫麻痺の反復, tomacula







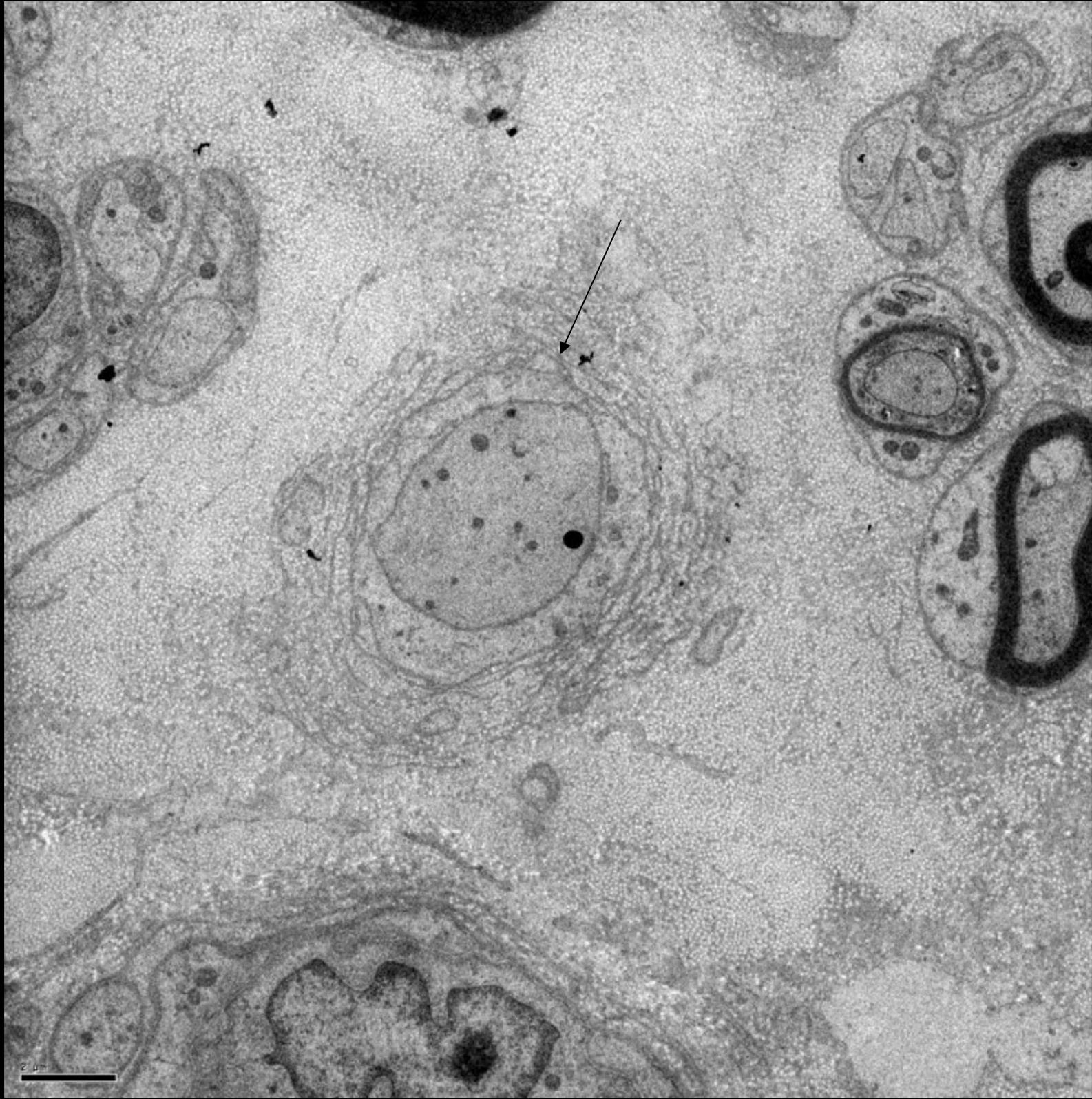




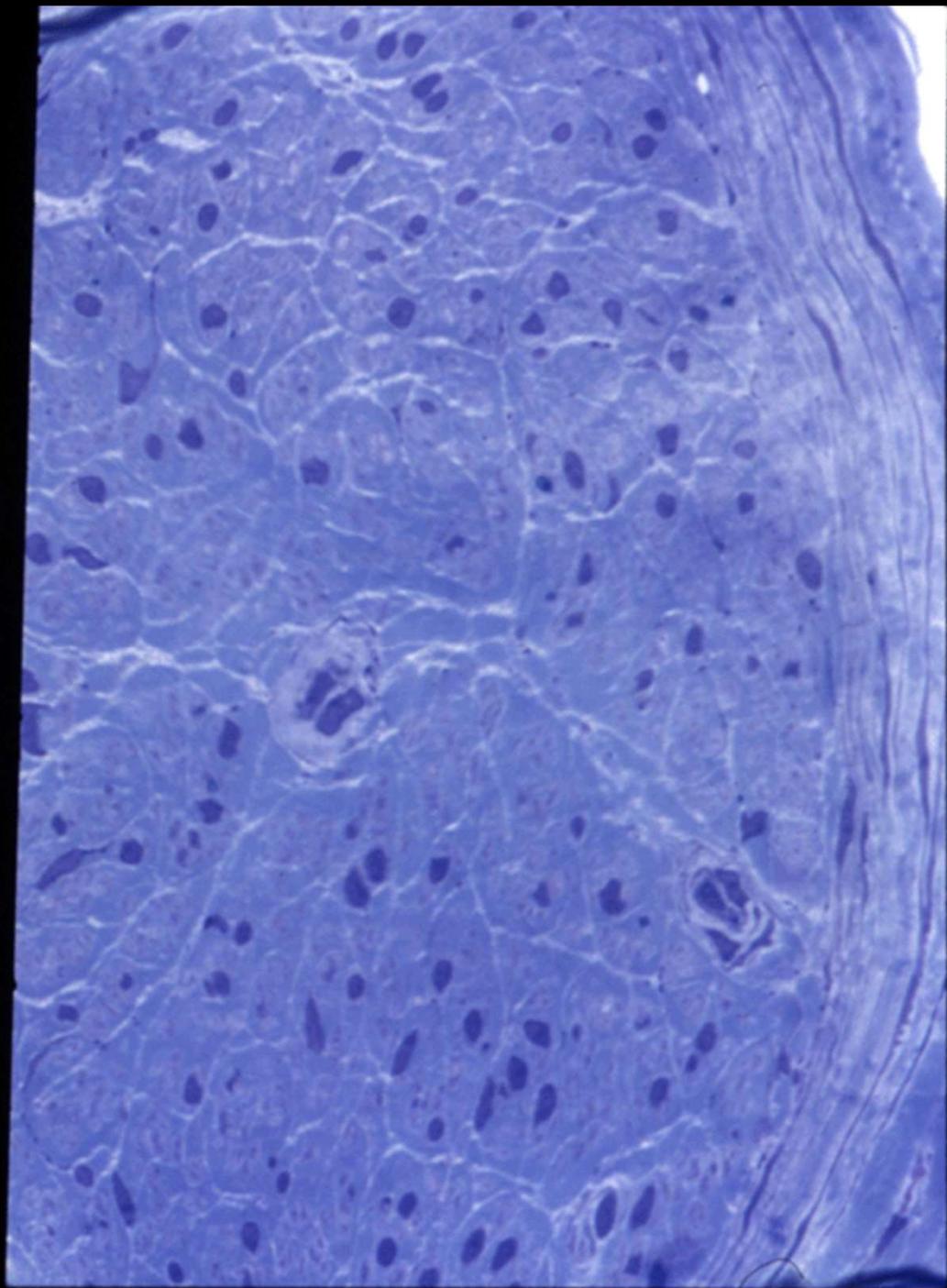
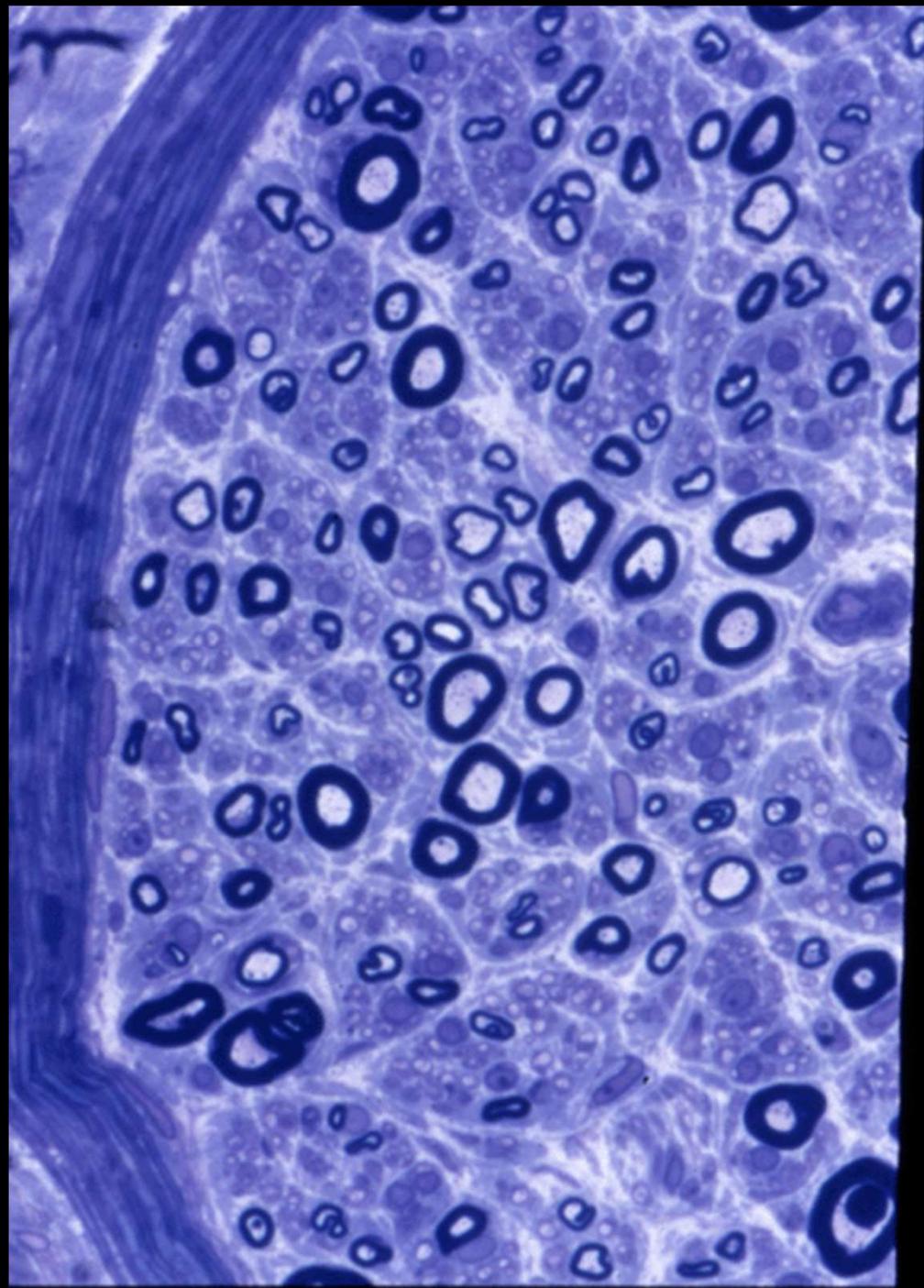
2 μm



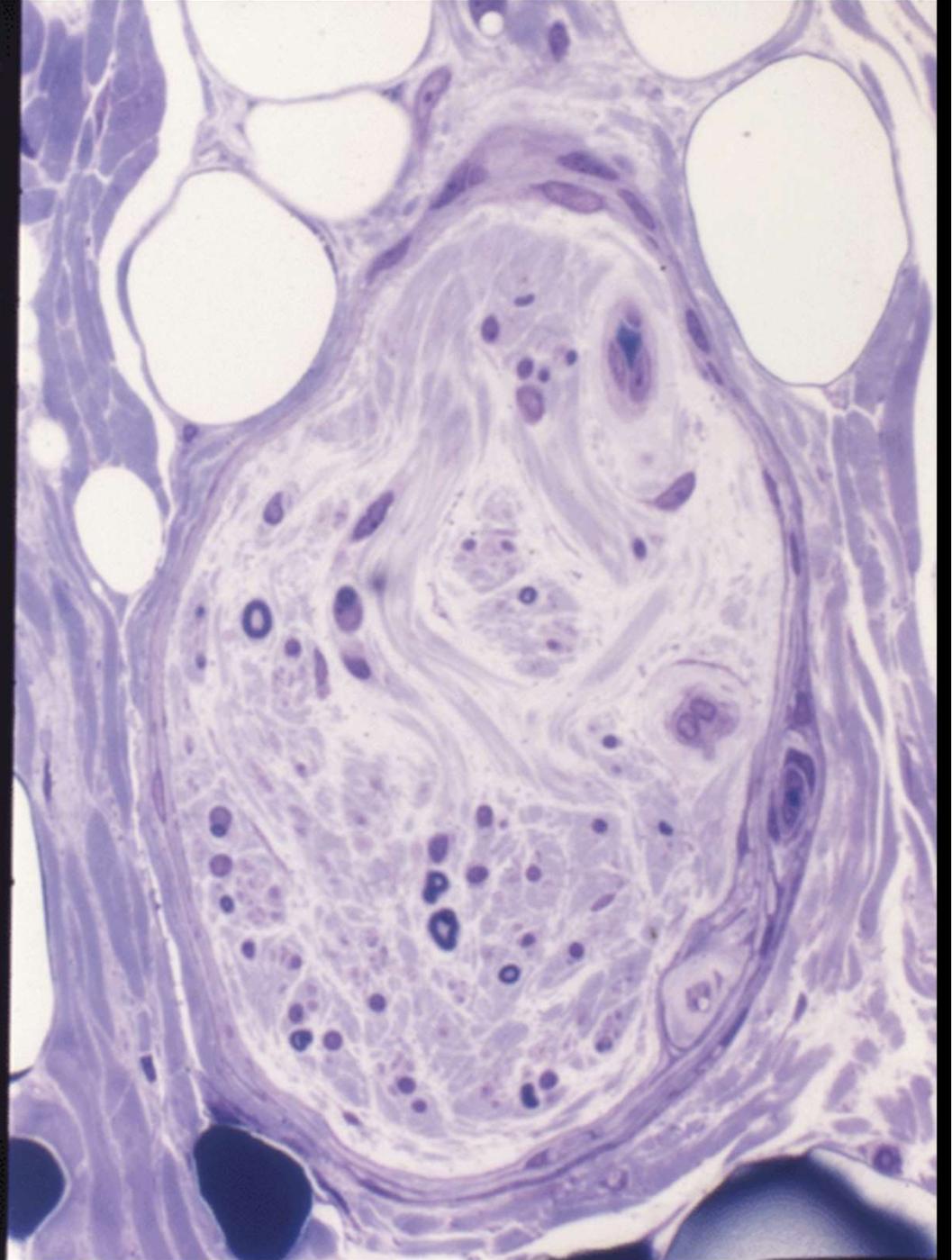
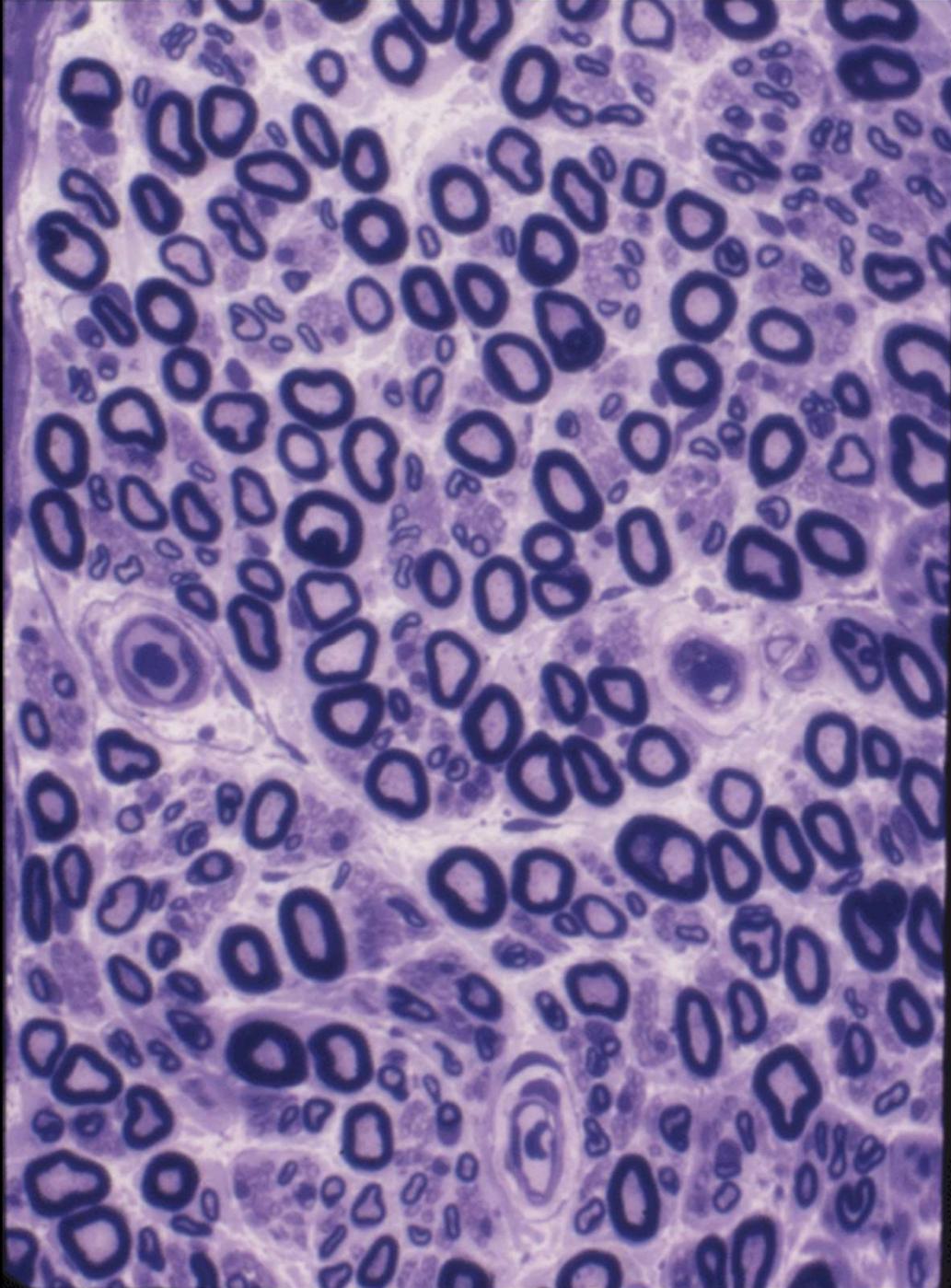
2  $\mu$ m





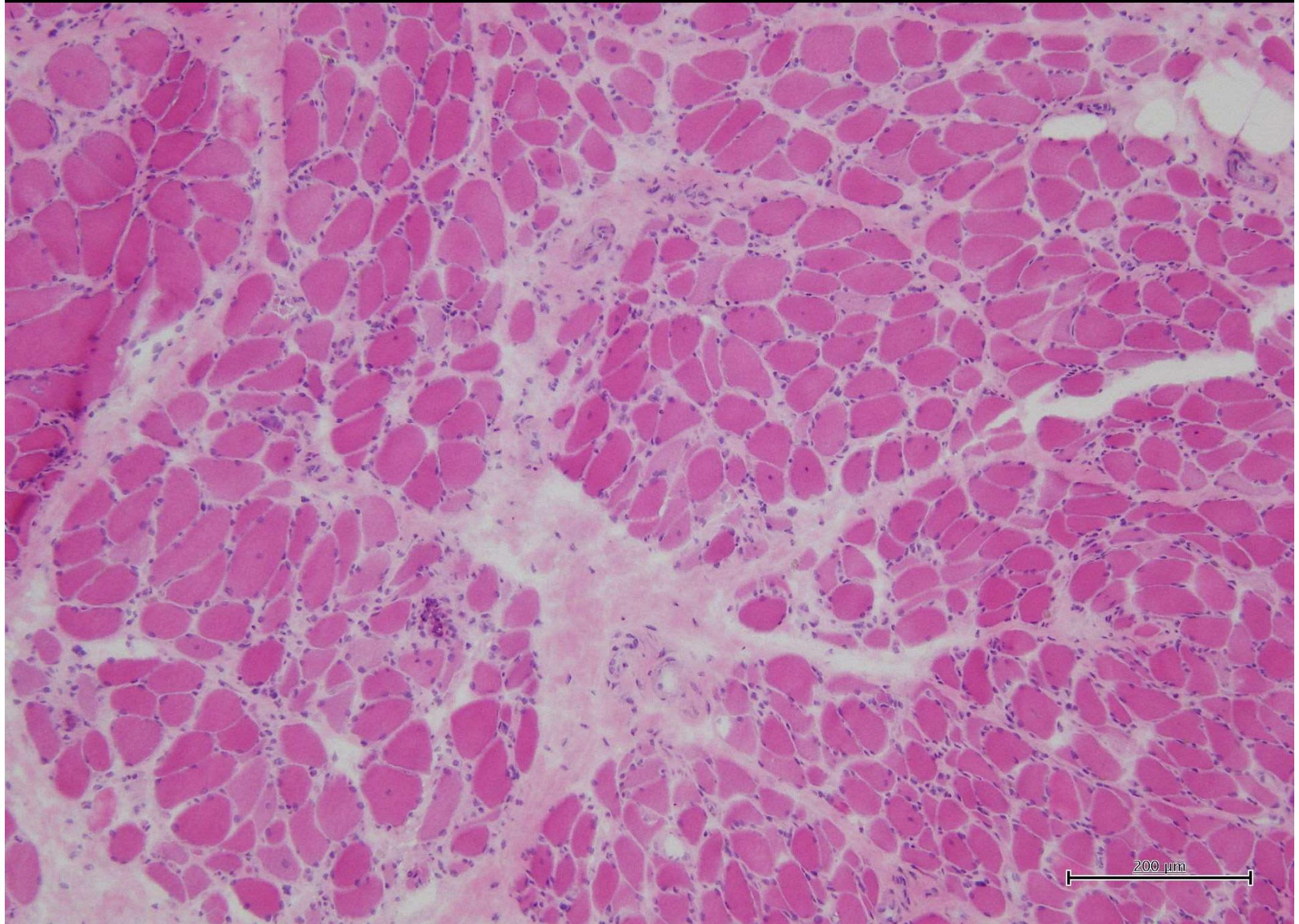


# 筋内神経

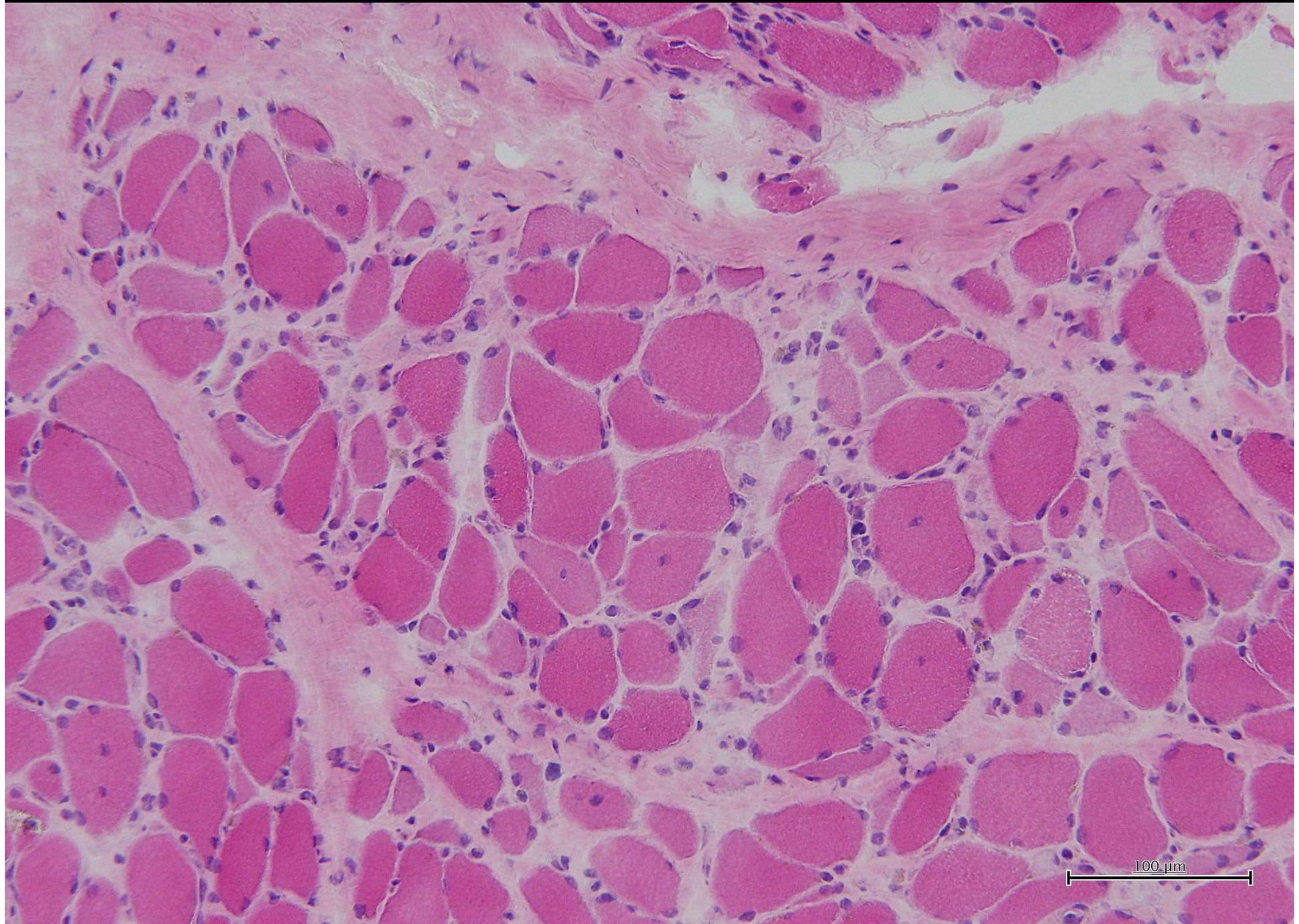


# 剖檢時採取骨格筋・末梢神經

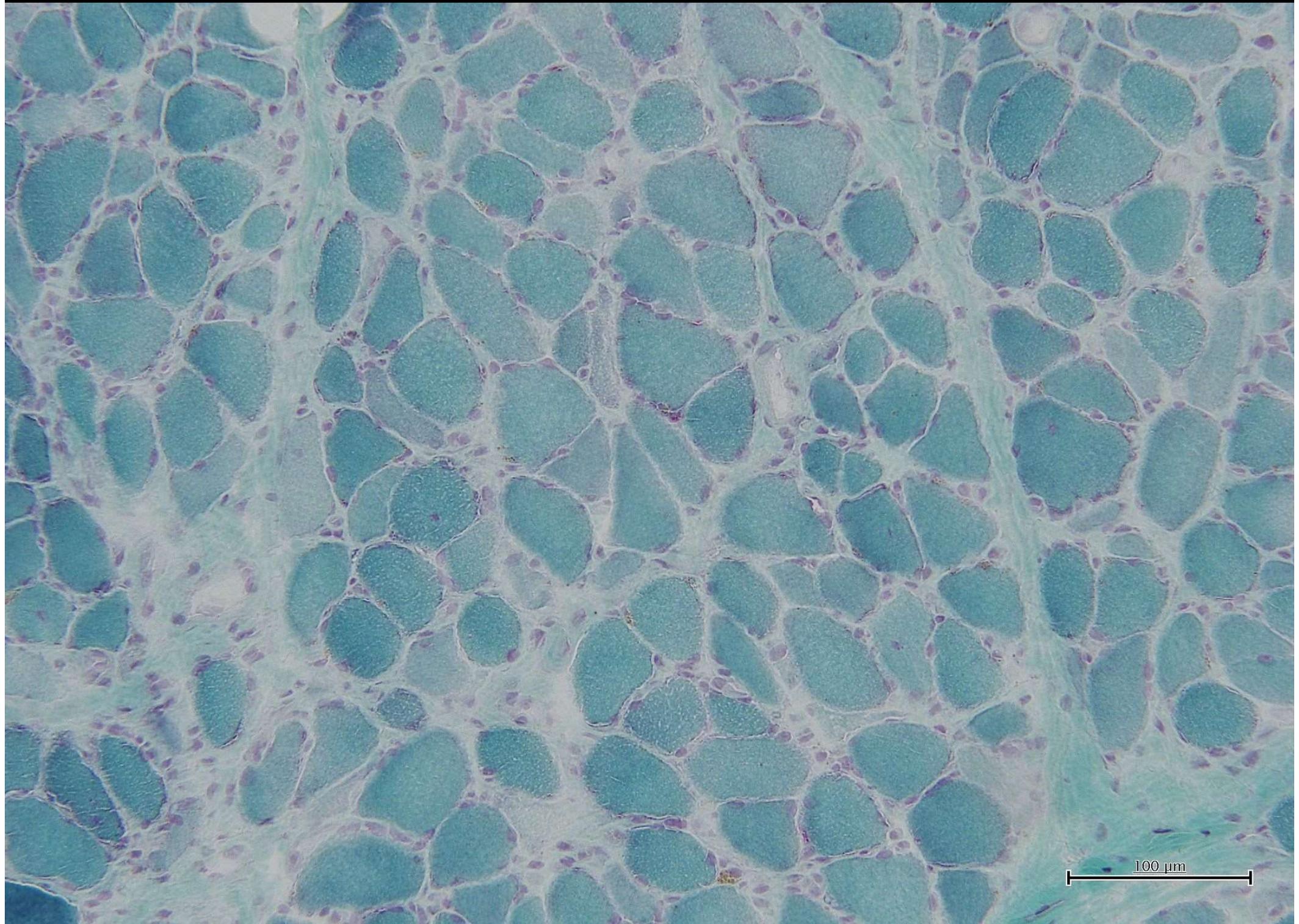
1. 上腕二頭筋
2. 後輪狀披裂筋
3. 肋間筋
4. 橫隔神經
4. 橫隔膜
5. 腸腰筋
6. 大腿直筋
7. 心筋
8. 腓腹神經

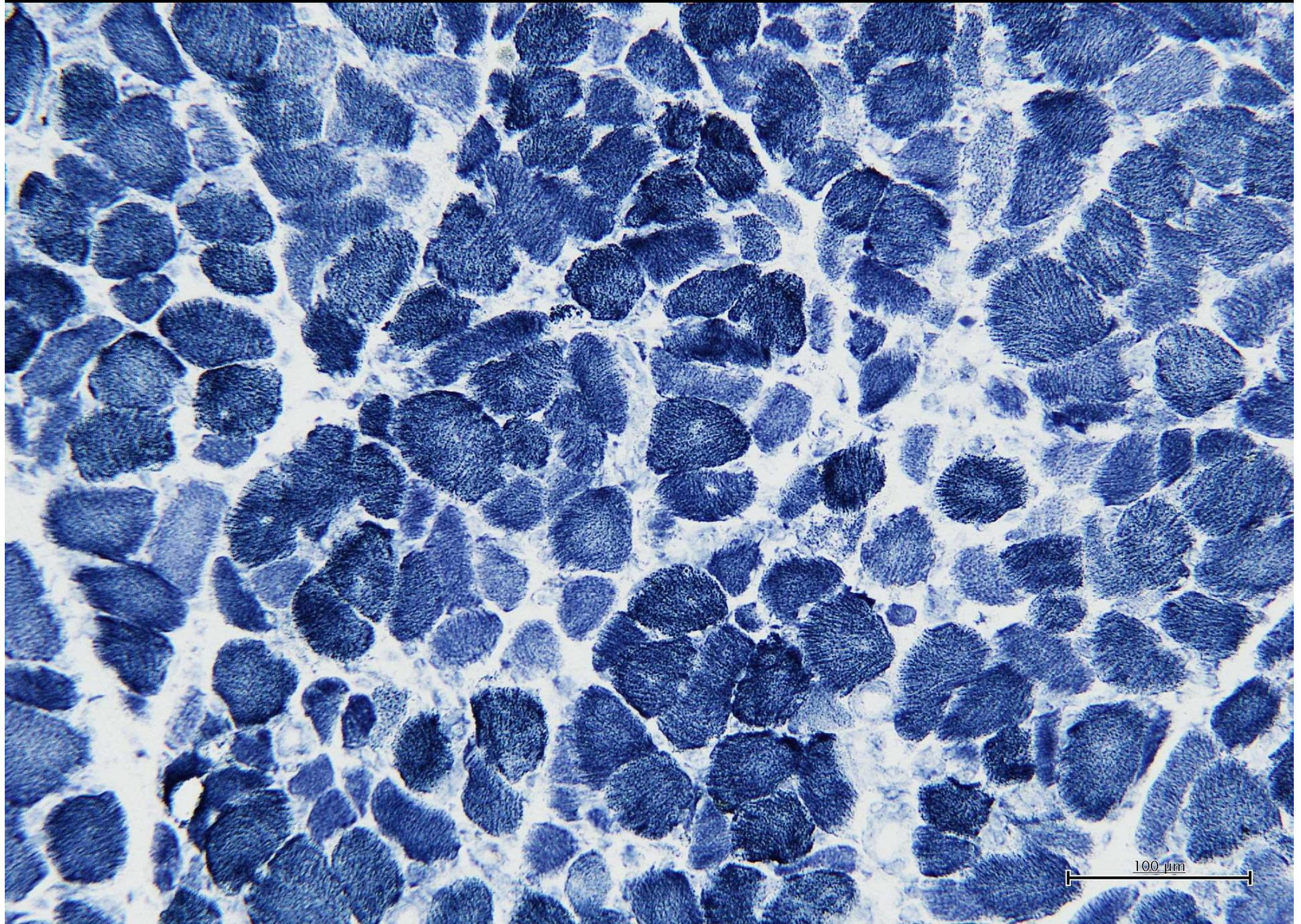


200  $\mu$ m

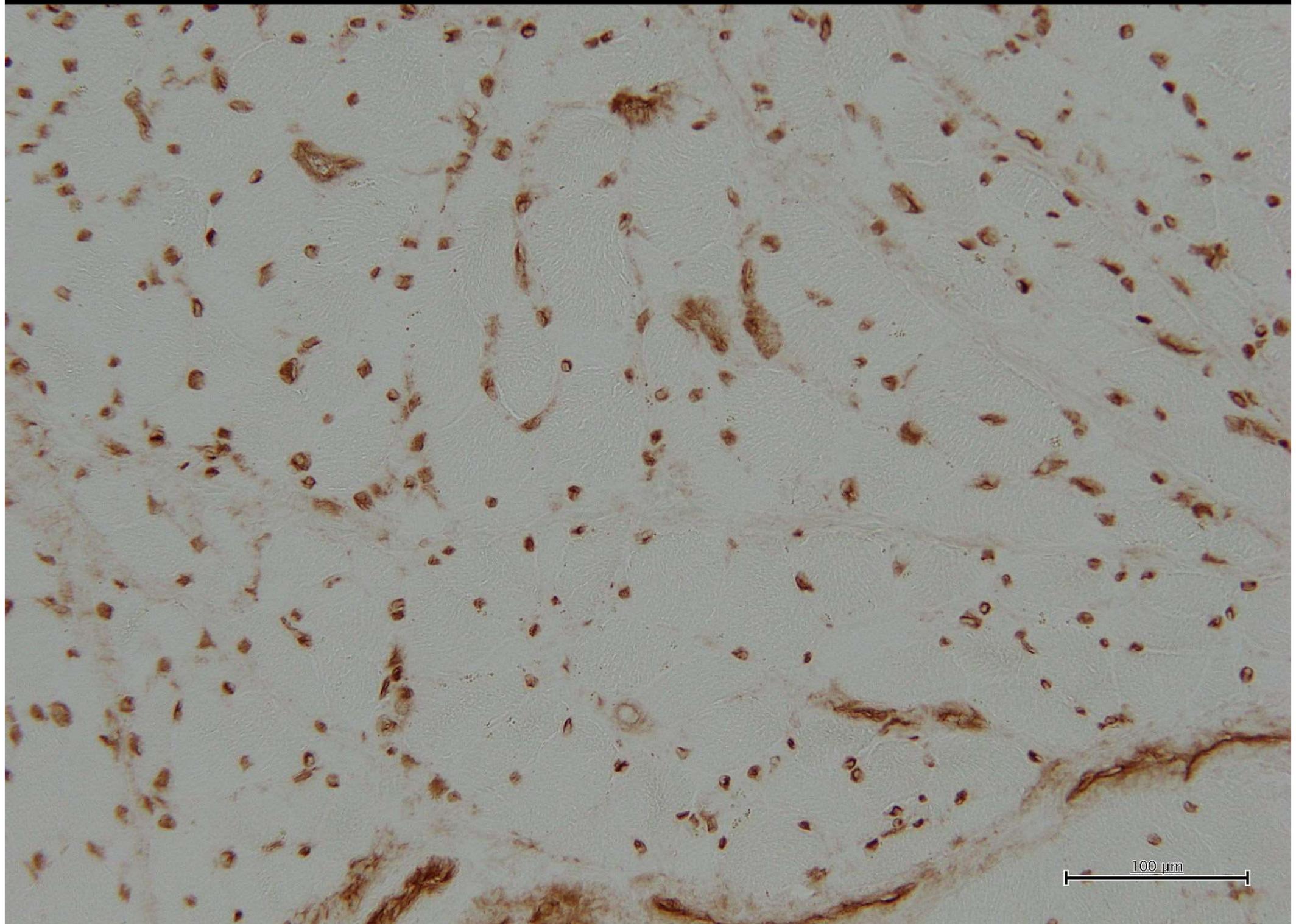


100  $\mu$ m

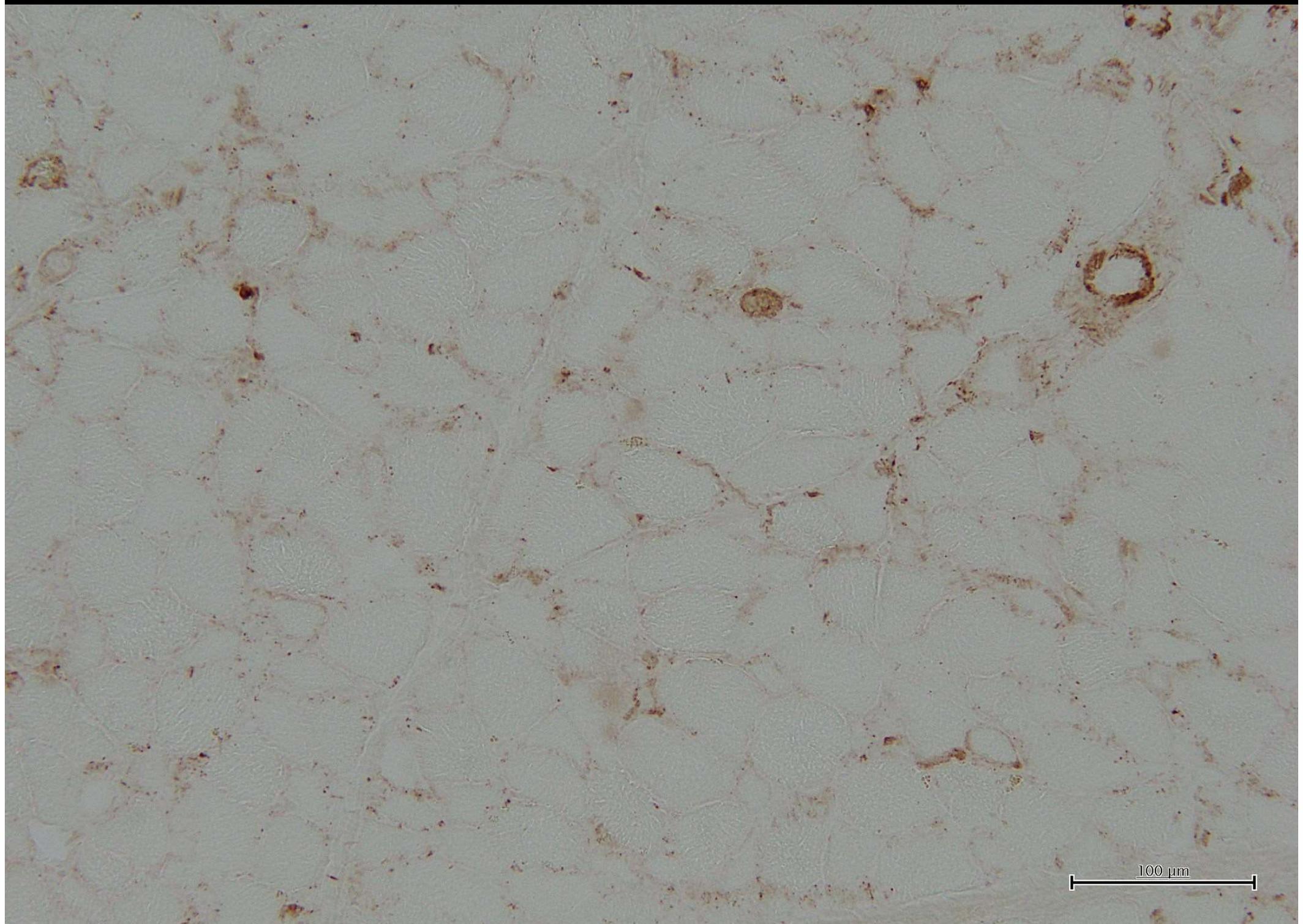




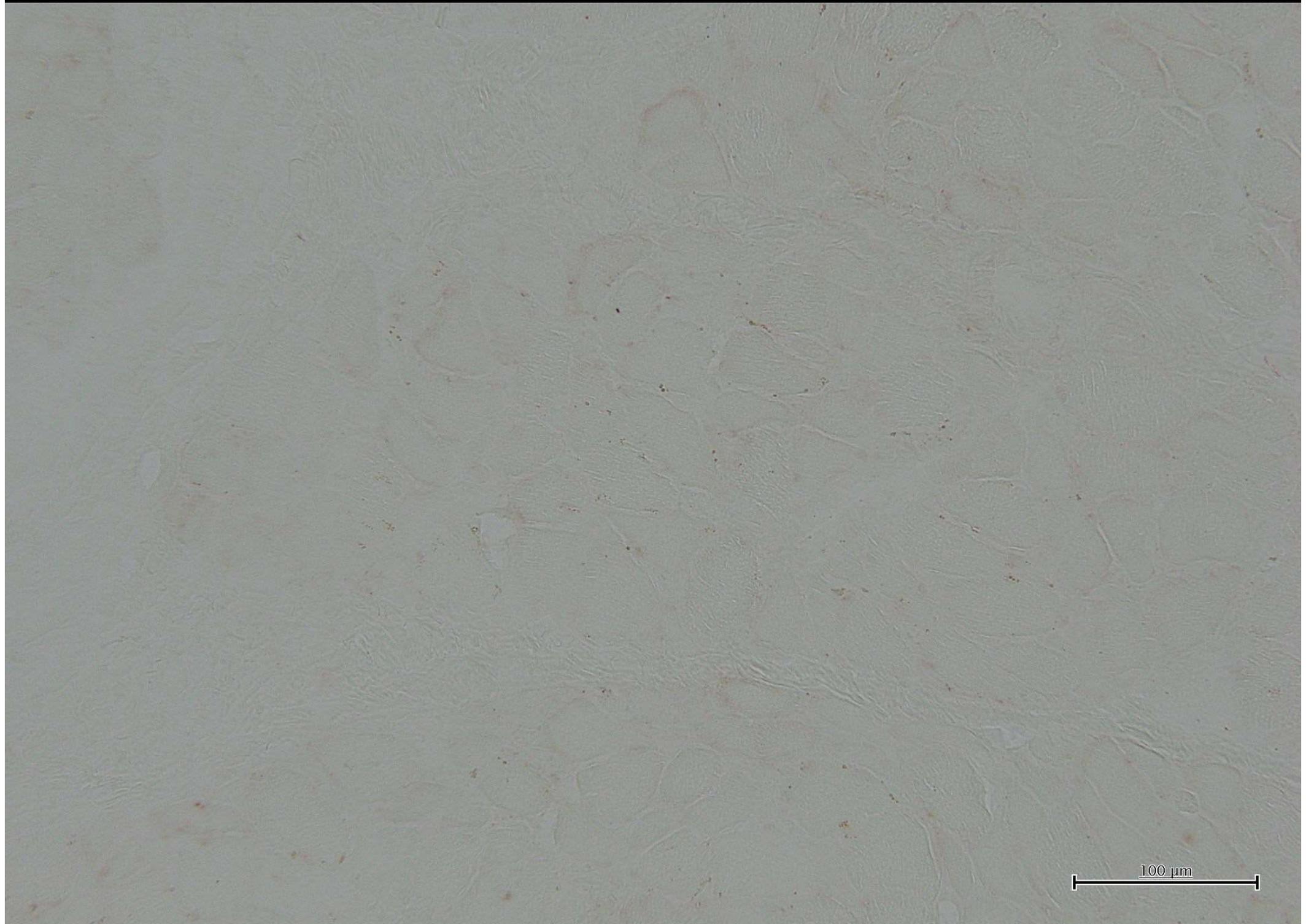
100 μm



100  $\mu$ m

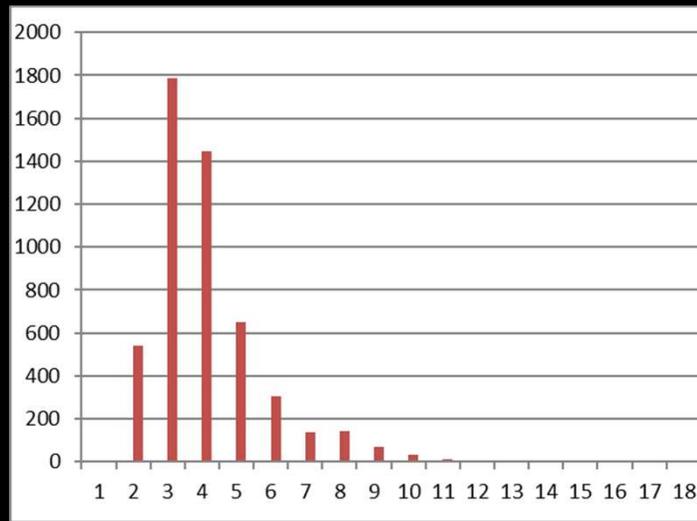
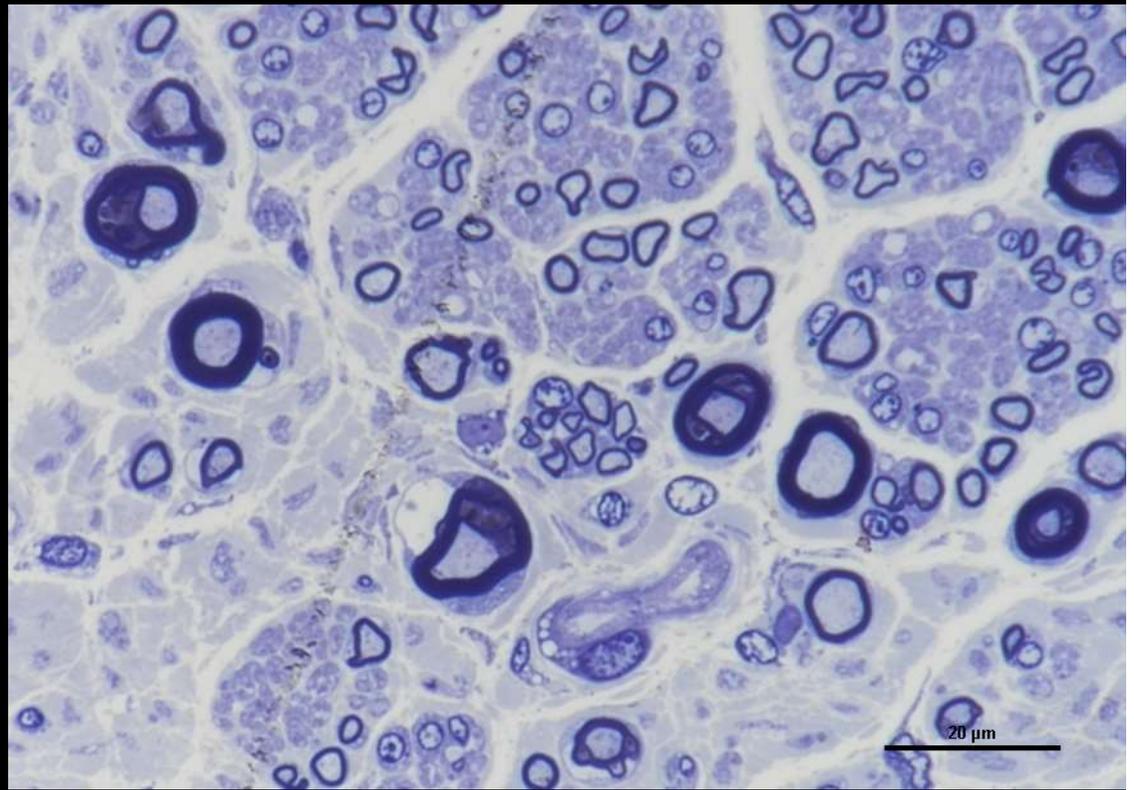
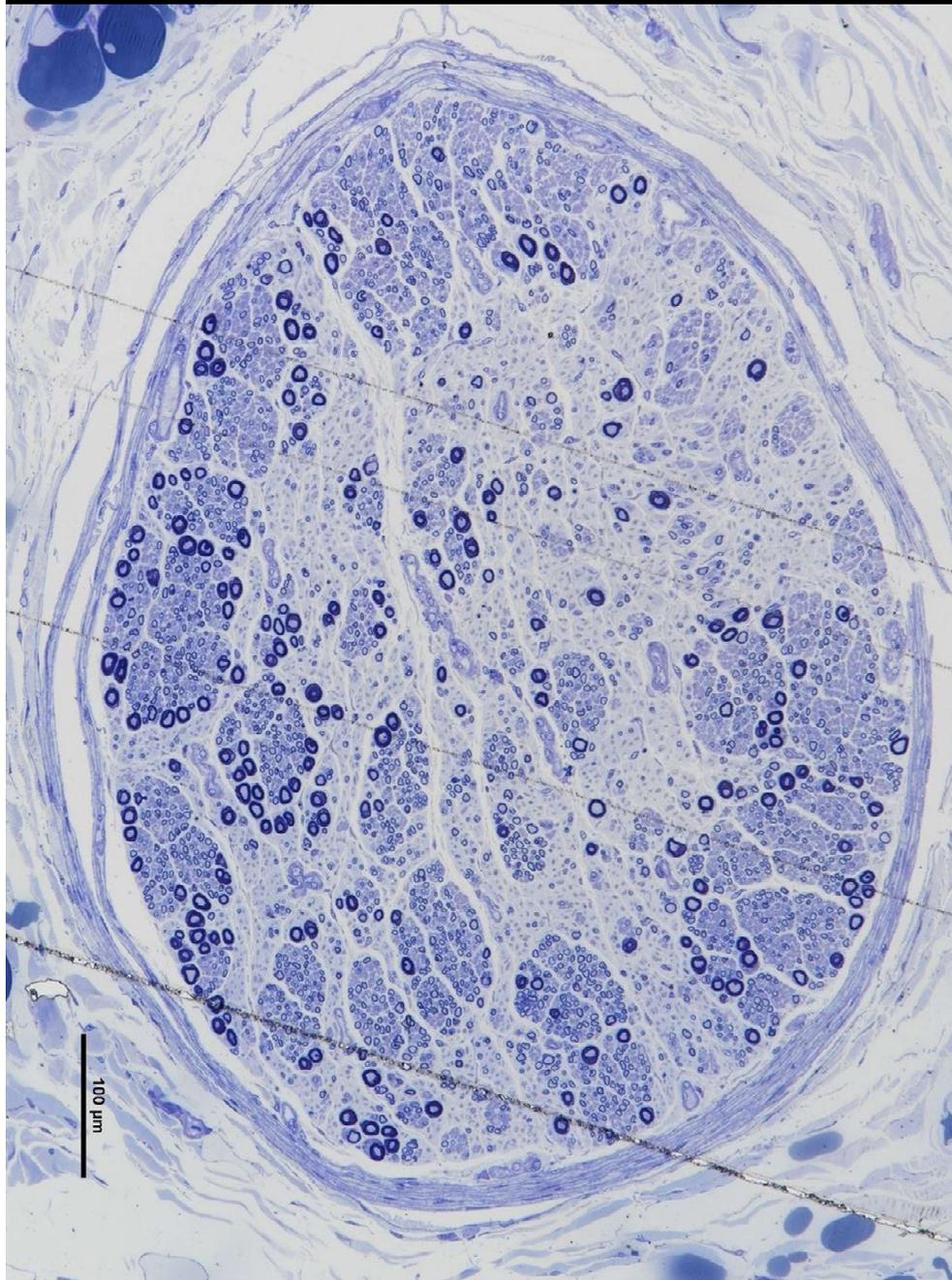


100  $\mu$ m



100  $\mu$ m

# 横隔神経 (エポソ包埋トルイジン青)

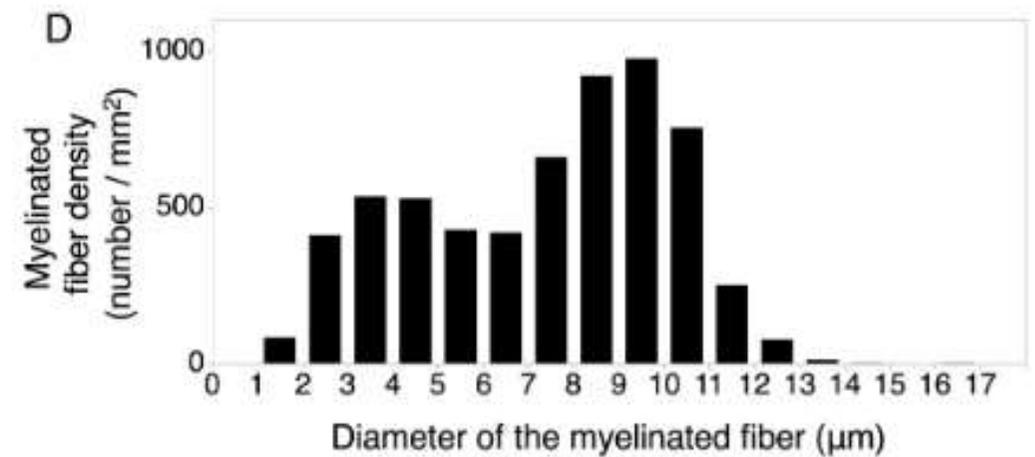
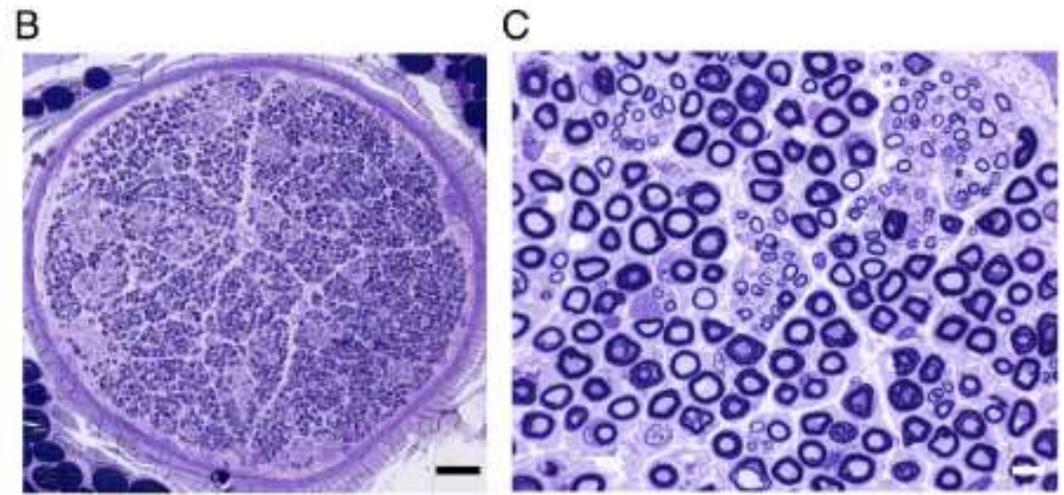
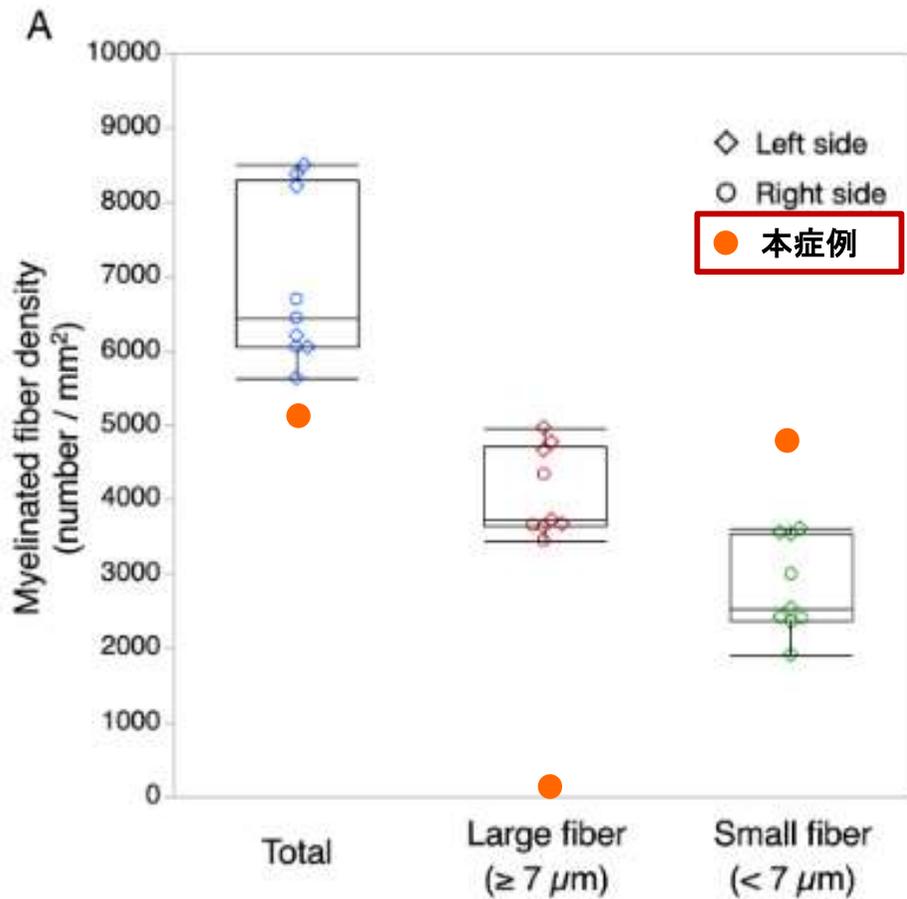


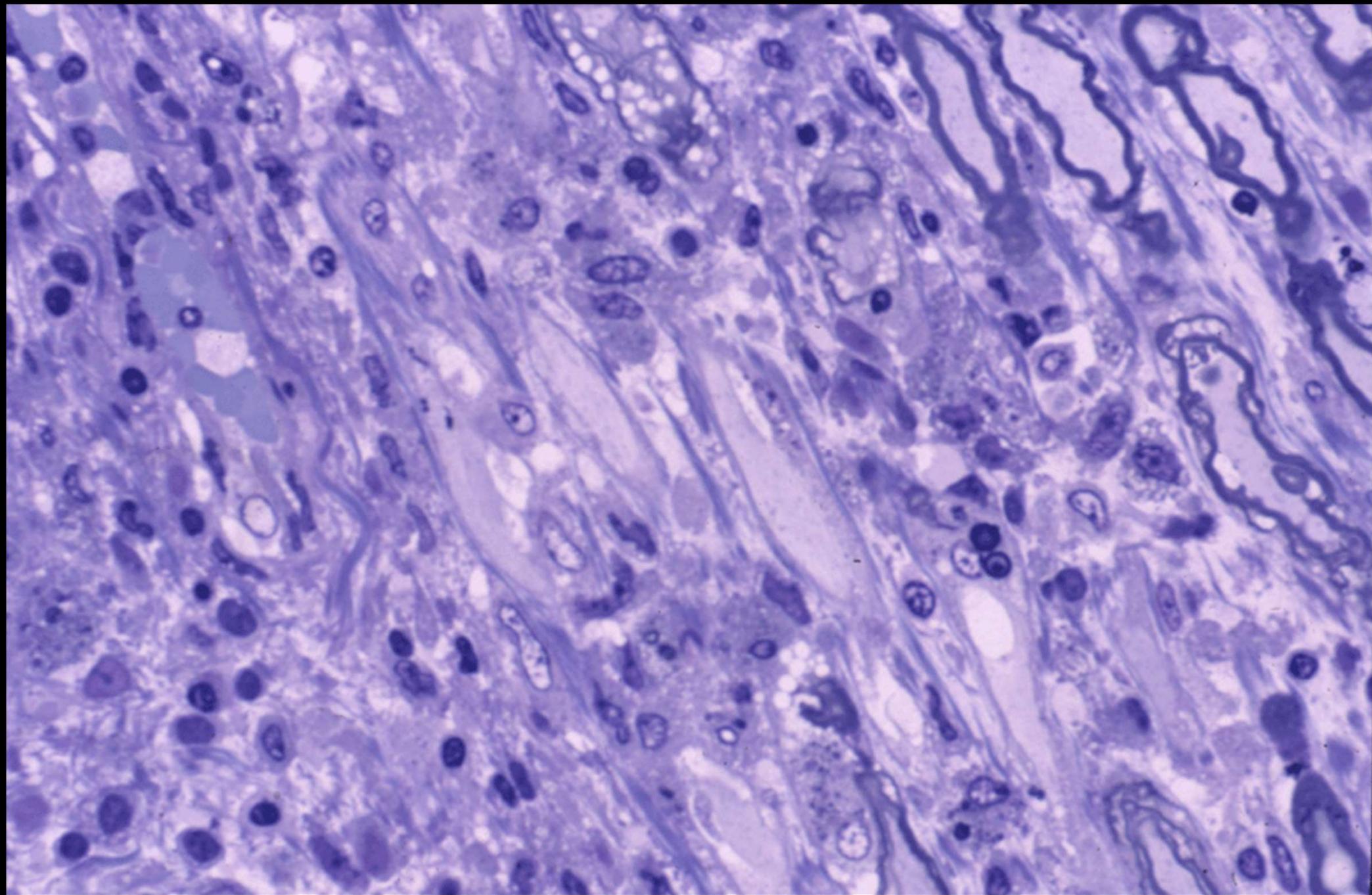
総本数: 1,637本  
有髄線維密度: 5,124/mm<sup>2</sup>  
小径: 大径=18:1

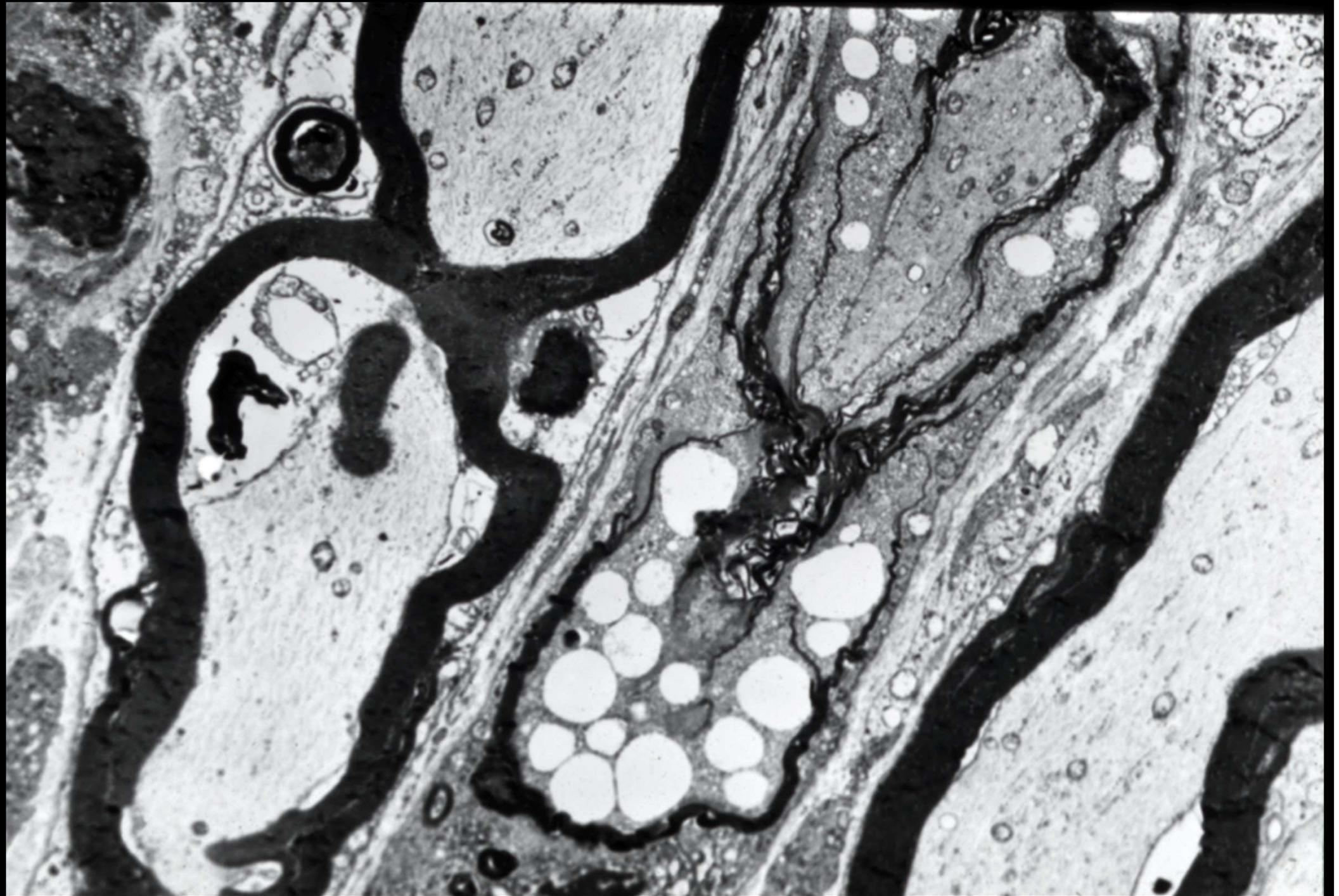
Original Article

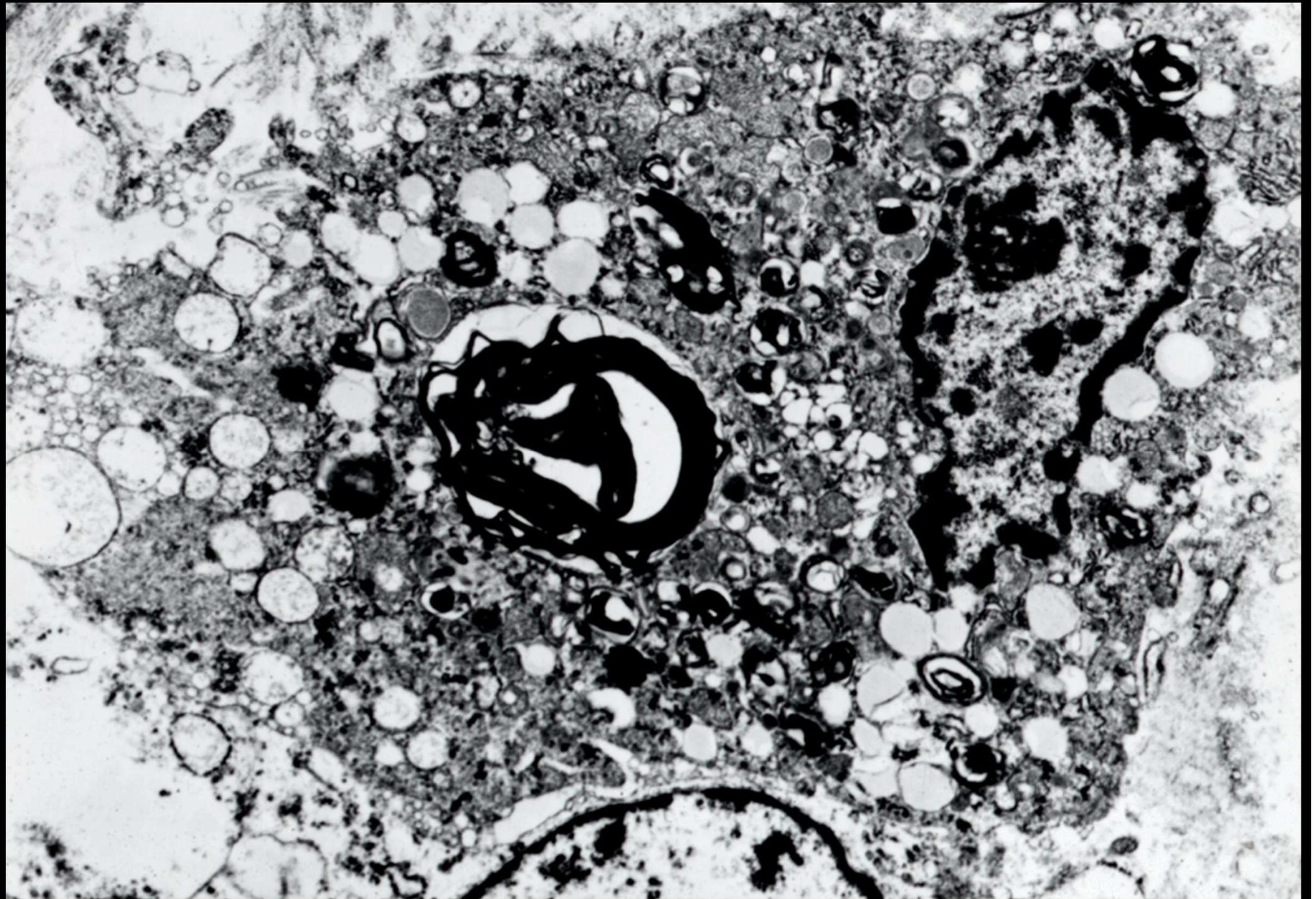
Morphological study of the phrenic nerve to determine a reference value for the myelinated fiber density in elderly individuals

Atsuko Motoda,<sup>1,2,3</sup> Tomoyasu Matsubara,<sup>1,3</sup> Zen-ichi Tanei,<sup>1</sup> Yasuhiro Sakashita,<sup>1,2</sup> Mikihiro Yamazaki,<sup>1</sup> Ito Kawakami,<sup>1</sup> Renpei Sengoku,<sup>1</sup> Tomio Arai,<sup>2</sup> Hirofumi Maruyama,<sup>3</sup> Yuko Saito<sup>1</sup> and Shigeo Murayama<sup>1,4</sup>









# AMAN

横隔神経

